Executive Highlights

Greetings from Bethesda, where the Glycemic Outcomes Beyond A1c: Standardization & Implementation Consensus Conference wrapped up Friday. The day was about making progress from last year's Outcomes Beyond A1c meeting, and boy, did we leave encouraged that the field is moving along. To date, A1c has been the primary endpoint used globally to explain "what happens" when a diabetes therapy is used. There is a single two-sentence exception on the EMA label for Trulicity, the only single label globally, to date, on which a "patient-reported outcome" is shared! The field of organizations present at "Glycemic Outcomes Beyond A1c" hopes to see that change. It was inspiring to be in a room with leaders gathered from ADA, AACE, ATTD, Endo Society, International Hypoglycemia Study Group, and JDRF, as well as from EMA and FDA, and we look forward to work together that results in clinicians and patients better understanding how various therapies "work" on outcomes beyond A1c.

The diaTribe Foundation, even before it was a formal 501c3 nonprofit, has been discussing this for some time (see our DIA presentation here from 2012), and in 2014 and 2016, given that diabetes was not included as a therapeutic area in a range of FDA PDUFA "stakeholder" meetings, it organized meetings at FDA to discuss patient needs and outcomes beyond A1c. JDRF has shown tremendous leadership over time on advocating for artificial pancreas guidance to include primary outcomes beyond A1c, namely using "time in ranges" data as primary outcomes, developed with CGM data (see one of multiple pieces including 2013's "It's Time to Move from the A1c to Better Metrics for Diabetes Control"). The community was proud to see that at the ADA Scientific Sessions last month, five glycemic "set-points" - namely, for hypoglycemia (<54 and <70 mg/dl), in-range (70-180 mg/dl), and hyperglycemia (>180 mg/dl, >250 mg/dl) - were confirmed by six professional organizations (AACE, ADA, ATTD, EASD, Endocrine Society, and JDRF) and the meeting last week raised these in a larger group and expanded this conversation.

While sentiments have existed for some time that additional outcomes "mattered," there was not a movement until more recently to standardize CGM measurement and reporting so that the information could ultimately be included on drug labels. Since the 2016 meeting co-hosted by FDA and AACE, ADA, JDRF, and The diaTribe Foundation, there has been increased commitment to emphasize the importance of hypoglycemia data and other patient-reported outcomes on labels. Specifically, on Friday, there appeared to be widespread agreement on the dangers of hypoglycemia and the need to use CGM in clinical trials; following the ADA meeting, where the thresholds for hypoglycemia, in-range, and hyperglycemia were agreed upon, Friday was remarkable for confirming the agreement and moving the conversation much further into terminology, implementation, and how future research could look. In his concluding remarks, FDA's Dr. Peter Stein of the Office of New Drugs expressed great enthusiasm for "remarkable progress" on the agreement for CGM-based endpoints, consensus that simply did not exist one year ago.

We were very happy to see a research-focused meeting (promised since last year) where clinical and patient voices were also present. For example, we heard many moving perspectives from a range of patients in person, on social media, through video, and through data analyses, including extraordinarily emotional stories of hypoglycemia (especially during the Open Public Hearing), a compelling video from HCM Strategists and The diaTribe Foundation, and hot-off-the press dQ&A Conjoint Analysis data. The diaTribe Foundation was honored to have NIDDK luminary Dr. Judy Fradkin participate in the final panel, where she said, "A really great meeting is one that touches the heart and the brain, and today proved in spades how important patient perspectives are." See our top highlights below! For the Twitter inclined, follow #BeyondA1c to continue to the conversation; Dr. Aaron Kowalski of the JDRF said, "If you're not on Twitter, you should be, if you want to see what happened today - it was exploding." On a final note, to add to the material prepared for attendees by The diaTribe Foundation, Drs. Rich Bergenstal and Roy Beck published

a major piece in Diabetes Care today, "The Fallacy of Average" - it's a phenomenal read, and now part of the material on The diaTribe Foundation website about the meeting.

Top 17 Highlights

1. In the clearest consensus yet, attendees and professional associations expressed agreement on the set of standardized, core CGM metrics that should be measured and reported in clinical trials that use CGM. The numbers that had been agreed upon at the ADA meeting were the following: <54, <70, 70-180, >180, and >250 mg/dl for time spent in different ranges. During today's work, further consensus was reached on glucose metrics, namely using coefficient of variation for glycemic variability and mean glucose. There was good debate over the glycemic ranges of interest; for example, some felt the "in range" bin should be narrowed to 70-140 mg/dl (in future years, we would not be surprised to see the "overall" range land here, particularly for type 2 diabetes). Another meaningful area of debate was whether 300 mg/dl could be the appropriate "high" threshold to measure, though 250 mg/dl was ultimately confirmed. Leading up to this gathering, the 70-180 mg/dl is what was agreed upon, as well as, at the high end, 250 mg/dl. It was terrific to see this agreement emerge following ADA and prior to three Consensus Statements pending publication (ADA/EASD on CGM Utility; T1D Outcomes Program from JDRF, Helmsley, ADA, AACE, ENDO, AADE, PES, T1D Exchange; and ATTD) that set the stage for these conversations beyond the "set points."

2. The consensus was gratifying, and attendees were already jumping to next steps and big picture questions - discussing "validation" of CGM outcomes (clearly some validation has been reached and what else CGM could enable is an exciting area), ruminating with FDA leaders on what they would like to see, benchmarks and clinically significant changes, "time out-of-range," blinded vs. unblinded CGM in trials, and the value of estimated A1c. While absolute consensus was not reached on terminology, many valuable conversations were had that will be instructive.

3. There was a very strong turnout from FDA at the meeting, and representatives were quick to voice their support to collaborate with the diabetes community on outcomes beyond A1c. Included in this group from the drug side (CDER) were Drs. Janet Woodcock, Peter Stein, and Lisa Yanoff, and from the device division (CDRH), Drs. Courtney Lias and Stayce Beck, among a range of others from various parts of the FDA. Dr. Woodcock opened the day with Kelly Close with a moving speech, while Dr. Stein shared the stage on the closing panel with NIH's Dr. Judy Fradkin, ADA's Dr. Will Cefalu, JDRF's Dr. Aaron Kowalski, and Steering Committee member Dr. Rich Bergenstal. Drs. Christine Lee and Dr. Frances Kalush also attended from Professional Affairs and Stakeholder Engagement and Dr. Lee even came to the stage at one point to inform attendees of an under-the-radar September 12 FDA workshop on hypoglycemia in the elderly population - we were very glad to hear this since there are so many safety issues associated with diabetes drugs, especially with one of the most popular generic, sulfonylureas.

4. Kicking off a panel discussion moderated by Dr. Rich Bergenstal and our very own Mr. Adam Brown, Dr. Aaron Kowalski cut straight to the chase with trademark passion: "I'm feeling this little bubbling rage. Guys, this is so blatantly obvious, the fact that we're having such a robust debate now, we should be past this." We suspect that not everyone is as far as people who think about this daily, so we were happy that participants had the chance to share with a much broader group the priorities in our field. Our highlight below includes quotable quotes from Drs. Stephanie Amiel (IHSG), Thomas Danne (ATTD), Zach Bloomgarden (AACE), Will Cefalu (ADA), Aaron Kowalski (JDRF), and Anthony McCall (Endocrine Society).

5. The excitement was high as Dr. Robert Ratner set the stage for the day's discussions with a stirring rallying cry: "We need to have the tools to move towards the goal of A1c, and A1c by itself doesn't tell you how to get there."

6. In his review of new diabetes technology and tools in clinical trials, Professor Philip Home made sure his take home message was crystal clear: "Diabetes is abnormal plasma glucose. We can now measure it - we should measure it. Let's get on with it!" It was phenomenal to have his leadership as well as that of other global leaders in diabetes whose decisions routinely influence public health.

7. Professor Bart Van der Schueren, member of the EU's CHMP and the cardiovascular working group at EMA, urged use of CGM in drug trials, noting that it gives valuable data for understanding therapies' risk-benefits (particularly adjunct therapies for type 1 diabetes). He noted that both the EMA and the FDA seek to evaluate "safety and efficacy in view of emerging scientific insight and better analytical tools."

8. In the early afternoon, there was a moving open-patient hearing featuring numerous clinical and industry professionals, plus one patient. Highlights included Joslin's Dr. Robert Gabbay's take on whether the community should move beyond A1c now that there are more valuable tools, Lilly's Dr. Jim Malone commending the EMA for including patient-reported outcomes on drug labels, an emotional anecdote from Joslin's Dr. Lori Laffel illustrating the devastating and irreversible impact of a single episode of hypoglycemia, Joslin's Dr. Medha Munshi on the need for care in assessing therapies in older and very heterogeneous patient populations, UC Denver's Dr. Greg Forlenza on diabetes related quality of life, sleep quality, and hypoglycemia fear, and diabetes patient advocate Mr. Stephen Shaul, whose final line rang especially true in terms of what can be learned from patient communities (over 500,000 globally are on CGM): "Patients have [CGM] data and are using it now. What you need to do is catch up to us."

9. Mr. Adam Brown presented hot-off-the-press data from dQ&A Market Research delving into the relative priority of different beyond-A1c outcomes in the eyes of people with diabetes. The analysis (n=4,268) revealed that although therapeutic preferences differ in people with type 1 vs. type 2 diabetes, time-in-range and weight loss emerged as critically important outcomes across the board.

10. dQ&A Founder and CEO Mr. Richard Wood presented patient survey data to support the importance of outcomes beyond A1c, first shared last August at the public workshop on Outcomes Beyond A1c co-organized by AACE, ADA, JDRF, The diaTribe Foundation, and Scripps. In the study shown by Mr. Wood, 3,461 patients with type 1 or 2 diabetes, emphasized the importance of time-in-range in patients' daily lives and how unsuccessful, relatively speaking, patients feel about current therapies. We believe were patients to better understand how current therapies are characterized, it would be helpful - there are currently no claims on hypoglcyemia or weight gain, for example, on product labels, so doctors and nurses cannot discuss this.

11. Over lunch, DSMA (Diabetes Social Media Advocacy) founder Ms. Cherise Shockley joined Kelly Close onstage to present the DSMA community's discussion on glycemic outcomes beyond A1c, focusing in particular on hypoglycemia. You have to hear these moving stories ... Ms. Close followed with her take on the insufficiency of A1c and what could be done about it.

12. Dr. Bruce Buckingham gave a most valuable update on the technology available in the rapidly evolving diabetes field, noting that data from CGM sensors has been "revolutionary" in evaluating therapies and is more actionable than A1c: "CGM provides a more comprehensive picture of dysglycemia than A1c, and it provides an easy, standardized, quantitative measure to compare therapies."

13. Dr. Steven Russell shared an uplifting summary of the glucose metrics/variability workshop, noting strong consensus on the time-in-range thresholds (<54, <70, 70-180, >180, >250) and unanimous approval for use of coefficient of variation (CV) to characterize glycemic variability. There was meaningful debate on 250 mg/dl vs. 300 mg/dl; consensus on 250 mg/dl was reached fairly quickly.

14. A workshop on hypoglycemia led by world experts Professor Stephanie Amiel of Kings College London and Professor Brian Frier of Edinburgh briefed attendees on "how we got here" and brought attention to the need for consensus on the terminology for different classes of hypoglycemia.

15. Joslin Clinic's Dr. Lori Laffel and Newcastle University's Professor Philip Home led an interactive breakout session to flesh out if and how future clinical trials should leverage CGM to determine the effects of therapies. The first order of business - getting everyone to agree that CGM should be used in clinical trials - was easy, but the question of how to convince FDA to accept CGM glycemic outcomes was more trying.

16. The "Implementation" workshop, facilitated by Columbia's Drs. Jane K. Dickinson and the Joslin Clinic's Robert Gabbay, uncovered many agreed-upon next steps for communicating points of consensus coming out of Friday's meeting, but it was notably harder to nail down terminology options free from reproach.

17. Ms. Kelly Close set the tone for the day by putting the progress toward consensus in perspective and emphasizing the need for patient-centricity and policy development. See Kelly's full remarks below!

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Top 17 Highlights

1. CONSENSUS ON CGM OUTCOMES FROM ATTENDEES AND PROFESSIONAL SOCIETIES: <54, <70, 70-180, >180, >250 MG/DL FOR TIME-IN-RANGES

In the clearest consensus yet, attendees and professional associations widely agreed on a set of standardized, core CGM metrics: <54, <70, 70-180, >180, and >250 mg/dl for time spent in different ranges. These ranges would be bookended by severe hypoglycemia and DKA, both using the standard clinical definitions. The morning presentations, featuring Drs. Stephanie Amiel (International Hypoglycemia Study Group), Zach Bloomgarden (AACE), Will Cefalu (ADA), Thomas Danne (ATTD), Aaron Kowalski (JDRF), and Anthony McCall (Endocrine Society), showed excellent alignment across all the organizations - a serious achievement and terrific to see following the positive ADA 2017 session and prior to three Consensus Statements pending publication (ADA-EASD on CGM Utility; T1D Outcomes Program from

JDRF, Helmsley, ADA, AACE, ENDO, AADE, PES, T1D Exchange; and ATTD). See the full list of core CGM metrics below from Dr. Bergenstal's presentation, which also includes mean glucose, Coefficient of Variation (CV), a consecutive 15 minutes to define a single "hypoglycemia episode" (a separate outcome from time-in-hypoglycemia), midnight-to-6am and 6am-to-midnight for overnight and day-time blocks, at least two weeks of CGM data, and AGP for viewing the data. There was still some mild debate on a few of these metrics (e.g., whether SD and estimated A1c should be included; whether there is evidence to support the specific 250 mg/dl), though attendees mostly raised additional considerations rather than disputing the value. Said Dr. Bergenstal, "It does seem like we're arriving; we're getting awfully close, and I don't think we can be accused of not agreeing - especially if we get these in print." See the next highlight for remaining questions and elements in the path ahead, and a later highlight for quotable quotes from these talks.

