MDDT SUMMARY OF EVIDENCE AND BASIS OF QUALIFICATION DECISION FOR INSPIRE QUESTIONNAIRES

BACKGROUND

MDDT NAME: INSULIN DOSING SYSTEMS: PERCEPTIONS, IDEAS, REFLECTIONS AND EXPECTATIONS (INSPIRE) QUESTIONNAIRES

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TOOL DESCRIPTION AND PRINCIPLE OF OPERATION

The **IN**sulin Dosing **S**ystems: **P**erceptions, **I**deas, **R**eflections, and **E**xpectations (INSPIRE) Questionnaires (the tool) are a set of self-administered questionnaires developed to evaluate the impact of automated insulin dosing (AID) systems on the psychosocial functioning and quality of life (QoL) of individuals with Type 1 diabetes (T1D). Automated insulin dosing systems are comprised of an insulin pump, a continuous glucose monitoring (CGM) system, and an algorithm that uses interstitial glucose values captured by the CGM system and insulin pump dosing history to automatically direct the pump to adjust insulin dosing.

The tool consists of eight questionnaires (baseline and post-intervention) for use with each of the following groups: youth with T1D (8 to 17 years of age), adults with T1D (18 years of age and older), parents/caregivers of youth with T1D, and partners of adults with T1D. The researcher created developmentally-sensitive questions through a qualitative research study that included a literature review, expert opinions, focus groups, and individual interviews.

The baseline and post-intervention questionnaires consist of 17 to 22 items each and are intended to measure expectations of how an AID system can improve overall diabetes-specific well-being. The youth questionnaires contain 17 items, the parent/caregiver questionnaire contains 21 items, and the adult with T1D and partner of adults with T1D questionnaires each contains 22 items. The items capture how the use of an AID system may impact the following dimensions of the users' psychosocial functioning and quality of life: (1) glycemic control, including reduction of nocturnal hypoglycemia, (2) activities of daily life (ADL) including diet and physical activity and for adult users, when driving, drinking alcohol, engaging in sex, and/or experiencing pregnancy, (3) social activities, (4) short and long-term complications, including managing sick days, and (5) overall individual and family quality of life. Additional items also capture respondents' preferences regarding ease of device use, size/appearance of device, and reliability of the device for maintaining glycemic control.

Respondents use a six-point rating scale for the questionnaires, from strongly agree to strongly disagree or not applicable, to indicate how much they anticipate the positive impact of using an AID system on each of the 17 to 22 dimensions of psychosocial functioning and quality of life items. The baseline and post-

intervention questionnaires include the same questions. The sponsor did not specify a duration of device use or a recall period between the baseline and post-intervention questionnaires. Participants in the validation studies of this tool completed online questionnaires and responded based on current device use. Future use will include online and paper self-administered questionnaires.

QUALIFIED CONTEXT OF USE

The self-administered INSPIRE (INsulin Dosing Systems: Perceptions, Ideas, Reflections and Expectations) questionnaires have been developed to determine the impact of automated insulin dosing (AID) systems on psychosocial functioning and quality of life in youth with T1D (8-17 years of age) and adults with T1D, as well as parents/caregivers of youth with T1D, and partners of adults with T1D. The INSPIRE questionnaires can be used by medical device companies and sponsors or investigators of clinical studies to determine the impact of automated insulin dosing (AID) systems on psychosocial functioning and quality of life in individuals with Type 1 diabetes (T1D) and to support the safety and effectiveness of these systems.

The INSPIRE questionnaires have been developed to determine the psychosocial impact of AID systems in a range of relevant factors specific to youth with T1D (8-17 years of age) and adults with T1D, as well as parents/caregivers of youth with T1D, and partners of adults with T1D.

The baseline and/or post-intervention versions of the INSPIRE questionnaires may be used as secondary or additional endpoints in a clinical study to evaluate subjects' perceptions of the impact of AID systems on their psychosocial functioning and quality of life. In addition, the baseline and post-intervention questionnaires can be administered longitudinally to characterize changes in these factors from baseline. Including user perspective information may be helpful to understand the benefits and risks of AID systems. Sponsors should engage with FDA to determine the applicability of the INSPIRE questionnaires to their clinical study.

