April 22, 2024

Tara Hall
MEDCAC Coordinator
Letter via email: MedCACpresentations@cms.hhs.gov
Cc: Tara.Hall@cms.hhs.gov

Dear Ms. Hall:

We, the undersigned clinicians, in partnership with the Diabetes Technology Access Coalition (DTAC)[1] appreciate the opportunity to provide these comments for consideration as part of the May 21, 2024, Virtual Meeting of the Medicare Evidence Development and Coverage Advisory Committee (MEDCAC).

As clinicians, we have served in a variety of positions, including leading major endocrinology practices, serving as faculty in endocrinology training programs, as investigators in numerous clinical trials, and on the standard setting committees for our professional societies.

The DTAC is a cross-industry group of diabetes stakeholders. Collectively, the coalition members represent millions of Americans with diabetes, health care professionals who treat them, and major manufacturers that develop diabetes therapies, equipment, and supplies. Thus, our coalition represents those who manufacture and develop diabetes technology, the health care professionals who rely on this technology to best treat their patients, and the patients who benefit from the technologies.

The purpose of the MEDCAC meeting is to consider three specific questions as they relate to 21 specific endpoints that could be used in clinical trials of devices used by people with either type 1 or insulin-requiring type 2 diabetes ("endpoints feedback"). Below, we provide our perspective on these questions across three of the four domains (surrogate markers, health outcomes, and quality of life) to which these endpoints are assigned. We appreciate the attention to these issues and the consideration of these comments.

However, before we address specific questions, we wish to express our concern that the meeting format and assessment does not clearly specify what MEDCAC is seeking to address. For example, the MEDCAC panel is examining "health outcomes in studies of devices for self-management" of type 1 and insulin-requiring type 2 diabetes that should be of interest to CMS. This scope does not specify or recognize the current state of diabetes care and clinical practice guidelines regarding diabetes technologies. The American Diabetes Association clearly states, based on "A" grade evidence, that real-time continuous glucose monitors (CGMs) and insulin pump therapy should be available for all individuals with type 1 or insulin-requiring type 2 diabetes (e.g., those individuals with diabetes using insulin).[2] CGMs and insulin pump therapy are the current standard of care for this population, with a voluminous, significant body of clinical evidence justifying use of these

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[1] DTAC signatories include: Association of Diabetes Care & Education Specialists; Beyond Type 1; Dexcom; Diabetes Leadership Council; Helmsley Charitable Trust; Insulet; Tandem Diabetes Care; Tidepool
[2] See, American Diabetes Association Professional Practice Committee; 7. Diabetes Technology: Standards of Care in Diabetes—2024. Diabetes Care 1 January 2024; 47 (Supplement_1): S126–S144. https://doi.org/10.2337/dc24-S007.

technologies among individuals across the age spectrum with type 1 and insulin-requiring type 2 diabetes.

This is important context as, when considering studies of new diabetes technologies, the control group is typically utilizing some existing diabetes technology. When developing clinical studies, it would not only be unethical to limit or restrict participant access to less than the standard of care, but also highly unfeasible to identify and include a statistically meaningful sample size of individuals not using any diabetes technology since the majority of people with type 1 or insulin-requiring type 2 diabetes are already using current technologies.

Additionally, we note that diabetes affects individuals differently and the evaluation of clinical endpoints must be comprehensive and flexible enough to meet all patients' clinical needs. Using concrete and specific measures in this context does not properly capture the highly personalized nature of diabetes and could omit or fail to capture patients' specific clinical needs and preferences. Further, we believe that CMS is improperly seeking combined endpoints feedback for all types of diabetes technologies. Diabetes technologies span different functions and do not necessarily have to be used in conjunction with each other. Thus, each diabetes technology has its specific endpoints and clinical outcomes that may not be appropriately captured in a grouped discussion and recommendation.

We also express our concern that the current roster of MEDCAC members and the roster of the MEDCAC subcommittee at the February 8 meeting does not include an endocrinologist or anyone who appears to be familiar with diabetes, the lived experience, or clinical studies involving diabetes technology. The body that CMS is depending on for advice consequently lacks a deeper, more personal understanding of the clinical benefit of diabetes technologies and how studies of new technologies should be designed, including the specific endpoints that will be truly meaningful to the Medicare population.

While we appreciate CMS's attention to this matter, we believe a better approach would have been to discuss endpoints, and coverage of diabetes technologies generally, in a more granular fashion that incorporates and acknowledges the differences between the varying types of diabetes technologies, the personalized nature of the disease, and the ability to design and implement meaningful clinical studies. CMS should also ensure that its committee members include multiple participants who are endocrinologists, diabetes patients, or representatives of diabetes technology manufacturers.