Core CGM Metrics Consensus	
Hypoglycemia	< 54 mg/dl < 70 mg/dl [Severe = Clinical diagnosis: Event requiring assistance]
Time-in-Range	70-180 mg/dl
Hyperglycemia	>180 mg/dl >250 mg/dl [DKA = Clinical diagnosis: ketones, acidosis (hyperglycemia)]
Overall	Mean Glucose [Estimated A1c?]
Glycemic Variability	Coefficient of Variation [Standard Deviation?]
CGM Visualization	AGP
Individual Episode of Hyperglycemia/Hypoglycemia (a separate metric from time in hypoglycemia)	15 minutes
Sleep-Wake Time Blocks	Midnight - 6am (night)* 6am - Midnight (day)
Data Sufficiency Recommended	Two weeks of collection 70-80% of CGM readings (minimum)

- **Professor Home made some valuable comments related to glycemic variability:** "Variability over a day (say midnight to midnight) can tell you something about the profile of a long-acting insulin - i.e., the flatter it is (less peak to trough), the purer a true 24-hour preparation patients will have, though this will be seen best if meal-time insulin is not used, or in clamps. There are other factors of pathophysiological origin. Variability between days, or between one time of day (both within individuals), suggests erratic insulin absorption, once erratic lifestyle is discounted. This will be related to hypo risk. It can be buffered by endogenous insulin secretion. It is highly clinically relevant and does vary between insulins. Variability between individuals is perhaps more familiar as a difference in insulin dose requirement, related to insulin sensitivity and degree of insulin deficiency." He continued by emphasizing that these properties have different meaning and utility and are relevant separately in drug development.

- **Continued Professor Home:** "Standard deviation is a useful measure, and is closely related to CV of course (CV = 100 * SD/mean). It is a bit of a sterile argument between them. A more real problem here is that the distribution of glucose values is skewed, and the better the control the more this is so. Even the distribution of time out of range is skewed. So, in trials practice we have to look at the data in each study and take a decision over what descriptive stats are valid, and whether to transform."

2. REMAINING QUESTIONS, RESEARCH NEEDS, AND THE PATH AHEAD

The consensus was encouraging, and attendees were already jumping to next steps and big picture questions - see some of the most common topics below.

- **Is "validation" research needed to show CGM-based outcomes matter for long-term diabetes outcomes, patients' quality of life, etc.?** This was a takeaway of Dr. Bob Ratner's presentation ("We have to certify the standards as surrogate outcomes for the FDA"), though in the morning panel, Dr. Aaron Kowalski argued that the connection is obvious - "The goal of diabetes therapy is to restore normal glucose. That means less hypoglycemia and hyperglycemia. Measuring these things with CGM is obvious." We agree on that point and wonder how the Agency will view this giving their comments that using CGM has not been validated. Following dQ&A's presentation on the value of time-in-range in type 1s and type 2s, an audience member wondered if pairing validated quality-of-life instruments with real-time CGM would be a possible avenue (dQ&A CEO Richard Wood characterized this as a "dream project") - we love this idea and perhaps the CGM manufacturers could band together and pursue this kind of research, similar to the JDRF CGM study back in the day.

In fact, NIDDK's Dr. Judy Fradkin said Outcomes Beyond A1c research proposals are definitely of interest - perhaps NIH could fund such a project. Patient advocate Ms. Anna McCollister-Slipp highlighted plans for exactly this kind of study at last August's Outcomes Beyond A1c meeting, though this has not moved forward yet due to funding challenges, as we understand it. On a more ambitious note, several people wondered whether the DCCT could be repeated with CGM, though some in the room felt this would be too costly and not worth the time and effort; the larger view seemed to be that designing such a trial would not be feasible. We would certainly see value in understanding, longer-term, if less glycemic variability contributed to fewer long-term complications (in addition to less severe hypoglycemia) but there were questions about whether such a trial is possible to design ethically. We are interested to know what could be learned from big data on this front, if anything (presumably, there are many confounders). It also may be challenging to hold A1c and other variables constant, but achieve *meaningfully* different variability profiles - this was a question following the FLAT-SUGAR pilot study reported at ADA 2016.

- **What does the FDA need to see to accept CGM-based time-in-range, -hypoglycemia, and -hyperglycemia data?** FDA reviewer Dr. Lisa Yanoff noted in Q&A that the Agency is looking at hypoglycemia with some current applications, but only severe hypoglycemia - "As the science moves forward with the accuracy of CGM - and we can detect numbers in the low range - we want to work with everyone to see how it will be incorporated in trials." It's our understanding that there will need to be more discussion about how CGM data is assessed. We are hopeful that this response does indicate that it is possible for companies to work with CDER on the specifics.
- **What should the benchmarks be for time in 70-180 mg/dl, time <70 mg/dl, time <54 mg/dl, time >180 mg/dl, etc.?** Once the field is all reporting the same CGM-based outcomes, which will be incredibly valuable for all stakeholders, this is the next obvious question - and a very important one. Most of those who commented on this suggested 70%+ for time in 70-180 mg/dl (based on closed-loop studies like the MiniMed 670G pivotal) and <2% or <3% time-in-hypoglycemia (<70 mg/dl) - these are obviously starting points, though we LOVE the idea of including these as benchmarks on the AGP. Currently, the benchmarks used on AGP for the different glucose metrics are for people without diabetes. We also loved that there was a lot of conversation Friday about what "sub-groups," such as newly diagnosed people with type 2 diabetes,

women with gestational diabetes, type 1 women who are pregnant, people with various complications, etc., should aim for.

- **What degree of change is clinically significant for time-in-range, time <70 mg/dl, etc.?** Is one more hour per day in range (a 5%-point bump) a clinically significant improvement? There was debate about whether and how this needs to be confirmed with patient preference studies (see the dQ&A conjoint below for one example). What level of benefit would be needed for a hypoglycemia indication? We had assumed that any "significant" benefit could be put on labels, but this remains naïve.
- **What terminology (if any) should be paired with CGM thresholds - e.g., "serious," "level 1," "alert," "Clinically significant," etc.** While many seemed to like "alert" or "action" for <70 mg/dl, indicating a warning before the more dangerous <54 mg/dl, many seemed to conclude that perhaps no adjectives are needed to describe the various levels. There was some support for "Level 1" (<70 mg/dl) and "Level 2" (<54 mg/dl), though some said this was too abstract. We are eager to learn what the researchers conclude about terminology for research, after which "translation" to clinicians and patients can be decided. Though several people liked "serious" for <54 mg/dl, the FDA commented that it's actually confusing from a regulatory perspective - "serious" refers to a serious adverse event (SAE), which includes severe hypoglycemia. This was the area with the least consensus at the gathering, hence why many proposed dropping the labels and just keeping the numbers - not a bad idea in our view. While all agree that patients are unlikely to use certain characterizations ("Oh shoot! I have level 2 hypoglycemia again!"), this could have some value for research. We understand the IHSG will continue thinking about this, partly stimulated and informed by this meeting.
- **"Wait, time-in-range doesn't tell me what I care about: what's the time-out-of-range?"** This was a frequent comment from several clinicians in the morning, and it's a point well-taken - time-in-range is useful, but it's not enough if it is used in isolation. The utility of CGM is in finding times of day where glucose is going out of range. Still, we like that time-in-range is an understandable number out of 100%, that more time-in-range indicates improvement, and a 5%-point improvement in time-in-range is roughly one more hour per day in range.
    - **On that latter note, several clinicians advocated for presenting time-in-range data in terms of hours/day in range** - rather than percentages. We like this idea for communicating with patients and hope to see much more of this as trials report data. Showing both the percentage and hours per day would perhaps be the best way to go.
- **If CGM is used in drug trials, should it be blinded or unblinded?** This will clearly need to be addressed with the FDA, and it strikes us as *very* complicated and nuanced. On one hand, blinded CGM like FreeStyle Libre Pro is perfect as a background diagnostic monitoring tool, minimizing the bias of adding real-time CGM in a randomized drug study. However, clinicians pointed out that real-time CGM is quickly becoming the standard of care - not using it might diminish the generalizability of the results to the growing population of CGM users (Prof. Van der Schueren noted this point in his talk, below). To complicate things further, running a study in which subjects are deprived of CGM may become unethical with future generations of CGM (at least for type 1s and insulin-treated type 2s), similar to not using SMBG. It's a tough call! However, if real-time CGM is used in randomized drug trials, especially in those naïve to CGM, it may raise the bar for therapies to show placebo-adjusted improvements.
- **What is the role of "estimated A1c?"** Several clinicians mentioned that "estimated A1c" is a confusing metric, given the typical observed difference from blood-measured A1c (glycation differences between individuals). As Dr. Bergenstal noted, someone with a mean glucose of 183 mg/dl could be predicted to have a measured A1c of 7% or 8% or 9%! This point is made further in a piece co-authored by Drs. Bergenstal and Beck, "The Fallacy of Average," published in *Diabetes Care* on Friday.

- **"*Overall* variability is a pretty meaningless metric in clinical practice." - Dr. Philip Home.** The point came up a couple times today. Knowing a patient's overall glycemic variability is not nearly as useful as knowing the variability at a given time - when is variability excessively high or low? Dr. Home later clarified that patients have always told him that erratic control, differences between days or times of day, was what really mattered to them. The beauty of CGM is that it can dissect out all aspects of variability, but that doesn't mean that overall CV or SD has no useful meaning. This reminded us of the argument for the reporting of time out-of-ranges vs. time in range: Time in range and overall variability give a single number denoting how well a patient is doing in a given glycemic domain, but don't offer much in the way of actionable data -presenting time out-of-ranges and granular, comparative glycemic variability by time of day gives clinicians a jumping off point for therapeutic adjustments. Dr. Home's was a great point for clinical practice, though we're not sure what implications it has for measuring therapies with outcomes beyond A1c. Would it be useful to know drug A improves overall coefficient of variation more than B? Could drugs eventually be indicated for reduction of glycemic variability? Does glycemic variability, itself, matter for long-term complications? A recent analysis (from the DCCT/EDIC Research Group) of long-term within day variability seems to suggest that it does not play a role in the development of microvascular complications, independent of mean glucose.

3. STRONG, SUPPORTIVE, AND COLLABORATIVE FDA PRESENCE THROUGHOUT MEETING

There was a very strong turnout from FDA at the meeting, and representatives were quick to voice their support to collaborate with the diabetes community. CDER Director Dr. Janet Woodcock highlighted the Agency's commitment to determining which outcomes actually matter to patients, emphasized that it will take a community effort to drive toward a consensus on standards, and expressed optimism for the future of diabetes therapy. In FDA terms, beneficial therapies must help a patient feel better, function better, and/or live longer, she said - but there must be a surrogate measurement for each of these criteria, and the link between the measurement and the magnitude of benefit must be well-characterized. Within diabetes, Dr. Woodcock specifically pointed to hypoglycemia and rate of glycemic change, acknowledging that we really don't understand how altering these parameters translates into benefit for patients. (Rate of change is not one we'd focus on.) To get at the questions of "feel better" and "function better," FDA has been focusing not only on CGM, "which reflects more clearly the departure from physiology and day-to-day fluctuations," but also more on patient-reported outcomes (PROs) - "we need to get away from saying [those metrics] are no good. Are you not able to go to your child's graduation? Do you need to walk out in the middle of an important family function? Do you have to curtail your daily activities half the time?" We loved this perspective and were elated to hear FDA's openness to other outcomes; no longer does it seem to be an antagonistic dialogue. She said that the Agency always learns an enormous amount from Patient-Focused Drug Development Meetings, since these events remind the reviewers what really matters to patients (sometimes, it's things they have never even thought of).

- **Dr. Woodcock concluded on a very encouraging note, especially considering her position as head of the FDA's Drug division: "We at FDA are very interested in collaborating with communities like this**, coming together with academic, industry and the FDA voice, and it will probably result in optimal outcomes moving forward. It's a long journey, and we hope to stand beside you and work with you - there are multiple mechanisms at FDA through which we can work together."
- **CDER Deputy Director Dr. Peter Stein echoed Dr. Woodcock's sentiments, underscoring FDA's interest in patient-reported outcomes and two-way collaboration with the Outcomes Beyond A1c community - "we're committed to participate in this progress. There are so many of us here; we want to be engaged."** He envisions a symbiotic relationship where FDA provides guidance to help the field settle on endpoints and how they tie into meaningful clinical benefits, and clinicians and researchers provide FDA with the data it needs to see. Lastly, CDER is interested in increasing the reporting of patient-reported outcomes in drug

labeling, but is cautious to ensure that that outcomes are properly reflected and collected so that patients and clinicians derive benefit. This seems very reasonable to us.