SUMMARY OF EVIDENCE TO SUPPORT QUALIFICATION

To support qualification, the sponsor collected data from a large-scale qualitative investigation to assess relevance of questionnaire items, conducted cognitive interviewing to assess understanding, and performed psychometric analyses to assess internal and construct validity. The objective was to develop and validate, in collaboration with key stakeholders, a measurement tool to assess the psychosocial impact of AID systems on individuals with Type 1 diabetes and their family members/significant others.

The sponsor also supported qualification by submitting four publications that (1) described the development of a working group to identify measures to adequately capture the extent to which human and psychological factors play a role in the uptake and efficient use of AID systems (Barnard, et al., 2015), (2) described the development of a second working group to foster exchange among key stakeholders in AID system development including users, health care providers, payers, and individuals with engineering, industry, academic, and regulatory, backgrounds (Weissberg-Benchell, et al., 2016), (3) discussed the need for a tool to explore users' and significant others' hopes and expectations of an AID system (Garza, et al. 2018), and (4) provided the results of a study of 284 children and youth with T1D, adults with T1D, parents/caregivers of youth with T1D, and partners of adults with T1D across four sites in the US and UK who completed structured interviews or focus

groups on expectations, desired features, potential benefits, and perceived burdens of AID systems (Naranjo, et al., 2017). Narango et al. identified three themes as critical for AID system implementation: considerations of trust and control, system features, and concerns and barriers to adoption.

Based on the focus groups and individual interviews, the sponsor identified 24 a priori codes (Table 1) representing common concerns and expectations regarding the use of AID systems. The sponsor subsequently identified 12 thematic clusters emerging from the 24 a priori codes (Table 2) that addressed similar concerns or expectations. For example, general financial questions related to AID systems, insurance coverage, and out of pocket expenses were combined into one thematic cluster identified as financial aspects of AID systems. Respondents in all four subject groups identified many of the same concerns and priorities. Overall, the following ten benefits of using AID systems were consistently reported: (1) reduced mental burden, (2) decreased daily management burden, (3) lowered HbA1C levels, (4) improved glycemic control, (5) reduced glycemic variability, (6) increased accuracy of bolus calculations, (7) improved health benefits, (8) improved quality of life, (9) improved quality of sleep, and (10) trusting the system to manage diabetes.

Table 1

A Priori Coding List (24 Codes
1. AID system benefits to quality of life
2. Mental burden
3. Physical burden
4. Concerns/minuses associated with AID systems
5. Desired features of AID systems
6. Physical aspects, wearability, and comfort of AID systems
7. User interface, sounds and aesthetics related ideas about AID systems
8. General financial questions regarding AID systems
9. AID systems out of pocket costs
10. Insurance coverage and insurance questions regarding AID systems
11. Trust and control of AID systems
12. Human vs. system conflicts related to AID systems
13. Taking breaks from diabetes technology
14. Blood glucose and glycemic control expectations/changes with AID systems
15. Hyperglycemia
16. Hypoglycemia
17. Stability of blood glucose levels using AID systems
18. Eating*
19. Exercise/physical activity*
20. Nighttime
21. Past experiences with technology or diabetes technology
22. Relationships and loved ones
23. Situations and contexts affected by use of AID systems
24. Trade-off analysis associated with automated insulin dosing systems

*Eating and physical exercise were related to several clusters, so they are considered stand-alone a prior codes in themselves as well as features within other thematic clusters.

Table 2

Thematic Clusters
1. Quality of life aspects of AID systems
2. Burden associated with AID systems
3. Concerns about AID systems
4. Features of AID systems
5. Financial aspects of AID systems
6. Trust and control of using AID systems
7. Human vs system control of T1D diabetes management (includes the ability to transfer control to an AID system)
8. Benefits of AID systems
9. Nighttime aspects of T1D management and relevance to AID systems
10. Social/family relationships and how AID systems may impact them
11. Technological and technical aspects of AID systems
12. Contextual, environmental, and situational aspects related to AID system use

Participants in all the groups expressed many of the same concerns and priorities and universally endorsed several concepts. Universally endorsed concepts result in the same positive response across respondents. These concepts lack variability and therefore value in identifying differences among respondents. The sponsor subsequently deleted items that were universally endorsed and did not provide new information to the questionnaires. The qualitative work resulted in tools that focus on what is most important to individuals with T1D, their parents/caregivers and partners when using an AID system and how AID systems impact psychosocial functioning and quality of life. The data collected from the focus groups, extensive cognitive interviews, and multiple meetings with a multidisciplinary team of health care providers and external independent experts supported that the items for each independent measure on the final versions of the questionnaires are not redundant and that each assess a relevant content area for the construct of positive expectations of AID systems.