Finally, we note that given the limited timeframe to review and provide feedback, our comments are limited to those endpoints for which we were able to develop and provide consensus recommendations. More time would be appreciated to meaningfully participate and provide feedback on all the identified endpoints.

With this context, we provide our recommendations regarding several of the specific surrogate markers and the four domains. More specifically, we provide the feedback as investigators in numerous clinical studies, which increasingly assess the benefit of next generation diabetes technology against the current standard of care. When performing these types of studies, the more important metric truly is whether there is non-inferiority for certain glycemic-related endpoints,

quality of life/social improvements, and/or the individual's experience living with type 1 or insulin-requiring type 2 diabetes. In many respects, absolute values or metrics as described in the some of the endpoints would not reflect of the clinical value of new technology, and therefore we caution against using such outcome metrics inappropriately. We appreciate your consideration of our comments and the opportunity to engage with you in this process.

COMMENTS

Surrogate Markers

Table 1 below shows our rating of the importance of each of these endpoints. We have used a scale of 1-5 with 1 meaning the least important and 5 the most important. We have provided such a rating only for those endpoints listed in the Surrogate Markers domain.

Across all of the endpoints in the Surrogate Markers domain, we believe that an appropriate duration for clinical trials of diabetes devices would be three months. With regard to the trials we have led or participated in, three months is typically the point at which a change in average blood glucose is observed, usually in the latter portion of that time period. We often see a leveling out of the change after that point and, in trials where therapy is withdrawn, a reversion back toward the higher baseline glucose levels.

In the table below, we have commented on a minimally-clinically important difference (MCID) for these endpoints.

Health Outcomes

Our comments on the endpoints in this domain are restricted to the appropriate duration of follow up. The nature of these endpoints is such that a useful trial to examine the impact of a device on these outcomes would likely last years, potentially decades, making such trials impractical as a routine matter and quite costly. Further, such trials would raise ethical challenges that might preclude them from being done.

The Diabetes Control and Complications Trial was a landmark study in diabetes, tracking more than 1,400 subjects with type 1 diabetes over 6.5 years. These subjects were randomized to an intervention group that sought to normalize glucose levels, while the control group did not have such interventions. The study conclusively demonstrated that good glucose control directly reduces the rates of several significant complications.[3, 4] Therefore, we have the requisite data to affirm that glucose control stands as a pivotal factor in the endpoints listed within the Health Outcomes domain. As a consequence, we strongly recommend that a device that demonstrates the capacity to assist patients in moving their glucose toward or into the target range demonstrates the capacity to impact the endpoints listed in the Health Outcomes domain.

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[3] The absence of a glycemic threshold for the development of long-term complications: the perspective of the Diabetes Control and Complications Trial. (1996). *Diabetes*, *45*(10), 1289–1298.
[4] Genuth S. (2006). Insights from the diabetes control and complications trial/epidemiology of diabetes interventions and complications study on the use of intensive glycemic treatment to reduce the risk of complications of type 1 diabetes. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists*, *12 Suppl 1*, 34–41. https://doi.org/10.4158/EP.12.S1.34

Quality of Life

We believe that the appropriate duration of follow up for the endpoints in this domain is three months. It is our belief that physiological changes directly impact these endpoints and that devices that permit a person with diabetes to directly observe positive physiological changes consequently improve their scores in these various endpoints. As noted in our discussion of the Surrogate Markers, a change in blood glucose associated with the use of CGM, insulin pumps or other diabetes technologies can typically be observed within three months.

We are not aware of a set of validated MCIDs associated with each of the endpoints listed in this domain. We would suggest that an appropriate MCID would be "no worsening" in the scores generated by these assessment tools.

Conclusion

CMS should seek to foster device trials that are both practical and flexible in terms of their outcomes. The guidance established under this process should permit more rapidly completed studies, rather than requiring very long or impractical trials. Further, the guidance should not establish fixed thresholds for minimally-clinically significant change that are so high that they do not pertain to individuals who have already achieved moderate success in their efforts – including through the current standard of care – and would thus prevent these individuals from accessing the best tools available to continue and even improve their prior success.

We thank CMS for the opportunity to comment and hope that our input is useful. We would be happy to provide additional studies, sources, or information if helpful. We also note that this letter reflects our views, and several DTAC members intend to submit comment letters with their respective perspectives. Should you have any questions about these comments, please reach out to Brian Lee at Brian.Lee@alston.com or (202) 239-3818.