- **At the end of the day, CDER's Dr. Lisa Yanoff informed the crowd that FDA is very much accepting severe hypoglycemia as an outcome, but needs to "continue to work on the challenges of hypoglycemia."** She said the Agency is comfortable taking severe hypoglycemia into consideration because it is a clear hazard, but regulators need to have further conversations with researchers about the inclusion of non-severe hypoglycemia (<70 mg/dl) - her comments implied a concern that CGM is not accurate enough, especially in hypoglycemia. Dr. Yanoff acknowledged that these efforts are still in the early stage and that firmer guidance on incorporating these metrics would be premature. Still, the door is clearly open, and with the right data, we are more confident these outcomes would be accepted by the agency.
    - **From the CDRH perspective, Dr. Stayce Beck shared that CDER has approached her team asking about CGM - they are open to outcomes beyond A1c and severe hypoglycemia, but need to see "some sort of clinical outcome."** In other words, CDER would be willing to make the change once a study shows that better time in range or less time <70 mg/dl leads to fewer complications, to which Dr. Philip Home replied: "Thank you for that perspective. It's frustrating, but thank you." We agree with Dr. Home - is validation really needed on this? More lows clearly drive a far higher risk of severe hypoglycemia - Dr. Amiel noted a 10-fold increase in one study today. We hope a minimally burdensome validation path is possible, since running a big outcomes study for something so obvious seems ridiculous.
- **Dr. Woodcock commented that diabetes therapies have temporarily "plateaued," but the future is "very bright."** Indeed, there have been 40+ diabetes drugs approved by FDA in the past decade, creating an expansive pharmaceutical toolkit for practitioners to employ, but the population with diabetes is not doing much better for a variety of reasons (we point to access, hard-to-dose therapies like insulin, invisibility of benefit, burden, limited number of care providers, etc.). Together with greater understanding, Dr. Woodcock shared enthusiasm for new technologies, cell therapies, and implantable devices coming down the pipeline.
- **As part of PDUFA, FDA sponsored a number of meetings with industry and patients to push toward patient-focused drug development.** These meetings took the form of all-day forums that gave patients from a variety of disease areas (not diabetes) the opportunity to speak about the burden of their disease, and even various therapies. According to Dr. Woodcock, a dermatologist left one of these meetings on psoriasis saying simply, "I never knew." We love the idea of greater patient input at the FDA and hope more can be done in diabetes - and far more frequently than ~1 per year at these public workshops. Hopefully patient experiences on a day-to-day basis can also be captured far better and more seamlessly and communicated to the FDA - what if FDA submissions included videos, interviews with patients, and beyond, along with PROs and CGM data? What can the FDA learn from the consumer world?
- **Dr. Christine Lee from FDA's "Professional Affairs and Stakeholder Engagement" division shared plans for a September 12 public workshop on "Reducing the Risk of Preventable Adverse Drug Events Associated With Hypoglycemia in the Older Population."** This meeting occurs during EASD, though we hope it gives the attention it deserves - this issue is so critical and far more nuanced than just, "Raise the A1c target."

4. REPS FROM SIX CONSENSUS WORKING GROUPS ON WHY OUTCOMES BEYOND A1C ARE "OBVIOUS"

Kicking off a panel discussion moderated by Dr. Rich Bergenstal and Mr. Adam Brown, Dr. Aaron Kowalski cut straight to the chase with trademark passion: "I have this little bubbling rage. Guys, this is so blatantly obvious, the fact that we're having such a robust debate now, we should be past this." What followed was a lively discussion regarding the standardization of data, definitions, and terminology among noted leaders in the field, including Drs. Stephanie Amiel (IHSG),

Thomas Danne (ATTD), Zach Bloomgarden (AACE), Will Cefalu (ADA), Aaron Kowalski (JDRF), and Anthony McCall (Endocrine Society). We were thrilled to hear that the six working groups had essentially arrived at consensus - there is some room for clarification in areas such as terminology, but the metrics and numbers are agreed upon (see above). We have come such a long way since last August's Outcome Measures Beyond Hemoglobin A1c Workshop, when the same groups threw many of the same concepts on the table, but with much less granularity. A point that came up during today's discussion was the separation of clinical vs. regulatory outcomes - just about everyone in the room was on the same page that outcomes beyond A1c affect quality of life and are clinically relevant, but there has been no DCCT-like outcomes study to irrefutably prove it. Drs. Kowalski and Ratner didn't think another such trial would be feasible nor necessary (we agree). The next step in this discussion is hopefully to sit down with CDER to discuss exactly what kind of CGM+ data it needs to see in order to get more comfortable with CGM-based metrics. At least the endpoints and thresholds are now clear. See below for some of our favorite quotes!

- **Quotable Quotes**
  - "**Folks, we have CGM, we're here.** The goal of diabetes care is to restore to the state before diabetes. A1c does not represent that. We're talking about hypoglycemia and hyperglycemia. These metrics are obvious and need to be implemented in clinical care. People will do better if we move beyond A1c." - Dr. Aaron Kowalski
  - "**We're at a turning point in many ways, especially for type 1 diabetes.** Even looking at adjunctive therapies like SGLT-2 inhibitors and combined inhibitors that may affect post-prandial excursions without changes in A1c - this would be missed if we only looked at A1c. We need these improved metrics to really look at the data. To not do so would be a mistake." - Dr. Thomas Danne
  - "**The alignment is really incredible to see**, especially as we think about this next-generation therapies that may not improve A1c but might improve time-in-range and hypoglycemia. That's why we're all here. It's a new paradigm." - Mr. Adam Brown
  - **"If you distill it down, we know hyperglycemia is bad.** All these data are driven by hyperglycemia. We know hypoglycemia is bad. To go revalidate that because we're now measuring with CGM vs. A1c - why? We know it. How do you quantify that benefit and convince payers and regulators it's good? I gave a presentation at ATTD where Irl Hirsch asked what should the target time-in-range percentages be. My answer is "*better*." If you're trying a comparator, you can measure benefit. I hear people throwing out 70%+ time in range, 4% or less <70 mg/dl, etc., but we know at the elemental level that hyperglycemia and hypoglycemia cause problems. So if we're reducing both of those, then we're moving in the right direction. It's not rocket science." - Dr. Aaron Kowalski
  - **"We all understand that A1C means many things for many different people.** If you could eliminate hypoglycemia and improve quality of life, that's where we're going and that's why everyone is here today. The question is how to implement this for regulatory bodies and the clinic." - Dr. William Cefalu
  - **"If you look at the spread of mean blood glucose that drives A1c, it shows you how flawed the measure is.** While it's validated in DCCT and UKPDS, it's really about the change in glycemic load over time in a person, and now with CGM we can measure this. DCCT already shows this and we're just not looking at this creatively enough in our analysis. We don't need another DCCT - we've talked about this already." - Dr. Aaron Kowalski
  - "**As a clinician, I worry about the use of precise glucose targets in specific individuals. If we're going to be using this for clinical trials, then we do need to agree on 54 or 70 mg/dl. It'll be a compromise.** But I have a great many patients with type 1 who look at me with disbelief when I say, 'oh, you have a number of blood glucose levels below 70.' Clinically, we need to incorporate individuals' wishes, feelings,

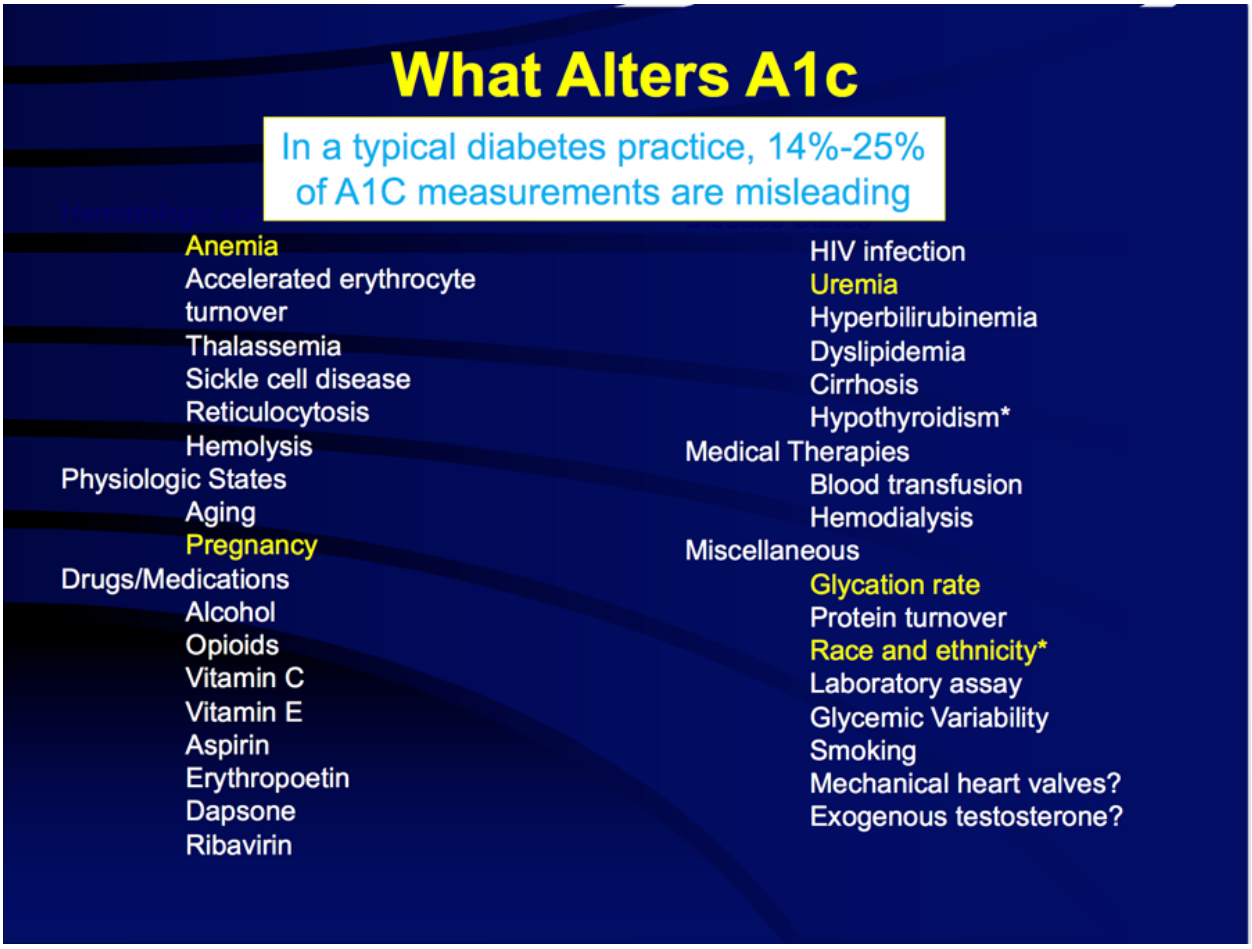
desires, and our experiences with them in trying to specify what ranges are appropriate." - Dr. Zach Bloomgarden

- "**I have an 81-year-old patient, who has had type 1 diabetes for 46 years. He said to me, 'I don't want to have my feet chopped off, lose my vision, and go on dialysis, and that's why I want to have an A1c that's perfect.'** I pointed out that he had no albuminuria, minimal nephropathy, and was not at high risk for complications. It's important to know how people think. We need to individualize and point out that hypoglycemia gets you in the short-run frequently, particularly as you age." - Dr. Anthony McCall
- "**We have patients in the Bionic Pancreas trials who see rises in mean glucose and they express concern about that**. Can we add another metric that's an adjusted A1c or mean glucose by removing the hypoglycemia impact that is making your A1c look artificially better than what would it be?" - Dr. Steve Russell
- **"We need to come up with parameters that regulators can use, which are validated on a short-term basis and correlate with long-term outcomes.** The FDA has asked, 'what's the relationship to long-term hard outcomes for a long time.' Unless [NIDDK's Dr. Judith Fradkin] has money to repeat DCCT - she says no - then we need validated surrogates." - Dr. Bob Ratner
- **"What's the endgame? To get it into the hands of the front line, the providers.** At the end of the day, to make an impact, it's going to have to be three or four simple metrics providers can use in their 15-minute visit to make a decision." - Dr. William Cefalu
- **"We're close to using real-world data, and CGM is uniquely available as a way of potentially having data that's going to be tracked with hospitalizations.** We have the ability to get huge amounts of data over huge amounts of time, which can be used for regulatory approvals and for additional indications of treatment. Is this insulin versus that insulin associated with differences in outcome? - we're going to be able to answer that question." - Dr. Zach Bloomgarden
- **"It seems to me one of the most vexing problems comes from the interpretation of ACCORD and the mistaken notion that good control is associated with harm.** I interpret it as hypoglycemia is associated with harm. If we only had CGM rather than A1c from all those participants in ACCORD, we would know exactly what the mediator of that outcome was." - Dr. Zach Bloomgarden

5. DR. RATNER: A1C NO LONGER SUFFICIENT; CALL FOR DEFINITIONS OF HYPOGLYCEMIA AND STANDARDIZATION OF GLYCEMIC VARIABILITY

The excitement in the room was high as Dr. Robert Ratner set the stage for the day's discussions with a stirring rallying cry: "We need to have the tools to move towards the goal of A1c, and A1c by itself doesn't tell you how to get there." Dr. Ratner detailed how the DCCT and UKPDS studies showing a correlation between A1c and microvascular outcomes paved the way for A1c as the FDA's gold-standard diabetes outcome several decades ago. This kind of hard data is difficult to ignore, and Dr. Ratner was clear in stating that A1c can be useful in some domains (particularly for the assessment of microvascular risk), but certainly doesn't capture every aspect of glycemia. He underscored that blood glucose is simply not the only variable reflected by changes in A1c: anemia, pregnancy, and kidney disease can render the value nearly useless, in addition to 30 other factors that influence A1c. Echoing Dr. Irl Hirsch, he noted that ~14-25% of A1c measurements in a typical diabetes practice can be misleading. Dr. Ratner also highlighted the just-published *Annals of Internal Medicine* paper (Bergenstal et al; see below), noting the tremendous individual variation in mean glucose for a given A1c. Furthermore, A1c is a frustrating metric on practical terms, as it provides no actionable information to advise patients and providers regarding how to improve - when is glucose going high or low and how should therapy be changed accordingly? Of course, A1c also fails to reflect glycemic excursions and quality of life. To certify a new surrogate moving beyond A1c, Dr. Ratner called for a hard look at available data and the needs of clinicians and patients. Achieving this goal

may require use of CGM to generate rigorous definitions and ascertainment of hypoglycemia and standardization of glycemic variability. He noted that a key next step is to "validate" CGM-based outcomes beyond A1c; what this would entail was a topic of debate throughout the day.