Quantitative evidence is necessary to support the analyses and interpretation of the scores; however, the questionnaires are currently supported by a relatively small body of quantitative evidence. The appropriate use and interpretation of the scores will only be addressed through the continued use and evaluation of the INSPIRE questionnaires. As there are no existing guidelines on how to analyze and interpret the scores, the current context of use should be limited to use of the tool as secondary or additional endpoints in a clinical study to evaluate subjects' perceptions of the impact of AID systems on their psychosocial functioning and quality of life. In addition, the baseline and post-intervention questionnaires can be used to characterize changes in these factors from baseline. Continued use of the INSPIRE questionnaires and publication of the results will provide additional information and guidance regarding analysis and interpretation of the scores.

In summary, the sponsor provided limited quantitative evidence to support the scoring of the tools as quantitative measures of psychosocial functioning and quality of life. However, the results of the qualitative work support the reliability and validity of the INSPIRE questionnaires to evaluate the impact

of AID systems on psychosocial functioning and quality of life in the populations sampled in the studies. The evidence submitted in support of the qualification of the INSPIRE questionnaires is summarized in the following sections.

Reliability

The items and concepts included in the INSPIRE questionnaires were assessed in 750 participants recruited from the Type 1 Diabetes Exchange Registry (the Type 1 Diabetes Exchange Registry is an online longitudinal database of people living with T1D). The sample included 292 youth with T1D, 8 to 17 years of age, 159 adults,18 to 86 years of age, with T1D, 150 parents/caregivers of youth, 3 to 17 years of age, with T1D, and 146 partners of adults with T1D.

The sample size is sufficient for psychometric analysis. However, the estimates for Cronbach's Alpha (a measure of internal consistency among responses to items) are high and could indicate redundancy among the items (Table 3). Very high internal consistency could result from items that respondents answer the same, resulting in limited variability and overlapping information.

Table 3

Measure	Cronbach's Alpha
Youth	0.95
Parent/Caregiver	0.97
Adults	0.97
Adult Partner	0.97

During interactive review the sponsor was asked to provide inter-item correlations to address this concern; the sponsor's response is summarized in the following section entitled Validity.

Validity

The sponsor submitted several published articles in addition to the results from questionnaires, focus groups and individual interviews to support the validity of the INSPIRE questionnaires. The publications support the need for tools to measure the psychosocial assessment of AID systems. There are multiple tools to measure quality of life and diabetes-related distress in people with diabetes who use different types of diabetes technology (e.g., insulin pumps, CGMs and blood glucose meters), but there is no existing tool that specifically addresses the use of AID systems as a novel technology. Compared to other diabetes technology (e.g., insulin pumps and CGMs), AID systems are unique in that they represent a more autonomous means of diabetes management than other diabetes technology thus requiring that a certain level of trust be transferred from the users, parents/caregivers, and partners to the AID system.

The sponsor conducted 48 focus groups (195 participants) and 89 semi-structured interviews (89 participants) to support validity of the tool. The focus groups included 35 adolescent/young adults with T1D (12 to 20.8 years of age), 16 children with T1D (9 to 11 years of age), 65 parents/ caregivers of children with T1D, 113 adults with T1D (18 to 77 years of age), and 55 partners of people with T1D. Participants were recruited online through diabetes blogs, flyers posted in clinics

and hospitals, and direct mail to current patients of diabetes clinics in Chicago, IL; Stanford, CA; Boston, MA; and Dorset, England. The focus groups were age and role specific. During interactive review the sponsor submitted to FDA several transcripts of the focus groups and interviews.

The following are examples of questions that were included in the focus groups and interviews:

1. "What would be some of the tasks that would be involved in using an automated insulin dosing systemwith T1D?"
2. "What are some of the possible benefits from the system?"
3. "What are your expectations about what the system might do?"
4. "Are there any aspects of automated insulin dosing systems that you think might hurt your diabetes management or worry you?
5. "Are there particular times of day or situations when you might find an automated insulin dosing system particularly useful?"
6. "What would stop you from wanting to try or use one of these systems or what might get in the way?"

Table 4 depicts the four steps and nine substeps the sponsor used to analyze the data.