Table 1. Endpoints Feedback – Surrogate Markers

Specific Endpoint	How appropriate is this endpoint in proving that a given device is reasonable and necessary for the diagnosis or treatment of type 1 or insulin-dependent type 2 diabetes. (Scale of 1-5 with 1 being the least appropriate and 5 being the most)	Ideal duration of follow-up required in a clinical trial for the detection of an impact on this endpoint measure?	Any conventional or validated thresholds known for defining a Minimally-Clinically Important Difference (MCID) for this endpoint?
Number of hypoglycemic episodes (<70 mg/dL), especially episodes of Level 2 hypoglycemia (<54 mg/dL)	2	3 months	Clinicians typically measure hypoglycemia using the percent of "time below range" data generated by a CGM. Consequently, we do not know of a conventional MCID for the number of hypoglycemic events.
Percentage of time in level 2 hypoglycemia (<54 mg/dL)	4	3 months	The generally accepted standard for hypoglycemia is that patients should experience less than 2% of their time in this range. For many patients, notably those with type 2 diabetes, there may be minimal or no hypoglycemia recorded at baseline and thus no improvement that could be used as the basis of establishing an MCID. We would suggest that interventions meant to improve glucose control should not result in hypoglycemia in this range or level 2 or level 3 hypoglycemic events. Therefore, the MCID should be listed as improvement in percent time in level 2 hypoglycemia if the baseline percent time is >4%, otherwise no increase in time below 54 mg/dL would be acceptable.
Impact on A1C (MCID = 0.5% change)*	5	3 months	We believe that a reduction in A1c of 0.3% or more is clinically meaningful,

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			especially in studies where the control group is already utilizing some diabetes technology. It is clear, however, that individuals who have a high A1c typically see larger drops in their average glucose levels when initiating device therapy than do those who initiate such therapy after having established reasonable control of their glucose levels. We would not want a coverage requirement established that created a perverse incentive for people with moderate control to worsen their condition in order to qualify for coverage for the tools that are most effective in moving them to the optimal glucose ranges. So, while we believe that a reduction of 0.5% in A1c is helpful in evaluating the effectiveness of a device for purposes of FDA clearance, we believe the appropriate MCID should be a change of 0.3% or more. We note that several studies have concluded that lower levels of

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			change in A1c are associated with meaningful impacts on health.[5, 6, 7]
Percentage of time in acceptable glucose range (70-180 mg/dL)	5	3 months	We believe that an increase of 5% in time in range is clinically meaningful and would recommend that figure to CMS as an appropriate change in this endpoint.[8, 9, 10] We also note that this is a higher priority endpoint than absolute change in A1c.
Percentage of time in hyperglycemia (>180 mg/dL)	5	3 months	As noted in the previous row, we believe that a 5% decrease in time in hyperglycemia is clinically meaningful.
Percentage of time in hypoglycemia (<70 mg/dL)	2	3 months	With regard to this endpoint, it is difficult to show an improvement because the amount of significant hypoglycemia can be quite low in a study population. This is particularly

[5] Lind, M., et. al., The shape of the metabolic memory of HbA1c: re-analysing the DCCT with respect to time-dependent effects. Diabetologia (2010) 53:1093–1098. DOI 10.1007/s00125-010-1706-z

[6] Lind M, Odén A, Fahlén M, Eliasson B. A systematic review of HbA1c variables used in the study of diabetic complications. Diabetes Metab Syndr. 2008;2(4):282-293.

7 Lind M, Polonsky W, Hirsch IB, et al. Continuous Glucose Monitoring vs Conventional Therapy for Glycemic Control in Adults With Type 1 Diabetes Treated With Multiple Daily Insulin Injections: The GOLD Randomized Clinical Trial. *JAMA*. 2017;317(4):379–387. doi:10.1001/jama.2016.19976

[8] Vigersky, R. A., & McMahon, C. (2019). The Relationship of Hemoglobin A1C to Time-in-Range in Patients with Diabetes. *Diabetes technology & therapeutics*, *21*(2), 81–85. https://doi.org/10.1089/dia.2018.0310

[9] Beck, R. W., Bergenstal, R. M., Cheng, P., Kollman, C., Carlson, A. L., Johnson, M. L., & Rodbard, D. (2019). The Relationships Between Time in Range, Hyperglycemia Metrics, and HbA1c. *Journal of diabetes science and technology*, *13*(4), 614–626. https://doi.org/10.1177/1932296818822496

[10] Saboo, B., Kesavadev, J., Shankar, A., Krishna, M. B., Sheth, S., Patel, V., & Krishnan, G. (2021). Time-in-range as a target in type 2 diabetes: An urgent need. *Heliyon*, *7*(1), e05967. https://doi.org/10.1016/j.heliyon.2021.e05967

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			true among people with type 2 diabetes where individuals ordinarily are hyperglycemic, rather than hypoglycemic. A reasonable MCID would be no increase in hypoglycemia, defined as time below 70 mg/dL while A1c and TIR criteria are met.

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