TANDEM
Diabetes Care

April 22, 2024

Tara Hall
Medicare Evidence Development and Coverage Advisory Committee Coordinator
Centers for Medicare & Medicaid Services
Department of Health and Human Services
Attention: CMS–3421–NC
P.O. Box 8013
Baltimore, MD 21244–8013

Submitted electronically via ***MedCACpresentations@cms.hhs.gov***
CC tara.hall@cms.hhs.gov

RE: Devices for Self-management of Type 1 and Insulin-Dependent Type 2 Diabetes

Dear Ms. Hall,

Tandem Diabetes Care, Inc. ("Tandem") is submitting this letter in response to the Centers for Medicare & Medicaid Services (CMS) announcement of Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) public panel meeting on clinical endpoints that should be of interest to CMS in studies of devices for self-management of Type 1 and insulin-dependent Type 2 diabetes.

Founded in 2006, Tandem Diabetes Care, Inc. is a medical device company dedicated to improving the lives of people with diabetes through relentless innovation and a revolutionary customer experience. Tandem takes an innovative, user-centric approach to the design, development, and commercialization of products for people with diabetes who use insulin. Tandem manufactures and sells the t:slim X2™ pump and the Tandem Mobi pump with Control-IQ™ technology that receives and utilizes glucose data from a therapeutic continuous glucose monitoring (CGM) system. Tandem's insulin pumps automatically adjust insulin levels based on CGM readings and allow users to manage their diabetes more effectively.

The MEDCAC meeting announcement lays out four endpoint domains in clinicals trials (surrogate markets, health outcomes, quality of life and device safety) for which MEDCAC panelist will discuss specific measures, appropriate duration of follow-up, and minimal clinically important differences (MCIDs). As experts in automated insulin

delivery systems, we appreciate the opportunity to provide our perspectives on these questions and endpoint domains below.

We also want to take this opportunity to note that there is a valid National Coverage Determination (NCD) reconsideration request for the continuous subcutaneous insulin infusion (CSII) pumps coverage policy in the External Infusion Pump NCD (280.14). This NCD reconsideration request was confirmed as valid in September 2022, and it is on the CMS Coverage Analysis Group's NCD waitlist.* While we appreciate that CMS is working on diabetes self-management devices for older adults with diabetes with the MEDCAC process, we believe working on the changes to the insulin pump NCD would have a more immediate positive impact on Medicare beneficiaries with diabetes. We ask that CMS focus its efforts on reviewing changes to the NCD that can potentially affect over 3.3 million Medicare beneficiaries with diabetes using insulin.†

ENDPOINT DOMAIN RATINGS

CMS identified four endpoint domains that should be addressed in evidence regarding devices for self-management of type 1 or insulin-dependent type 2 diabetes in older adults. Of the four domains, we believe **Surrogate Markers** is the most important one with regards to clinical trials for devices used by people with diabetes. Some endpoint measures in the Surrogate Markers domain are the most appropriate for demonstrating that a device is reasonable and necessary for the treatment of type 1 or insulin-dependent type 2 diabetes.

We also believe that the **Device Related Safety** endpoint domain is an important and relevant domain for older adults. The other two domains, Health Outcomes and Quality of Life measures provide less clarity and are less important for determining the safety, effectiveness, and medical necessity of newer diabetes self-management devices.

Long term health outcomes require longitudinal studies which are not only costly but also vulnerable to the effect of therapy changes during the study period. This makes it difficult to state with certainty that the studied device is responsible for the outcome being measured. Further, the longitudinal trajectory of health in older adults is particularly heterogeneous. Outcomes in older adults should prioritize both short term and long term impacts, with short term complications such as acute hypoglycemia receiving higher priority. Additionally, it has been unequivocally demonstrated that improved glucose control leads to better health outcomes. The Diabetes Control and Complications Trial (DCCT) tracked 1,441 subjects with type 1 diabetes over 6.5 years and demonstrated that good glucose control directly reduces rates of diabetes related