Table 4

Step 1	• Transcription and transcript review • Primary coding with 24 a priori codes
Step 2	• Code distillation and grouping (24 a priori codes reduced to 12 thematic clusters) • Summation of idea units per stakeholder group • Focusing matrix to inform quantitative measure development
Step 3	• Multi-site research team review of findings and discussion • Drafting of survey items for five stakeholder groups
Step 4	• Measure testing and refinement, including cognitive interviewing • Measure piloting and implementation

The total number of interviews and focus groups reasonably captures the aspects and features of AID systems that are most important to persons with T1D, parents/caregivers of children with T1D, and partners of adults with T1D. The themes that emerged from the interviews and focus groups were consistent across the different populations, indicating that they share similar concerns and identify similar features desirable in AID systems.

The quantitative evidence provided by responses to the questionnaires is generally supportive of the meaningfulness and interpretability of the scores produced by the INSPIRE questionnaires. There is some mixed evidence based on previous exposure to or use of different diabetes devices and technology. For example, youth with previous experiences with insulin pumps and CGMs scored higher, that is, their use of AID devices was associated with more positive functioning and quality of life than youth who did not have previous experience with insulin pumps and/or CGMs. Adults with previous pump use scored higher than adults who use multiple daily injections (MDI) to manage their diabetes, but previous CGM use was not associated with differences in scores among adults with

T1D.

Due to the high Cronbach's Alpha scores, the sponsor was asked during interactive review to provide inter-item correlation tables and to justify the inclusion of multiple items with potentially overlapping concepts. The items with the highest correlations included items on the youth questionnaire that dealt with some aspect of glucose control, specifically, impact of AID system on decreasing the frequency of hypoglycemia and hyperglycemia, staying within target glucose range, and maintaining target HbA1C levels.

The sponsor responded that the research team determined that a purely statistical approach was not the best approach for the design of the tool since the questions were intended to capture novel perceptions associated with a very different way of managing T1D. Existing diabetes-related questionnaires focus on the individual as almost solely responsible for diabetes self-management (including associated behaviors and burdens) whereas AID systems are intended to largely manage an individual's diabetes with limited input from users, e.g., calibrating the CGM and inputting number of carbohydrates prior to meals and snacks. To address this concern, the sponsor conducted multi-faceted analyses including statistical analysis, extensive participant interviews and focus groups, further cognitive interviewing, and input from a multidisciplinary team of health care providers.

Based on the information gained from the above sources, the sponsor created items and defined concepts that are important to individuals with T1D, their parents/caregivers, and partners. The sponsor stated that the data collected from interviews and focus groups supported the inclusion of all items even if some of the items overlapped in content, e.g., low blood glucose, high blood glucose, target range, and HbA1C, because each of these concepts is uniquely important and assesses different expectations of AID systems. The sponsor further stated that extensive cognitive interviewing together with multiple meetings with health care providers and external independent experts supported that the items for each independent measure on the final versions of the questionnaires are not redundant and that each assess a relevant content area for the construct of positive expectations of AID systems. The review team determined that the sponsor's explanation supported inclusion of all items in the questionnaires.

DISCUSSION OF THE EVIDENCE STRENGTH TO SUPPORT QUALIFICATION

The INSPIRE questionnaires have been tested in a large sample of youth and adults with T1D as well as in parents/caregivers of youth with T1D and partners of adults with T1D. The questions were developed and subsequently refined through focus groups, extensive interviews with study participants, and the clinical expertise of health care providers, primarily endocrinologists, pediatric endocrinologists, and health psychologists. The sponsor submitted evidence that included peer-reviewed publications, a robust qualitative analysis of data from focus groups and cognitive interviews, and expert opinion from a multidisciplinary team of health care providers to support that the INSPIRE questionnaires are valid and reliable for use.

There is little published literature on the psychosocial and human factors assessment of AID systems. Currently, there are only four publications identified in the literature that are specific to AID systems. The reliability as measured by Cronbach's Alpha was consistently high across all measures and suggested redundancy among the items. However, the sponsor's inclusion of items that appear to overlap in content, e.g., low blood glucose, high blood glucose, target range, and HbA1C, is reasonable because each concept

is uniquely important. For example, low blood glucose is applicable to the potential benefit of AID systems managing nocturnal hypoglycemia, as well as the reduction of hypoglycemia contributing to overall glycemic control (time in target range) and target HbA1C. In addition, a reduction in nocturnal hypoglycemia can contribute to improved quality of sleep, improved quality of life, and decreased sense of diabetes-related burden. The qualitative work supports the inclusion of the overlapping items; there is no conclusive evidence that the overlap may produce bias in the scores. Overall, the INSPIRE questionnaires capture important aspects of treatment effectiveness from users, parents/caregivers, and partners' perspectives in a reliable and reproducible manner.