What Alters A1c
In a typical diabetes practice, 14%-25% of A1C measurements are misleading
Hematologic conditions
Anemia
Accelerated erythrocyte turnover
Thalassemia
Sickle cell disease
Reticulocytosis
Hemolysis
Physiologic States
Aging
Pregnancy
Drugs/Medications
Alcohol
Opioids
Vitamin C
Vitamin E
Aspirin
Erythropoetin
Dapsone
Ribavirin
HIV infection
Uremia
Hyperbilirubinemia
Dyslipidemia
Cirrhosis
Hypothyroidism*
Medical Therapies
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Protein turnover
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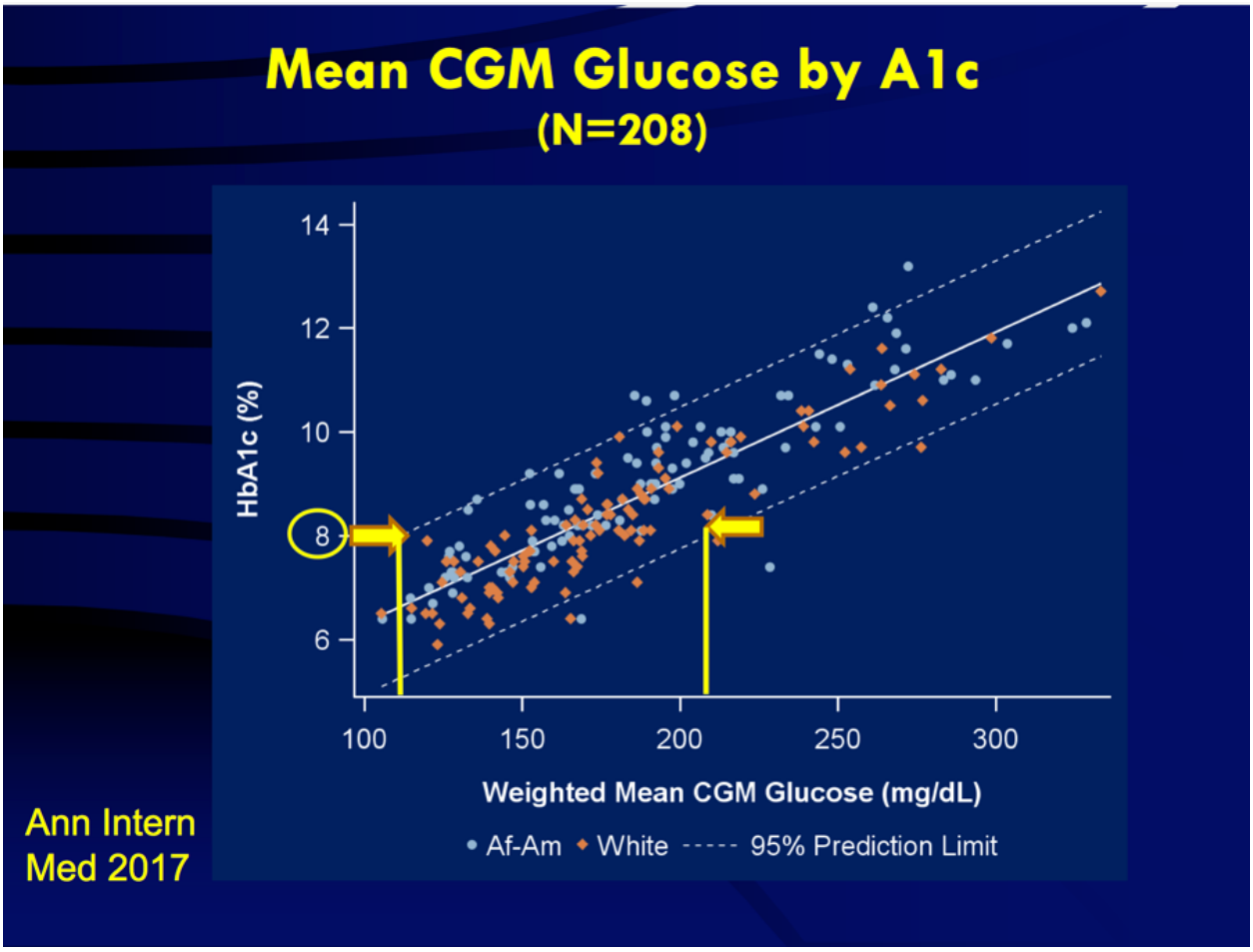
Glycemic Variability
Smoking
Mechanical heart valves?
Exogenous testosterone?



6. PROF. PHILIP HOME: "DIABETES IS ABNORMAL PLASMA GLUCOSE. WE CAN NOW MEASURE IT - WE SHOULD MEASURE IT. LET'S GET ON WITH IT!"

In his review of new diabetes technology and tools in clinical trials, Professor Philip Home made sure his take home message was crystal clear: "Diabetes is abnormal plasma glucose. We can now measure it - we should measure it. Let's get on with it!" He began by explaining that diabetes used to be a primarily symptomatic disease, monitored and tracked by weight loss and polyuria. With the advent of quality 20th-century care, diabetes is no longer a pure symptomatic condition, so plasma glucose must be measured as a surrogate to quantify the extent of exposure to hyperglycemia (weighted for impact on vascular damage) and hypoglycemia (weighted to impact on cognitive disability and *perhaps* to acute vascular risk). However, Prof. Home stated that lab-measured clinic plasma glucose concentrations are not valid and should've been abandoned years ago, and SMBG is accurate and precise in trained hands, but unreliable in the grand scheme. CGM, on the other hand, is (i) already used in clinical practice, (ii) accurate, precise, objective, and clinically relevant, and (iii) the only device capable of capturing hypoglycemic and hyperglycemic excursions (especially overnight), so Prof. Home firmly believes that it should be employed in clinical trials. In addition, the data transmission enabled by CGM allows for monitoring of appropriate sensor use and advising of insulin dose changes within studies. Yet Prof. Home pointed out that we still need to achieve better consensus on what constitutes acceptable time and extent out of range, as well as how to ensure accuracy (proper calibration technique; and are factory-calibrated systems reliable enough?). We agree with Dr. Home that CGM is ready to be used in trials, though he raised many great points - we hope as the field gains more experience in the higher-touch trial setting, many of these questions on benchmarking, optimal use, etc., will start to get answered.

- **In alignment with many of the other speakers (including MGH's Dr. Steven Russell and CHMP/EMA's Dr. Bart Van der Schueren), Prof. Home asserted that time out of**

range is much more interesting to him than time in range. Time in range is a one-stop shop - a single number that illustrates general glycemic control (and is mostly a proxy for hyperglycemia) - but the separation of time in hypoglycemia and time in hyperglycemia is much more enlightening. We think all three are valuable, and of course, with CGM all three are immediately available.

- **New insulin titration software has been arriving on the market, but Prof. Home is hesitant to endorse them fully.** For the time being, he emphasized it is difficult for patients to accurately estimate the intake of food, and more importantly, how can a software cope with erratic insulin absorption? Until (if) it is possible to better gauge quantity and composition of food, as well as characterize insulin absorption status, Prof. Home would not presently recommend any *one* insulin dose titration software application for use in clinical trials. These were some good points and it's worth noting that the cleared software in the US is for basal-only thus far (lower risk); Voluntis' basal-bolus software is cleared in Europe, though only the basal one is cleared in the US.

7. PROF. VAN DER SCHUEREN: EMA ENCOURAGES USE OF CGM IN DRUG TRIALS, COMMITTED TO INTERNATIONAL ALIGNMENT ON NEW OUTCOME MEASURES, INCORPORATING PATIENT PREFERENCES

Professor Bart Van der Schueren, member of both CHMP and the cardiovascular working party at EMA, kicked off his lovely talk by affirming that both the EMA and the FDA share the common goal of evaluating "safety and efficacy in view of emerging scientific insight and better analytical tools" in a forward-leaning manner, though noted that the FDA has thus far better-involved patients in the process (in part due to fewer language barriers). He conveyed the EMA's encouragement of CGM use in the clinical development of new drugs, which actually appears in its drug development guidance. (In Q&A, he further noted that such data improves the EMA's ability to understand benefits of new therapies.) Of course, this is something the FDA has to-date demonstrated more hesitance in doing, especially as it pertains to making claims. He also said the EMA has recognized the necessity to go beyond A1c to address unmet needs: "Although nobody debates the value of A1c as a surrogate," he said, "everybody agrees that it has limitations." One especially noteworthy aspect of diabetes is the huge impact of treatment itself on quality of life, as few conditions are as labor-intensive and "high stakes" on a daily basis. He made sure to state the importance of not obliging companies to have to run multiple trials to please different regulatory agencies so that the ultimate goal, "pleasing patients," can be best realized. To do so, he believes it is imperative to align international standards. In many ways, US and European regulators can learn extensively from each other, and we imagine an international alignment would harvest the best from both. We applaud representatives from both organizations for allowing patients to steer the ship, dictating where the agencies should push and focus resources.

- **In a session later in the day, Prof. Philip Home said the understanding in Europe is that confirmed symptomatic hypoglycemia is a real outcome, but that is not yet accepted on this side of the Atlantic.** Indeed, EMA has accepted comparative hypoglycemia data from SMBG into the label of an insulin - the FDA is still reviewing the data, and Novo Nordisk CMO Dr. Alan Moses is not sure what its action will be. CHMP is certainly more willing to accept CGM data for a drug than the FDA at the moment - CDRH has made tremendous strides over the past few years behind the leadership of Dr. Courtney Lias, while CDER hasn't addressed some of the issues in such a head-on way. Dr. Robert Ratner is adamant that CDER will come around, and we wonder how much of that transition will be attributed to watching EMA experiment with putting these outcomes on labels vs. performing its own diligence.
- **EMA is currently revising its guidance, with the 2016 revision set to go under public consultation this October (commenting will be open to all, European or not).** The 2016 revision builds off the 2012 document that already includes a recommendation that CGM "be considered to provide additional relevant information" on new therapies. The latest revisions are seeking to address three central areas: (i) patient concerns that A1c is insufficient to estimate the benefits of glucose-lowering therapies; (ii) the lack of consensus around hypoglycemia definitions; and (iii) the need to provide companies with guidance on which of the many possible outcomes

measures beyond A1c to focus on in the development of adjunct therapies for type 1. The current revision and upcoming review of EMA guidance brings forth the timely opportunity for very specific dialogue with the FDA about what to include, and not include, on outcome measures beyond A1c so that American and European regulatory priorities can be aligned - something event attendees frequently asserted both the need for and their commitment to throughout the day. On the other hand, the EMA seems to believe in accepting more risk in its decisions than the FDA, so we're not sure that a total alignment will be possible.

- **In line with a common sentiment expressed throughout the day, Professor Van der Schueren added that co-primary endpoints, such as an A1c below 7% with no weight gain, may be helpful to contextualize treatment.** That said, and judging from his comments, it seems the EMA may not be fully convinced and/or enthusiastic about the utility of co-primary outcomes. He added that companies have asked the EMA if it would be interested in co-primary outcomes like achieving an A1c below 7% without hypoglycemia, but that he and colleagues have questions about how such endpoints may translate into an indication for a drug. He further stated that the EMA will not acknowledge the reduction of insulin needs alone as a valid endpoint (citing DKA-related safety concerns), though did leave open the option for considering reduced insulin needs in combination with a reduction in weight or hypoglycemia. The combined endpoint he had the most trouble with is A1c < 7.0% with no severe hypoglycemia and DKA, (i) because it conflates safety and efficacy and (ii) the components do not have similar clinical weighting - in Prof. Home's view, the general tone of the meeting was not to support composites for the latter reason. Most throughout the day were fairly negative on composite outcomes, since they have an arbitrary nature to the definition.
- **Professor Van der Schueren also stressed how the EMA really wants to include PROs in its new 2016 guidance, but underscored how much work still remains to be done to fully develop and validate such outcome measures.** In addition, he spoke to the need to consider the full metabolic profile (cholesterol, weight, blood pressure, etc.) during therapy evaluation.
- **Multiple attendees asked about the use of CGM in clinical trials during Q&A.** Professor Van der Schueren suggested that it may become increasingly challenging to perform blinded CGM in drug trials because it won't reflect what is seen in the real world. He also noted that discussions among EMA regulators are only in the early stages on a number of issues, such as what to do with missing data (something discussed only very generally to this point) or suspected artifacts from sensor compression overnight. He added data collection and analysis will be key to figuring out where to go next. As he said, "A1c wasn't perfect at the beginning either" - a great reminder that the outcomes we're all accustomed to seeing did not have a smooth start.