* https://www.cms.gov/files/document/ncd-dashboard.pdf
† https://www.cms.gov/priorities/innovation/innovation-models/part-d-savings-model#:~:text=One%20in%20every%20three%20Medicare,the%20common%20forms%20of%20insulin.

complications.‡ As such, there is agreement among scholars and clinicians that glucose control is a key driver of improvement in the specific endpoint measures included in the Health Outcomes domain.§ Therefore, it is accepted that devices that can help patients with diabetes improve their glucose control will improve health outcomes for those patients.

Finally, **Quality of Life**, while very important, is a domain that is difficult to measure in a consistent and useful way. There are no agreed upon Patient Related Outcomes (PROs) that have been shown to indicate consistent differences across devices or device categories. We do not believe that the measures available for this domain are specific enough to device-related quality of life to be prioritized for a funding decision. Device discontinuation and device adherence may be more salient and direct measures of quality of life and are measured in the Device Related Safety domain.

As a final note, we understand CMS's desire to ensure clinical trials are appropriately representative of older adults. Tandem has prioritized a clinical trial specifically dedicated to this vulnerable population (data not yet published), and also encourages sub-analyses specific to this population(1)

Prioritizing Surrogate Markers

Across all of the endpoints in the Surrogate Markets domain, the appropriate duration of follow-up in clinical trials of diabetes devices is **three months**. This is a standard across the industry(2), and it is typically the point at which change in average blood glucose is established and stable.

Regarding glycemic targets: Time in Range (TIR) is important for both short term and long term complications of diabetes, and should therefore be considered an important measure for older adults, even with an uncertain life expectancy(3). Tight targets are unnecessary and not appropriate to the totality of the heterogeneous older adult population. International consensus indicates that glucose targets for older adults should be to be in range (70-180mg/dl) at least 50% of the day and to be below 70mg/dl no more than 1%of the day and above 180mg/dl less than 50% of the day(4). These glycemic goals are less restrictive than the goals established for younger people with diabetes because older adults are at greater risk for hypoglycemia due to erratic meal intake, progressive renal insufficiency, and treatment with multiple hypoglycemic

‡ Nathan DM; DCCT/EDIC Research Group. 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.

§ Specific endpoints in Health Outcomes domain: Diabetes-related emergency department visits, diabetes-related hospitalizations, complications of diabetes, e.g. kidney disease, MACE, restoration of hypoglycemia awareness, cognitive function changes.

agents (3). Thus, the American Diabetes Association Standards of Care in Diabetes recommend individualized glycemic goals in order to mitigate the risk of hypoglycemia as the primary glycemic safety concern (3).

In light of the unique attributes of this population, we ranked the importance of the Surrogate Markers to prioritize TIR and hypoglycemia reduction. We ranked the specific endpoint measures in the Surrogate Markers domain in Table 1 using a Likert scale (5-extremely important, 1-not at all important) and recommended Minimally-Clinically Important Difference (MCID) for these measures. We highlight that the most important specific endpoint measure is the Percentage of Time in Acceptable Glucose Range. For all the of these measures, the appropriate duration of follow up is **three months**.

It is important to note that as clinical trials evolve, the standard care group will evolve as well, likely to include some versions of automated insulin delivery (AID) as the comparator. As such, outcomes should be considered that are within person (not between groups), to determine the safety and efficacy for the individual. This will minimize the risk that true clinical effectiveness is washed out by study design with comparison to similar technologies.