ASSESSMENT OF ADVANTAGES/DISADVANTAGES OF QUALIFICATION

Assessments of Advantages of Using the MDDT:

The main advantage of the INSPIRE questionnaires is that they are currently the only tool that specifically assesses the impact of AID systems on psychosocial functioning and quality of life in individuals with T1D, parents/caregivers, and partners. In addition to assessing the impact of AID systems on activities of daily living (ADL), social activities, short and long-term complications, burden of disease, and overall individual and family quality of life, AID systems are unique in that they assume more responsibility for the management of diabetes than other devices such as insulin pumps, sensor-augmented insulin pumps (SAP), or CGM devices. Users and their caregivers must transfer a certain amount of trust from themselves to AID systems for diabetes management. The tool addresses this and other factors, including the burden of disease associated with the advanced technology specific to AID systems. No other existing measure adequately address these important factors.

The tool was developed with a robust qualitative study, relying on many focus groups and interviews. Although the sample population lacks diversity, there is substantial evidence that the results of the interviews and focus groups are indicative of what users, parents/caregivers, and partners prioritize. The content of questionnaires is appropriate and important to users, parents/caregivers, and partners. As expectations are better understood and addressed, the tool has the potential to impact the effective implementation and sustained use of AID systems.

Assessments of Disadvantages of Using the MDDT:

We did not identify any disadvantages of using the INSPIRE questionnaires to assess the impact of AID devices on the psychosocial functioning and quality of life in people with T1D, their parents/caregivers, and partners. However, we did identify two limitations. First, although the prevalence of Type 1 diabetes is highest among Caucasians, it still impacts persons of other races/ethnicity. Nearly 78% of the study participants were Caucasian; additional research should include a representative number of the intended use population to determine whether the themes are consistent across different racial/ethnic populations. Second, the statistical analysis of the questionnaires indicates possible overlap in several questions concerning blood glucose and HbA1C levels. However, there is no conclusive evidence that the inclusion of these items will cause issues with the interpretation of the scores. The appropriate use and interpretation of the scores will only be addressed through the continued use and evaluation of the INSPIRE questionnaires.

Despite these limitations, the INSPIRE questionnaires are a useful qualitative tool due to the extensive and robust amount of data collected from focus groups and interviews with individuals with T1D, their

parents/caregivers, and partners and the clinical expertise of a multidisciplinary team of health care providers.

Additional Factors for Assessing Advantages and Disadvantages of Using the MDDT:

There is minimal uncertainty associated with the tool with respect to the specified context of use based on the submitted evidence and documented history of use in a limited number of clinical trials. The tool can be used to facilitate an understanding and regulatory evaluation of the impact of automated insulin dosing systems on psychosocial functioning and quality of life in individuals with T1D, their parents/caregivers and partners.

Publications

Barnard, K.D., et al. (2015). Psychosocial assessment of artificial pancreas (AP): Commentary and review of existing measures and their applicability in AP research. *Diabetes Technology & Therapeutics, 17*:295-300.

Weissberg-Benchell, J., et al. (2016). Toward development of psychosocial measures for automated insulin delivery. *Journal of Diabetes Science and Technology, 10*(3), 779-801.

Garza, K.P., et al. (2018). Automated Insulin Delivery Systems: hopes and Expectations of Family Members. *Diabetes Technology & Therapeutics, 20*(3), 222-228.

Naranjo, E., et al. (2017). What end users and stakeholders want from automated insulin delivery systems. *Diabetes Care,40*: 1453-61.

CONCLUSIONS

The materials submitted for qualification included a small number of published studies describing the development and utilization of the INSPIRE questionnaires, quantitative analysis of responses to the eight questionnaires, and a robust qualitative investigation including focus groups and individual interviews. The INSPIRE questionnaires should be qualified as a Medical Device Development Tool (MDDT) that can be used to facilitate the understanding of the impact of AID systems on psychosocial functioning and quality of life. Qualification of this tool will enable its use in supporting regulatory decision making for pre-market submissions for automated insulin dosing systems, and the potential for inclusion of results of the tool in device labeling to help inform user decisions related to adoption and use of these types of devices.

CONTACT INFORMATION FOR ACCESS TO TOOL

For access to the INSPIRE Questionnaires, please contact:

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