8. MOVING PUBLIC OPEN SESSION DRAWS 11 SPEAKERS

The early afternoon saw a moving open-patient hearing featuring numerous clinical and industry professionals, plus one patient. Highlights were many, and included, among others, Joslin's Dr. Robert Gabbay's take on whether we should move beyond A1c, Lilly's Dr. Jim Malone commending the EMA for including patient-reported outcomes in drug label, an emotional anecdote from Joslin's Dr. Lori Laffel illustrating the devastating and irreversible impact of a single episode of hypoglycemia, and Mr. Stephen Shaul's final line: "Patients have the data and are using it now. What you need to do is catch up to us."

- **The Joslin Diabetes Center's Dr. Robert Gabbay made a plea to all in the room: to make the most of the historic opportunity today to come together, to come to consensus, and move to "change our quality metric to incorporate things beyond A1c."** Speaking to the broad diabetes ecosystem and stakeholders beyond the walls of the conference center, Dr. Gabbay warned that "everyone outside of this room needs to come on board, and that's going to be a challenge - not only people with diabetes and their providers, but also payers need to understand the importance." To illustrate the dire need for such consensus, Dr. Gabbay shared the

story of a new patient of his from a couple of months back, a 50-year-old Red Sox fan, husband, and person with diabetes who had experienced two severe hypoglycemia events, the most recent one of which involved an ambulance coming to his aid in full view of neighborhood onlookers. This man's previous doctor had told him his 7.5% A1c wasn't good enough, and that he had to "work harder and do better." A couple weeks after getting this gentleman set up with a glucose monitor, he came back smiling, head high. Apparently, he'd been afraid that he wouldn't make it to his daughter's wedding in a few months, but with CGM he had "great hope for the future." Dr. Gabbay's account was one of so many that highlighted the very immediate, very real effects that new technologies can have for the health and happiness of patients - positive health outcomes and effects that are not captured by A1c alone.

- **Senior Medical Director of Lilly Diabetes Dr. Jim Malone issued a heartfelt call for greater emphasis on patient-reported outcomes and real-world evidence in addition to glycemic outcomes beyond A1c.** He underscored that this kind of information is what actually resonates with patients - in stark contrast to the unintelligible clinical data they are typically confronted with in product labels. Without mentioning Trulicity, he noted that its EU label does include two sentences on patient reported outcomes: "Patient reported outcomes - Dulaglutide significantly improved total treatment satisfaction compared to exenatide twice daily. In addition, there was significantly lower perceived frequency of hyperglycemia and hypoglycemia compared to exenatide twice daily."
- **Joslin's Medha Munshi's statement, read for the record by diaTribe Managing Editor Ms. Lynn Kennedy, noted that there is no association between A1c levels and duration of hypoglycemia.** She dispelled the common fallacy that higher A1cs are protective against hypoglycemia - in reality, there is a U-shaped curve, as people with high A1cs are also at high risk for hypoglycemia. Keeping A1c elevated in patients, regardless of insulin regimen, therefore raises risk of both short-term and long-term complications! She concluded by calling for better glycemic measures (from CGM), encouraged the use of easy-to-use medicines that lower the risk of hypoglycemia in the elderly population, and better studies identifying surrogates that are more suited to the lived experience of diabetes than A1c.
- **Joslin's Dr. Lori Laffel shared a heartfelt tribute to her patient Sean Peters, a 23-year-old who had had type 1 diabetes since he was 17 months old and passed away after experiencing a devastating episode of severe hypoglycemia in late April.** He was found unresponsive in his bed and passed away days later. Her message doubled as a compelling call to seriously and urgently develop better ways to assess the impact of hypoglycemia and the ability of current and emerging therapies to reduce the frequency and severity of this all-too-common occurrence. As Dr. Laffel told the audience, Sean's A1c was 7.1% when he passed away. She finished by imploring companies, payers, and regulators to focus more on outcomes beyond A1c, noting, "When it happens to a person, it is personal. And you can't reverse it." Our hearts go out to Sean's family and friends at this difficult time and hope that his tragic, all too soon passing can serve as another impetus needed to quash any and all doubts that the time to move on hypoglycemia as an outcome measure is now - not a minute later.
- **Dr. Barry Ginsberg drew a comparison between the current path to CGM outcomes consensus to that of BGM accuracy consensus in the early 1980s.** When he first started in BGM analysis three decades ago, if anyone asked for specifications about a BGM, the response would include accuracy, bias, linearity, and no one cared about any of it until the field settled on one number - mean average glucose. Today with sensors, Dr. Ginsberg said that there are "3, 4, 5, 10 different factors, and it's hard to evaluate them. Blood glucose below 54, below 30, time in range 70-140, 70-180, various high thresholds. A single number might be significantly better." There are a number of summary statistics that Dr. Ginsberg believes could be better employed to give a single glance at how a patient is doing (he specifically referenced Dr. Boris Kovatchev's risk analysis). Similar to other speakers, we're not entirely sold on combining time in range, time in hypoglycemia, time in hyperglycemia, and glycemic variability into one composite measure. It may help for

understanding how things are going overall, but the more important part are the sub-components (highs, lows, in range) and when the concerning patterns are occurring.

- **University of Denver's Dr. Gregory Forlenza shared the story of how CGM saved a three-year-old's life.** The boy was referred to Dr. Forlenza after experiencing two seizures in the same week. He had never worn CGM before, and as he was small and thin, his parents were reluctant to put him on devices. Dr. Forlenza finally convinced the family to try CGM with remote monitoring, and the boy has worn one ever since. His mother now describes this as life-changing, even though the child's A1c has been constant since adding CGM. The parents can now sleep at night, and leave their boy at his grandparents' house while they go on dates without worry. We love nothing more than to hear uplifting stories like this one, especially as it illustrates the utter insufficiency of A1c to describe life with diabetes.
- **Dr. David Price, Dexcom's VP of Medical Affairs, discussed the history of regulatory barriers for utilization of CGM in clinical trials, arguing that recent advancements in CGM technology have largely resolved these.** He specifically highlighted three aspects of CGM that have given regulators pause in the past - ease of use, accuracy, and calibration - underscoring that CGM is highly advanced in all of these parameters, and only continues to improve in subsequent generations. In short, the past regulatory (and perhaps industry) concerns over using CGM are hardly concerns anymore.
- **Mr. Stephen Shaul, a Baltimore resident with type 1 diabetes since 1991, delivered one of the most memorable lines of the day: "Patients have the data and are using it now. What you need to do is catch up to us."** He illustrated this by explaining how he had been skirting the line throughout the morning's proceedings - something he knew from his CGM and was able to treat by temporarily suspending basal insulin on his pump and eating some candy. We view this as the perfect articulation behind the "beyond A1c" movement - we must understand what patients are doing and what they find valuable, and then incorporate that into regulatory decision making.
- **Dr. Alan Moses, Global CMO at Novo Nordisk, discussed and shared what many described later as a most valuable diabetes "State of the Union," underscoring that the "time has come to reach a consensus on issues in diabetes management that matter most to patients."** He set the stage by remarking that the most informative part of his career in diabetes (first as a researcher, then as a clinician, and now as a drug developer) is having a son living with type 1 diabetes, describing how this has informed his understanding of the regulatory tension surrounding "softer" aspects of diabetes such as fear of hypoglycemia. This matters immensely to patients but is difficult to capture in a product's label. He cautioned the audience not to discard A1c entirely, but surmised that outcomes must go much further to address patients' real concerns and adequately recognize the way they feel about their diabetes. What can we do? Dr. Moses underscored the importance of defining outcomes that matter objectively and are directly translatable to action for the patient. He also articulated the need for a future in which meaningful differences between therapies are incorporated into regulatory labeling in a way that "truthfully and clearly" educates those who care for people with diabetes. Dr. Moses closed on an optimistic note, reasoning that although we may not have everything we need today to have all the fine points of outcomes beyond A1c incorporated into clinical trial programs, we have far more today than we did yesterday, and this is a very promising start.
- **Dr. Jyothis George, Global Head of Diabetes Clinical Development at BI and a representative for The Endocrine Society, said that going beyond A1c applies to type 2 diabetes as well as type 1.** "Regulators and academics wake up to address unmet needs," he noted, saying that it is particularly challenging for those working in type 1 diabetes therapy development "because you need to meet an A1c target to get a drug approved, and non-inferiority isn't enough." Without meeting the superiority bar for A1c, it's hard to justify the multi-year investment of resources (i.e., patients' time, researchers' money, etc.). Nonetheless, Dr. George

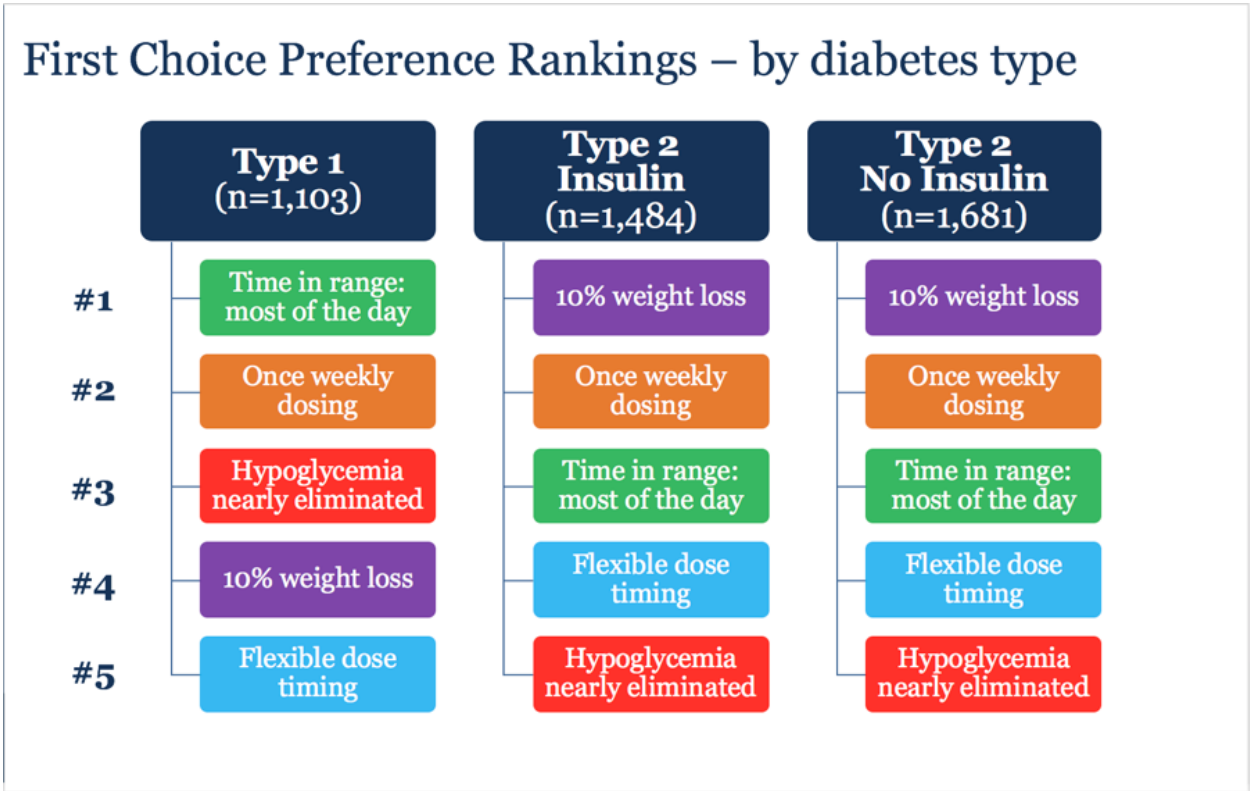
expressed the commitment of manufacturers to going beyond A1c, stating, "The time of action is now. Unless we start acting, we'll be back again in two years talking about the same things."