TABLE 1. SURROGATE MARKERS SPECIFIC ENDPOINT MEASURES RANKING

Specific Endpoint	**Appropriateness**	**MCID recommendation**
Percentage of time in acceptable glucose range (70-180 mg/dL)	5	Per clinical trial guidelines, the MCID of 5% change in time in range is clinically meaningful when it occurs *within an individual in a trial*. This within-person change is important and should be emphasized more than improvement compared to control group, as control groups will evolve over time, but will likely be in-class for AID (4, 5).
Percentage of time in hypoglycemia (<70 mg/dL)	4	Any reduction in percentage of time in hypoglycemia is clinically meaningful given that older adults are at high risk for hypoglycemia (3)
Number of hypoglycemic episodes (<70 mg/dL), especially episodes of Level 2 hypoglycemia (<54 mg/dL)	3	Hypoglycemia is typically measured in percent of time below range, and number of events is not as important as the total duration. As such, we would recommend higher priority to time <70 mg/dl. We do not believe there is a MCID for specific number of episodes.

Percentage of time in level 2 hypoglycemia (<54 mg/dL)	3	If no level 2 hypoglycemia is recorded at baseline, there should be no increase in time under 54mg/dL. If the baseline is greater than 0, then any improvement in percent time would be clinically meaningful.
Percentage of time in hyperglycemia (>180 mg/dL)	3	Similar to change in TIR, a 5% reduction in hyperglycemia should be considered clinically meaningful (5), though not prioritized to the same degree as TIR and reduction in hypoglycemia (above).
Impact on A1C (MCID = 0.5% change)*	2	0.3%-0.5% or more reduction in A1c is clinically meaningful. However, individuals who start therapy with higher A1cs will see larger reductions in A1c than those individuals with moderately controlled A1cs. Typically, older adults with type 1 diabetes already have more moderate A1Cs and therefore, will start at a lower baseline (6). Further, many conditions associated with increased red blood cell turnover are more commonly seen in older adults and can affect the accuracy of HbA1c (e.g. hemodialysis, blood loss/transfusion, erythropoietin therapy) (3). Therefore, a more direct measurement of glycemic control (TIR and TBR) should be prioritized.

Prioritizing Device Related Safety

Device related safety is an important measurement for assessment of diabetes devices and is routinely collected in clinical trials. We ranked the specific endpoint measures in the Device Related Safety domain in Table 2 using a Likert scale (5- extremely important, 1-not at all important) and recommended Minimally-Clinically Important Difference (MCID) for these measures. We believe that device discontinuation rates and adherence to device use are important measures to determine quality of life impact. A patients continued use of the device indicates that they see value in its use and don't find the use burdensome Further, long term adherence requires that older individuals some of whom suffer from a variety of cognitive and functional challenges and/or their caregivers are able to use and derive benefit from the device.

TABLE 2. DEVICE RELATED SAFETY SPECIFIC ENDPOINT MEASURES RANKING

Specific Endpoint	Appropriateness	MCID recommendation
Device discontinuation rates	5	Less than 20% discontinuation rates
Patient preferences (comparing the device with conventional self-management) ***and adherence***	4	Adherence to AID therapy can be measured in percent time of continuous glucose monitor (CGM) use and percent time using automated insulin delivery. These metrics are available for all systems, and directly indicate whether an individual is adhering to the therapy. Adherence to therapy in the short term often predicts adherence in the long term and can be assessed in the first few months of device use in the real world. MCID: Greater than 75% device use.
Hypoglycemia-related emergency department visits	2	Infrequent in clinical trial level data, better for real world surveillance. Any reduction is clinically meaningful.
Harms such as tissue damage, if appropriate	1	n/a

In conclusion, we recommend that CMS encourage practical trials and not require long and costly trials to make decisions about the coverage of new diabetes technologies. We strongly believe that establishing highly rigid and hard to reach MCIDs would inappropriately deny coverage for some new diabetes treatments that would be of clinical benefit to Medicare beneficiaries with diabetes.

Thank you for the opportunity to provide input on this important discussion. Please contact Laurel Messer at **lmesser@tandemdiabetes.com** should you have any questions.

Sincerely,

Laurel Messer, PhD, RN, MPH, CDCES
SR DIRECTOR, MEDICAL AFFAIRS

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