- **Dr. Nicholas Argento, a clinician who has had type 1 diabetes for nearly 50 years, primarily emphasized the importance of clear and concise language with regards to hypoglycemia and time in ranges.** "Level 1 and level 2 hypoglycemia? They can't even keep straight type 1 and type 2. I think this is a little crazy - we should be respectful of their needs. I think serious hypoglycemia should be the term because it is serious, and we don't want to minimize that." Dr. Argento said that time in ranges should be reported in hours (minutes when <one hour), and never in percent of the day. "Everyone knows what an hour is, but when you see that 7% of time you're in hypoglycemia, that doesn't resonate as much as 'two hours a day.' AGP is great, but instead of percentages, I'd love to see time. Let's translate into language that everyone knows what it means." He also said that using A1c to dictate therapy is "like trying to gauge someone's haircut from across the parking lot."
- **Dr. Bruce Buckingham (Stanford University) closed out the Open Public Hearing with a reminder to not forget beyond-A1c outcomes that are non-glycemic.** Specifically, he explained the importance of sleep quality and so-called "hassle factors" like the frequency of alarms, how many devices a person has to wear, and how often they need to be changed, noting that these are as important as time-in-range at promoting quality of life.
- **Ms. Rebecca Killion, an FDA patient representative, couldn't make the meeting but she wrote to us with the following note: "**In the 21 years since I was diagnosed with type 1 diabetes, we've seen great strides in its care and management - new therapies, more and better drugs, improved monitoring options. As a person with diabetes, it's thrilling and empowering - but it is not enough. It is nowhere near enough. Diabetes is relentless. There are no days off, no vacations, no ability to put it up on the shelf and pick it back up tomorrow when we have more time to deal with it. The burden - and it is a burden - of day-to-day management falls on the patient. Consider how easy it is to be overwhelmed by the hundreds of decisions that need to be made each day. I know I am not alone when I confess that, while I work hard to ensure that my blood sugar is not too high, the fear of a dangerous and possibly lethal hypoglycemic event drives much of my decision-making. And every few months, the results of all that effort is summed up in an A1c number that is a maddeningly incomplete record of the nuance of life with diabetes. Knowledge is power. Technology - specifically CGM devices - offers better real-time data that empowers patients and doctors to make better choices. We now have the ability to move beyond a measurement that aggregates information but fails to capture detail. We need to embrace the benefits bestowed by technology in our treatment and research if we are to advance better outcomes for people with diabetes."

9. ADAM BROWN ON UNTANGLING PATIENT PREFERENCES FOR VARIOUS BEYOND-A1C OUTCOMES

Adam Brown presented hot-off-the-press dQ&A data delving into the relative priority of different beyond-A1c outcomes in the eyes of people with diabetes. Commissioned by the diaTribe Foundation from dQ&A, this study surveyed 4,268 members of the dQ&A Patient Panel in a conjoint-based design to assess preferences for different potential beyond-A1c features of a diabetes therapy: time-in-range, time spent in hypoglycemia, dose timing, dosing frequency, and weight loss. Within the study design, these features all came in different levels - a therapy could promote time-in-range (70-180 mg/dl) for "most of the day"; for an hour more per day, or no change; hypoglycemia (<54 mg/dl) could be "nearly eliminated," reduced by 30 minutes per day, or not changed; weight loss could be 10%, 5%, or no change; dosing could be once weekly, once daily, or three times daily; and dose timing could be flexible or fixed. Conjoint analysis pits different features against one another at different levels - after enough data is amassed, researchers are able to tease out the relative importance of different therapeutic attributes, and even extrapolate to how patients may weigh two hypothetical therapies with a vastly different set of pros and cons. Primarily, dQ&A's conjoint analysis revealed that therapeutic preferences differed by patient group (though time-in-range and weight loss emerged as critically important outcomes across the board). In people with type 1 diabetes (n=1,103) , time-in-range "most of the day" had the highest share of first choices, followed by the option of once-weekly dosing,

elimination of hypoglycemia, 10% weight loss, and flexible dose timing. On the other hand, people with type 2 diabetes (on insulin [n=1,484] and not on insulin [n=1,681] alike) most often indicated 10% weight loss with the highest share of first choices, followed by once-weekly dosing, time-in-range, flexible dose timing, and the elimination of hypoglycemia. Beyond exemplifying interesting heterogeneity in patient preferences, these results further underscore that the risk/benefit calculus for a certain diabetes therapy may change markedly based on inclusion of outcomes beyond A1c in product labels. Adam underscored that patients all have unique concerns, and we need to arm them and their caregivers and providers with clear and succinct information on drug labels to help them better make these decisions. He showed several Therapy A vs. Therapy B examples to illustrate how dramatically patient preferences change based on what outcomes are included. Adam noted that patients make tradeoffs in their choices based on the composite profile of a therapy - though a particular may give a highly desired outcome (e.g., 10% weight loss), if it has to be taken three times daily, it may be quite undesirable overall. To conclude, Adam asked the audience to imagine a future where product labels include "therapy facts" that are as simple to digest as nutrition facts on foods - we love this idea and wholeheartedly agree that there is opportunity for design improvement in how safety and efficacy information is conveyed on drug labels, though we also realize that the regulatory requirements are not something we understand well and we would welcome learning much more on this from FDA. He closed with a call for action, underscoring that the FDA has a historic opportunity to update regulatory science and include new technology - namely CGM - in clinical trials to measure outcomes beyond A1c. He urged the audience of clinicians, scientists, patient advocates, and regulators to work together to pave the way for a next generation of effective diabetes therapies and much greater success for patients and providers alike.



10. DQ&A DATA REVEALS THE IMPORTANCE OF TIME-IN-RANGE FROM A PATIENT PERSPECTIVE

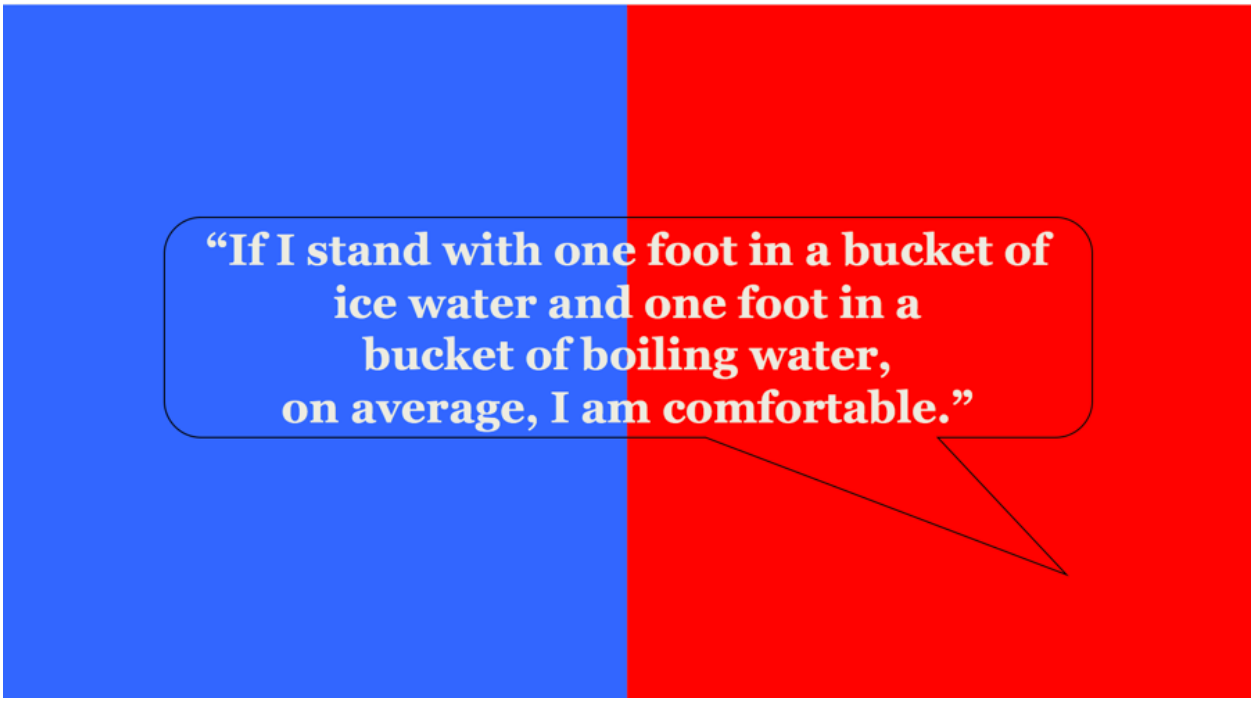
dQ&A Founder and CEO Mr. Richard Wood presented patient survey data to support the importance of outcomes beyond A1c. Results, first shared at last year's Outcomes Beyond A1c meeting, were collected by surveying members of the dQ&A Patient Panel. Respondents were asked about the factors that have the greatest impact on their daily lives and are potential drivers of improvement in mindset and diabetes management. The evaluation received responses from a remarkable 73% of those invited, totaling

3,461 people with type 1 and type 2 diabetes (n=1,026 and 2,435, respectively). Participants said that current therapies are coming up short in a number of areas, most notably in terms of helping patients achieve their desired time-in-range numbers, diet/exercise goals, and emotional well-being. Patients rated "time spent in the ideal blood glucose range" as having the biggest impact on their daily lives (outside of food choices) - significantly higher than the impact of A1c for type 1s (T1), and numerically higher in type 2s on insulin (T2I) and type 2s not on insulin (T2NI). Despite the importance placed on time-in-range, however, only 23% of T1, 25% of T2I, and 38% of T2NI reported that their current therapies are "very successful" at delivering in-range numbers (70-180 mg/dl). These results underscored the need to consider the full spectrum of patients' daily glycemia, rather than simply the average (as measured by HbA1c over a two-to-three-month period). Not only does time-in-range correspond to successful outcomes of a particular therapy, but it also is a powerful driver of freedom from stress and worry: 54% of respondents with type 1 diabetes and 36% of respondents with type 2 diabetes on insulin ranked being in-range as the number one factor in establishing a positive mindset. Further survey data revealed that we are in sore need of positive mindset drivers in diabetes care - on psychological health, results showed that emotional well-being was disturbingly low across all three groups, with only a tiny minority rating therapies as "very successful" at achieving this outcome (22%-34%). Mr. Wood closed with a nod toward the questions that lie ahead - namely how people with diabetes weigh tradeoffs in outcomes when comparing diabetes therapies side-by-side, and whether the inclusion of outcomes beyond A1c such as time-in-range and hypoglycemia on product labels would encourage meaningfully different prescribing and therapy choices by clinicians (see Adam's presentation above). dQ&A's work deeply resonated with us as a reminder that there is a significant need to more expansively evaluate what matters to patients, and to incorporate these priorities into therapy development, reimbursement, and regulatory decisions. We hope this work inspires regulators to understand the importance of closer alignment of diabetes outcomes with patient priorities. For a deeper dive on this dQ&A data, see our coverage of the corresponding poster presented just last month at ADA 2017.

11. UPDATE FROM THE COMMUNITY: THE DIATRIBE FOUNDATION AND DSMA SHARE DATA REGARDING PATIENT EXPERIENCE; SNEAK PEEK AT UPCOMING FDA MEETING ON HYPO IN ELDERLY

DSMA founder Ms. Cherise Shockley joined Kelly Close onstage to present highlights from the DSMA community's twitter chat on glycemic outcomes beyond A1c, focusing in particular on hypoglycemia. Ms. Shockley shared a number of tweets from chat participants, overwhelmingly illustrating that people with diabetes don't find A1c meaningful or actionable on a day-to-day basis. There was much less consensus in response to a question about perceived hypoglycemia threshold - while one man considers anything from 65-80 mg/dl hypoglycemia, another didn't consider hypoglycemia to begin until his blood glucose drops below 60 mg/dl. Further, while participants varied in how often they thought or worried about hypoglycemia, many shared their experiences of the job-impairing effects of low blood glucose: A news anchor couldn't speak clearly on air because he was shaking and sweating, a touring musician couldn't remember lyrics, a photographer had to stop photoshoots because of blurred vision and shaky hands. Most disturbing, however, were the stories of "worst hypoglycemia" episodes, in which one woman forgot her own name as a 14-year-old, out alone in public; a man drove into a ditch and thought his wife was an alien trying to hurt him; and a pregnant woman passed out while on a walk, only to wake up in her friend's apartment to paramedics hovering over her. Ms. Shockley mentioned that in the seven years she has run these chats, she can count on one hand how many times she has teared up from hearing patient stories - this was one of them. These #DSMA chats have done wonders for people with diabetes, offering an outlet for their voices to be heard and to know that they are not alone - all thanks to the incredible Ms. Shockley! She concluded her talk with her high-level perspective on the day's proceedings: A1c is not the best or most useful measure for people living with diabetes; time in range and short-term blood glucose trends are far more meaningful and actionable.

- **Ms. Close began her portion of the session with a compelling analogy:**



- **Ms. Close noted the huge burden of hypoglycemia for individuals and the healthcare system, totaling an estimated $10+ billion in US healthcare claims, ~$3 billion in lost productivity, and ~300,000 US hospitalizations and ER visits annually** (according to Truven Data, CDC, and some experts' estimates). She called for movement away from drugs like sulfonylureas that carry a high risk of lows and toward therapies and devices that target hypoglycemia reduction. Time-in-range, she continued, is clearly associated with emotional wellbeing and predicts quality of life, whereas A1c says nothing regarding glycemic excursions or danger. Furthermore, she added, adherence is negatively impacted by high glycemic variability, adding to the evidence that boosting time-in-range and diminishing times in hypoglycemia and hyperglycemia should be prioritized. Ms. Close was optimistic regarding CGM driving a new generation of therapies to improve outcomes - her slide showed pictures of Dexcom's G5, Medtronic's Guardian Sensor 3, and Abbott's FreeStyle Libre Pro. Still, there is much to improve; In just one example, Ms. Close called for better labeling, showing a picture of an unfolded insulin label stretching half the length of a dinner table - this information is necessary to convey, but we would love to see something like a standard "nutrition facts" label for drugs that is easy to read, but directs readers to another source (perhaps online) for more depth as needed. An easy to remind label summary with outcomes that matter is far better than what typically happens now: no label reading at all.
- **FDA's Dr. Christine Lee came to the stage at the request of Ms. Close to discuss what Close has been characterizing as a very exciting upcoming September 12 public workshop hosted by the Agency where participants will discuss preventable harm in older people (65+)with diabetes.** The agenda will focus on hypoglycemia outcomes, showcasing work produced from safety initiative partnering with private and public sectors, including CMS, Kaiser, the Mayo Clinic, and the Endocrine Society. The meeting unfortunately takes place during EASD on September 12 (keep an eye out for our upcoming preview!), but for those unable to attend, there will be a follow-up meeting at a later date, and a live webcast. See the Federal Register notice here.

12. DR. BRUCE BUCKINGHAM ON MAJOR IMPROVEMENTS IN CGM TECHNOLOGY AND WHY MEAN GLUCOSE BEATS A1C

Dr. Bruce Buckingham gave a most valuable update on rapidly evolving technology in diabetes, particularly the CGM field, noting that data from sensors has been "revolutionary" in evaluating therapies and is more actionable than A1c: "CGM provides a more comprehensive picture of dysglycemia than A1c, and it provides an easy, standardized, quantitative measure to compare therapies. It's also a direct measure of glucose levels bathing the tissues throughout the body, avoiding the errors associated with an indirect measure such as A1c." On that latter point, Dr. Buckingham added that he places more importance on CGM-measured mean glucose, rather than A1c, since high glucose is what matters for tissue damage. For regulators, he noted that CGM provides numerical, objective measures of hypoglycemia (better than infrequent severe hypoglycemia endpoints, which can be subjective and/or skewed by just a few patients who have many severe events in a randomized trial), and distinguishes glycemic excursions related to basal vs. postprandial conditions. Dr. Buckingham was enthusiastic about the progress in CGM devices, and a slide noted the compelling evolution in Dexcom's sensor accuracy (from an MARD of 26% in 2006 with the STS to now 9.0% with the G4/G5) - "If you get a cheap meter, you might see much worse accuracy now than with CGM." He flashed quick slides showing Dexcom's G5 ("you don't need to be a model to wear one"), Medtronic's Guardian Sensor 3/670G ("much more accurate"), and Abbott's FreeStyle Libre ("useful for measuring outcomes in randomized studies" - it has also been used in several Jaeb studies, including the recent T1D Exchange mean glucose vs. A1c study, just published in Annals of Internal Medicine). In the most poignant story of his talk, Dr. Buckingham shared that when his daughter was pregnant, she had a normal A1c, but she carried a baby that was large for gestational age. It wasn't until he placed a sensor on her that they noticed large postprandial excursions; she subsequently changed her eating behavior, and the baby was ultimately born healthy and at a normal weight.

- **For use in clinical trials, Dr. Buckingham emphasized that two weeks of CGM data has a high correlation to three months of data** - this was a recurring theme of the day, since there is plenty of trial data now to back this up. He added that systems like FreeStyle Libre Pro can be worn blinded in randomized trials, minimizing bias from real-time systems.
- **On the CGM evidence front, Dr. Buckingham mentioned the JDRF CGM study, STAR 3, and DiaMonD.** He pointed out the impressively high wear time in the DiaMonD study in the type 2 cohort, a good sign as CGM expands into more study populations.
- **"It's easier to compare one closed-loop system to another when you report the same metrics."** Dr. Buckingham highlighted the Artificial Pancreas Outcomes paper published last year (Maahs et al., *Diabetes Care*) - since that time, published closed loop studies have almost uniformly used the consensus thresholds, with the major exception of Medtronic's MiniMed 670G pivotal study (which unfortunately used 71-180 mg/dl). This standardization is great to see.

13. GLUCOSE METRICS WORKSHOP: AGREEMENT ON TIME-IN-RANGE THRESHOLDS AND USE OF CV FOR GLYCEMIC VARIABILITY

Dr. Steven Russell shared an uplifting summary of the glucose metrics/variability workshop, noting strong consensus on the time-in-range thresholds (<54, <70, 70-180, >180, and >250 mg/dl) and unanimous approval for use of coefficient of variation (CV) to characterize glycemic variability. Though the latter has long been a point of discussion, there was actually no debate in this session - Drs. Bergenstal and Beck convinced the room, through lots of CGM trial data, that standard deviation is *highly* correlated with mean glucose, limiting its incremental value. Coefficient of variation, which is simply standard deviation divided by mean glucose, has no such correlation problem and was praised in the room. Notably, a paper in this month's *Diabetes Care* by Monnier et al. suggests that a CV of less than 36% is a good target (i.e., a SD that is less than ~1/3 of the average). Dr. Russell emphasized that the ordering of CGM metrics is also really important, since it implies a hierarchy - therefore (and we agree), the standardized CGM outcomes metrics should be presented with (i) mean glucose first (linked with complications, based on the DCCT), followed by time-in-hypoglycemia and then everything else. The group agreed on using the Ambulatory Glucose Profile for data visualization, that 15 consecutive minutes constitutes a hypoglycemia

"episode" (i.e., for documenting "X hypoglycemia episodes/week" - a separate metric from time spent in hypoglycemia), and that 14 days of CGM data strongly aligns with three months. Though there was some debate, the group agreed that time blocks of midnight-to-6am (overnight) and 6am-to-midnight (daytime) should be standard practice, in addition to reporting 24-hour CGM outcomes. There was no consensus on composite endpoints, given their somewhat arbitrary nature, infinite number of combinations, and masking of individual components. Many also brought up simplicity - though some metrics like LBGI and HBGI have a nice mathematical basis, several in the room felt that the educational burden these metrics would require aren't worth their incremental value (Adam was particularly vocal on this topic - LBGI and HBGI are confusing to patients and would therefore require lots of teaching). Naturally the conversation drifted to the next step relevant for regulatory decisions and clinical practice - what are the benchmarks for different glycemic outcomes like time-in-range and time-in-hypoglycemia, and what constitutes a clinically meaningful improvement?

14. BREAKOUT SESSION DELVES INTO HYPOGLYCEMIA TERMINOLOGY

A very important workshop on hypoglycemia led by the International Hypoglycemia Study Group's Dr. Stephanie Amiel of King's College London and Edinburgh's Dr. Brian Frier, brought attention to the work on hypoglycemia done leading up to ADA and the need for consensus on the terminology for different classes of hypoglycemia. Moderated expertly by Professors Amiel and Frier, workshop attendees expressed agreement on the cut-offs of <70 mg/dl and <54 mg/dl to divide the different classes of hypoglycemia, though had less unanimity on how to name these. Though the audience of physicians, patients, and researchers expressed little argument regarding the terminology of "severe hypoglycemia" to describe events requiring assistance and "alert hypoglycemia" to describe episodes <70 mg/dl (though it was acknowledged that "severe hypoglcyemia" isn't uniformly used this way), naming the intermediate category of blood glucose levels <54 mg/dl proved quite challenging. Attendees expressed concern that adjectives such as "dangerous," "serious," or "action-required" subtly insinuate that other slightly-higher blood glucose levels aren't dangerous, serious, or demanding of action, and to this end JDRF's Dr. Aaron Kowalski argued for a more neutral classification system featuring value-free terminology, such as "class 1, 2, and 3" that avoids these semantic issues. Further, CDER's Dr. Lisa Yanoff asserted that FDA is uncomfortable with the term "serious" to describe blood glucose <70 mg/dl because of connotations with SAEs. The group seemed to agree that this kind of terminology would lend itself well to regulatory discussions, but whether more descriptive terminology is needed in clinical care remains an unresolved question. Notably, Dr. Amiel left the meeting motivated to take some of the discussions from the session back to the IHSG to solidify some recommendations on terminology - we were thrilled to hear this from such a noted leader.

- **Impaired awareness of hypoglycemia was another topic of discussion at this workshop, and attendees debated how this should be measured.** Though there is no clear gold-standard measurement, several existing scales are widely used. The Gold Scale is attractive insofar as it is a single question ("Do you know when your hypos are commencing?") and thus takes only seconds to administer. By contrast, a different measure, the Clark Score, is more comprehensive but takes longer to administer because it is eight questions long - it remains unclear which approach (if either) would be ideal to cement into the regulatory process moving forward. Beyond this, attendees also spent a fair amount of time discussing the nuances of what impaired hypoglycemia awareness truly means - whether it is the ability to perceive symptoms, or the inability to acknowledge and subsequently act on the symptoms due to cognitive impairment. This is a rich area of future investigation.
- **Additionally, the workshop briefly touched upon the issue of short- and long-term consequences of hypoglycemia.** Perhaps unsurprisingly, attendees arrived at the conclusion that we need much more data regarding both the acute consequences of hypoglycemia (cognitive impairment, coma, seizure, accidents, etc.) and morbidity secondary to hypoglycemia (such as the consequences of a fall).

15. BREAKOUT SESSION DISCUSSES USE OF CGM IN TRIALS AND HOW TO GET FDA TO ADOPT HYPOGLYCEMIA AS A SURROGATE

Joslin's Dr. Lori Laffel and Newcastle University's Professor Philip Home led an interactive breakout session with the aim of fleshing out if and how future clinical trials should leverage CGM to determine the effects of therapies. The first order of business - getting everyone to agree that CGM should be used in clinical trials - was easy, but the question of how to get the FDA to accept CGM glycemic outcomes was more trying. Georgetown's Dr. Robert Ratner began by establishing the over-arching framework of the conversation, that clinical trials should be designed with an eye for what it will take to get regulators to include CGM metrics in labels; otherwise, it will never be used in everyday practice.

- **Dr. Laffel pointed out one of the paradoxes of CGM use in clinical trials:** "If you have an outcome of a CGM metric and the drug gets approved because it demonstrates superiority in time in range or reduced hypoglycemia, does it only get approved for people who wear CGM? Or for everyone? How would payers view that?" With the clinical benefit of real-time CGM well-documented, it becomes difficult to parse out the relative contributions of the therapy and use of the sensor. Not everyone in the real world will wear a sensor, so would the drug have to show superiority over existing therapies in the presence and/or absence of CGM? But at the same time, it may soon be considered unethical to not give trial participants intensively treated with insulin CGM, so how can the isolated profiles of drugs be evaluated? For now, this discussion is exactly the argument, according to a Dexcom rep, for blinded CGM in studies. Blinding the patient to the sensor will eliminate CGM as a variable for the drug indication. He has seen more and more companies present adaptable, stratified protocols, such that study participants are randomized to drug or placebo in two strata - those already using real-time CGM and those not. Then, the study can include blinded CGM in both groups with the group already using CGM wearing two CGM devices (one blinded and one unblinded) and the other group using blinded CGM.
- **With stratified trial designs, the group then asked for how long CGM outcomes should be collected.** ADA's Dr. Cefalu believes that long-term wear would help researchers to pick up on issues of "adherence and compliance" over time, but the Dexcom rep reminded the group that no drug trials currently require continuous use, rather 10-14 days around run-in and then again toward the end of the six months. According to the glycemic outcomes consensus, 14 days is enough to learn about the effects of a treatment and compare times in ranges and glycemic variability - two weeks correlates nicely with 30 and 90 days.
- **Finally, the conversation turned to - and didn't leave - hypoglycemia.** The group broadly agreed that hypoglycemia should be considered as not just a safety outcome but also a negative efficacy measure (Dr. Zan Fleming called hypoglycemia at best a "reverse adverse" metric - something that can't be an efficacy outcome in isolation). But if the FDA is to consider non-severe hypoglycemia as an outcome (something CDER's Dr. Lisa Yanoff suggested her department is open to), the link between diminished hypoglycemia and better long-term outcomes may need to be demonstrated, as it was for A1c with the DCCT. That's not to say that there needs to be another DCCT; Dr. Laffel, Dr. Roy Beck, and most others believe there is likely enough data to confirm that spending time <54 mg/dl puts patients at significant risk for neurocognitive impairment and progression to severe hypoglycemia. But as Professor Home said, "I *think* it, but that's not the same as convincing someone else." According to Novo Nordisk Global CMO Dr. Alan Moses, convincing regulators is far more challenging than one may initially think: "The endpoint that FDA wants to see is severe hypoglycemia. You know the size of the trial you need, and the duration of the trial you need to have a sufficient number of severe hypoglycemic events to demonstrate a statistically significant number of events. That, plus what is the definition of non-severe hypoglycemia that matters? Less than 54? Or symptomatic and less than 54? What about those with hypoglycemia unawareness?" To complicate matters further, the use of real-time CGM in comparative clinical trials is hopefully going to reduce the incidence of hypoglycemia, certainly severe hypoglycemia, but that means that sample sizes necessary to generate the power to show differences in safety and efficacy will balloon even further. AACE's Dr. Zachary Bloomgarden proposed a real-world

observational study, investigating the interaction of biochemical hypoglycemia with pre-specified adverse events - "thousands and thousands and thousands" of Medicare patients will soon be on the Dexcom G5, providing the perfect study setup. CDRH's Dr. Stayce Beck cautioned that sensors tend to under-read in the hypoglycemic range, so if low blood glucose doesn't track with adverse events, it could simply be a product of sensors reading low. In a randomized trial, however, even if CGM performance in the lower range is slightly reduced, both groups would experience the same CGM performance and data could still be helpful in assessing outcomes (further, setting CGM low alerts at a higher threshold could be a safety feature). Dr. Beck also provided some insight into the perspective of her CDER counterparts: CDER is focused on A1c and severe hypoglycemia at the moment because it has strong evidence that both factors contribute to poor outcomes. The division is open to alternative measures, but the researchers in the room need to talk with them to figure out what kind of study needs to be performed. "There is currently no evidence showing better time in range is going to lead to less or more complications. That's the trick, right?" Meanwhile, Dr. Fleming warned that it's a slippery slope to start asking for validation, and he doesn't see how it can be done practically: "You can't do an uncontrolled, un-randomized study to show that CGM is a good tool for hypoglycemia, and that that tracks with outcomes. You just can't do that to the satisfaction of the current mentality without doing a large study, and that would just be a shame if we had to do that. There has to be some reasonable way forward to use technology to get beyond the DCCT." This conversation was absolutely fascinating, and we are hopeful that the stakeholders in the room will move forward with discussions to compromise on a reasonable study design or use of Big Data/ registries that will leave everyone satisfied. After all, Abbott has 300,000+ people using FreeStyle Libre, while Dexcom has 200,000+ users worldwide; what can these half million people teach us about time <54 and <70 mg/dl and the link to negative adverse outcomes*?*

    - **Dr. Fleming later clarified his point on hypoglycemia as a reverse adverse metric: "Though hypoglycemia risk reduction is by far the most importance performance measure of insulin therapies, it is not helpful to call measures of hypoglycemia an efficacy outcome in isolation.** The exception would be a product that is intended only to reduce hypoglycemia but does not affect glycemic control. Clinically meaningful hypoglycemia is the key secondary outcome of any insulin trial and the measure of an insulin product's value, but hypoglycemia results from the exaggerated pharmacologic effect of insulin. To claim a benefit on hypoglycemia first requires showing similar glycemic control with the comparator."

16. IMPLEMENTATION WORKSHOP: THE CHALLENGE OF CLEARLY COMMUNICATING AGREED-UPON CONCEPTS WITH CONTENTIOUS TERMINOLOGY TO A WIDE AUDIENCE

The "Implementation" workshop, facilitated by Drs. Jane K. Dickinson and Robert Gabbay, uncovered many agreed upon next steps for communicating points of consensus. However, it was notably harder to nail down terminology options free from reproach. The latter was especially apparent in the "report back" session when participants from many other workshops added important qualifiers to the "consensus" presented by the implementation group. This wasn't surprising in the least as a common theme throughout the implementation breakout session was that everyone seemed to be in agreement about the conceptual details of the glycemic cutoffs for hypoglycemia and time-in-range much more so than they were on the nuances of how to accurately communicate those cutoffs to a range of diverse stakeholders - patients, clinicians, and payers especially. As one workshop participant mentioned, the ultimate goal is figuring out how to get new outcome measures on product labels in a clear, concise, and easy-to-use manner so that patients and providers can make risk-benefit decisions on a personalized basis. Getting there will inevitably require close collaboration with regulatory agencies in the US and abroad - discussions regulators seem very open to having - so that guidance can be updated to reflect new outcome measures beyond A1c and pave the way to expanding label indications.

- **A repeat sticking point encountered during the session was terminology used to communicate concepts, especially for hypoglycemia**: some methods propagate unwelcome stigma (e.g., using red/green/yellow stoplight model could present a message that would be

interpreted as red = low = bad = blame); others are too easily confused ("hypo" vs. "hyper" are very similar to those not fluent in diabetes jargon); some terms conflict with pre-existing definitions (e.g., "serious" and "severe"), etc. In the "report back" session at the workshop's end, this theme was again evident. Many seemed in favor of the suggestion to welcome input from user-experience and design professionals to guide a strategic naming process that includes - and furthers - the many considerations raised at today's meeting to settle into some standard terms.

- **Workshop participants unanimously expressed the need to widely and clearly communicate all consensus stemming from Friday's meeting for it to have any relevance to patients and providers.** One striking comment from a physician in the room characterized the sizable challenge of getting the broader scientific and medical community on the same page, saying, "Where I practice, primary care doctors for people with type 2 diabetes do not believe that checking glucose is ever worthwhile unless they're on insulin." The acceptance of new glycemic outcome measures is going to be significantly stymied if the wider medical world can't even agree that the most basic building block of glycemic outcomes - glucose levels - has relevance and/or value for all people with diabetes.
- **All in attendance favored the involvement of professional writers and usability experts in the design and dissemination of joint materials communicating consensus reached by the scientific community.** Mention of a two-page document was frequent, with multiple workshop participants promoting the notion of a "brief" that incorporated graphics, testimonials, and other multimedia, for example, to quickly communicate the essentials to a time-strapped audience. Furthermore, participants enthusiastically welcomed the idea of all organizations represented at Friday's meeting coming together to sign onto a joint consensus statement that would then be widely published on as many websites and in as many journals as possible. The need to include a professionally written executive summary for clinicians was stressed too many times to count. This is important to empower physicians (and a whole range of other healthcare providers - nurse practitioners, PAs, CDEs, etc.) who are busier with administrative burdens more than ever; those professionals will need the outcomes science that will enable them to provide the best, most individualized care to help patients do better.
- **Not only must core concepts be communicated clearly, but they must also resonate with many types of stakeholders, especially payers.** Insurers and government agencies like CMS need to understand what an outcome-beyond-A1c metric is, how it translates to improved clinical outcomes/adherence, and how it will save them money. Combined with big data from more than half a million people using sensors globally, we have to imagine there is cost data to link to sensor data and make a baseline case!
- **A common concern, albeit one anticipated further down the road, is the challenge of educating many diverse populations about new outcome measures** - A1c has been a lonesome and stalwart surrogate for so long. How will medical schools, which spend about two hours on diabetes in general training, train future generations of clinicians to use an expanded portfolio of metrics and rapidly evolving technologies? How easy or hard will it be for current practicing physicians to become proficient at interpreting and communicating any new metrics to patients? And how can information be packaged at the appropriate granularity for people with diabetes when the population is so heterogeneous on so many fronts? As one attendee added, "There's a reason we all start out in kindergarten and go from there."

17. MS. KELLY CLOSE SETS THE STAGE WITH COMMENTARY ON AMAZING PROGRESS TOWARD CONSENSUS, CALLS FOR PATIENT-CENTRICITY AND POLICY DEVELOPMENT

Ms. Kelly Close set the tone for the day by putting the amazing progress of diabetes care in perspective and emphasizing the need for patient-centricity and policy development. "It took 39 years for finger stick blood glucose testing to replace urine glucose testing," she began. "In the past 11 years, we've seen CGM enter the market, tremendously improve in accuracy, and receive FDA approval to replace blood glucose testing. Now? We are looking to implement CGM as the standard of care." However, Ms. Close

emphasized that the goal of the day's meeting was not just to advocate for CGM. Rather, it was about progress, in many areas -patient outcomes, physician empowerment, cost reduction, and of course, policy implementation. These areas are intimately connected: Regulatory decisions can have a significant impact on what therapies are developed, which in turn impacts the daily burdens of living with diabetes. The primary goal of therapy should be to help people think less about diabetes while also helping them lead safer and healthier lives. Ms. Close noted that CDER is already evaluating outcomes beyond A1c, such as cardiovascular endpoints, alluding to the recent FDA Advisory Committee that voted 17-2 in favor of a cardioprotective indication for Novo Nordisk's Victoza. Ms. Close would love for this movement to expand beyond cardiovascular and into therapies that promote fewer adverse hypoglycemic events (a HUGE cost and productivity drain), time in range, and patient-reported outcomes. At the end of the day, she said, we need clear guidelines for accepted metrics, which will undoubtedly lead to more innovation, increased access, and more success. And above all, we need to keep the patient view front and center. As Ms. Close said, "People with diabetes think about their condition a lot. Hundreds of times a day. And I guarantee that 95% of these thoughts have nothing to do with the number of hemoglobin molecules that have been tagged with glucose." Ms. Close concluded with a heartfelt thanks to everyone who has helped bring the movement this far: "Before we end our program, I want to recognize the groups that have brought the conversation this far, including people who took major steps to reach consensus at the ADA meeting: AACE, ADA, ATTD, EASD, EMA, Endocrine Society, FDA, IHSG, and JDRF. We are so grateful that the FDA has helped facilitate the rapid movement around CGM data collection, which is an incredible feat given the lack of resources. We won't forget that people worked nights and weekends to get this done." See immediately below for a full transcript of Ms. Close's remarks.

Full Transcript of Ms. Kelly Close's Opening Remarks

"I would like to start today's meeting by putting things in perspective. Remember that Benedict's solution, the first method of measuring urine glucose, was invented in 1911. In 1964, blood glucose test strips were introduced to hospitals and clinics. It took *39 years* to move from urine testing to finger sticks. Meanwhile, CGM entered the market 11 years ago - in that time, accuracy has been improved by magnitudes, the FDA has approved CGM to replace fingersticks, and we're on the doorstep of figuring out how to implement this remarkable technology as the standard of care. So, though progress on outcomes beyond A1c may feel slow at times, in the broader scheme of things, we're really moving along at the speed of consumer electronics. We have every reason to be excited and hopeful.

My name is Kelly Close. I'm the Founder and Chair of The diaTribe Foundation, a non-profit that works to improve the lives of people with diabetes and prediabetes and to advocate for action, and I'm delighted to welcome you to our gathering on standardization and implementation of outcomes beyond A1c.

To be clear, this is not a meeting *about* CGM. This is about progress. CGM enables us to measure time in range as well as hypoglycemia, but CGM is also about a cultural shift toward a more holistic view of diabetes. According to health psychologist Dr. Katharine Barnard, people with diabetes think about their condition A LOT - hundreds of times a day by her estimate. And I guarantee that 95% of these thoughts have nothing to do with the number of hemoglobin molecules that have been tagged with glucose. High-level regulatory decisions, as well as the conclusions we'll heard toward today, are going to have a significant impact on this day-to-day burden. Don't underestimate how deeply today's data wrangling and semantics will affect real lives.

Progress, in my view, requires a more rigorous understanding of the impact of therapies on the things that matter to people with diabetes. I would argue that the ultimate goal of a therapy is to help people think less about their diabetes while also helping people be safer and healthier. A1c alone is a pretty poor indicator of how safe we are or even how healthy we are, so we are all undertaking the task of revamping how we evaluate therapies in all phases of development and deployment - asking the questions that matter to people living with this disease. The FDA has shown their commitment by approving *over 40* diabetes drugs in the last decade, and now it's on us to make sure that clinicians and patients can benefit from those. Right now, I'm not sure the average patient or even healthcare provider knows best *how* to use most of this expansive pharmaceutical toolkit to address the most pertinent concerns of people with diabetes. This is why I'm excited

to hear the experts talk about the potential value of collecting standardized data on time-in-range, hypoglycemia, glycemic variability, and eventually a host of patient-reported outcomes, like mental health, both in clinical trials and standard practice. And it doesn't stop there, as we need to present this information in a clear, concise, and consistent manner so that everyone can understand the profile of a therapy.

We're already seeing this in motion. Last month, our team attended an FDA advisory committee hearing that set out to determine whether the label for Victoza, a GLP-1 agonist made by Novo Nordisk, should be updated to include a cardioprotective indication, based on data from the LEADER cardiovascular outcomes trial. After a long day, which included testimony from four members of our diaTribe team, the Committee voted 17-2 in favor of the update - a major victory for patients and providers, who we hope will soon have access to the right information to make better-informed health decisions moving forward. It's sometimes easy to forget that most people with diabetes are treated by general practitioners. Standardization will increase the ability of less-specialized clinicians to adopt newer, safer therapies, and to use them optimally. And, clearer terminology empowers patients to understand and be involved in their treatment decisions.

We would all like to promote access to therapies that result in fewer adverse events - not only fewer cardiovascular events, but less hypoglycemia, for example. A single inpatient admission for an episode of severe hypoglycemia costs over $17,000 on average, according to a 2011 study - there were 10 *billion dollars* in hypoglycemia claims in 2014, according to Truven and other sources. How do we get that number to approach zero? First, we need a consistent definition of what hypoglycemia is, and then to make it crystal clear how every drug and device influences time spent there. The requisite trials may be expensive and time consuming, but with severe hypoglycemia as the alternative, and a very debilitating and very expensive one, there really is no choice.

This foundational work is essential. Standardization of glycemic variability data may not make for good small talk (unless you're Dr. Bergenstal), but clear guidelines are the spur to progress: more innovation, increased access, and better outcomes. The FDA fully understands that efficiency and access matter, especially in a world skewing more toward value-based care - if no one can get a therapy, it doesn't matter who approves it. Today's work is how we get there.

And we've made so much progress already - this whole movement is about patient-centrism, and this meeting - *at the FDA* and with *so* many rock star clinicians, researchers, and advocates - was put together by a woman with diabetes and her organization. A year ago next month, we held a meeting in the White Room with many of the same people on Outcomes Beyond A1c, and just last month, there was a packed session at ADA where Dr. Buckingham proclaimed that "we were all there" when consensus on CGM outcomes metrics was achieved.

Before we begin our program, I want to recognize the groups that have brought the conversation this far, including people who took major steps to reach consensus at the ADA meeting: AACE, ADA, ATTD, EASD, EMA, Endocrine Society, FDA, IHSG, and JDRF. We are so grateful that the FDA has helped facilitate the rapid movement around CGM data collection, which is an incredible feat given the lack of resources. We won't forget that people worked nights and weekends to get this done. And of course, as a small nonprofit, we need support to gather people - everything we're talking about today wouldn't be possible without the support of our sponsors, and we thank them for their help."

--by Adam Brown, Ann Carracher, Abigail Dove, Divya Gopisetty, Lynn Kennedy, Brian Levine, Maeve Serino, and Kelly Close