FOOD AND DRUG ADMINISTRATION (FDA)

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH)

REGULATORY SCIENCE CONSIDERATIONS FOR SOFTWARE USED IN DIABETES MANAGEMENT

PUBLIC WORKSHOP

Thursday, November 13, 2014

FDA White Oak Campus

10903 New Hampshire Avenue

Bldg. 31, Room 1503

Silver Spring, Maryland 20993

Reported by: Michael Farkas

Capital Reporting Company

A P P E A R A N C E S

Dr. Jacqueline Yancy

Dr. Alberto Gutierrez.

Dr. Alain Silk

Mr. Howard Look

Dr. Joe Cafazzo

Dr. James Mullally

Dr. Steve Scott

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OPENING REMARKS

DR. YANCY: So my name is Jacquline Yancy and I am one of the scientific reviewers in the Office of In Vitro Diagnostics in the Diabetes Branch. And we'd like to welcome you to our Public Meeting on Regulatory Science Consideration for Software Used in Diabetes Management.

We are excited to have you all here. And we sincerely appreciate your attendance and participation today both in person and via the webcast. I hope you are all looking forward to a full day of great discussion surrounding the topics of interoperability for diabetes devices and insulin bolus calculators.

Before we begin I'd like to share with you a few logistical details, then I'll introduce Dr. Alberto Gutierrez our Office Director who will officially open this meeting this morning.

There are going to be two sessions this morning and then a third session this afternoon after lunch. Following those sessions we'll have a public comment section; and then also a panel meeting or a panel discussion where all of our speakers will discuss some items for the meeting.

There will be two fifteen minute breaks; one this morning and one this afternoon. And then lunch will be on your own.

Outside of this room is a kiosk where you can get coffee and sandwiches during your breaks and during lunchtime.

The public comment section will be about four minutes per person and we will have a timer so I hope to not have to cut anyone off but please keep your comments brief and

to the point. And then we will open it up for our panel discussion.

There are microphones set up in the aisles so if you have a comment or a question we ask that you go to those microphones, introduce yourself, say where you are from, and then ask your question or make your comment but we ask that you limit it to maybe one or two minutes per question or comment.

Let's see the meeting will be Webcast today and will be archived later for viewing on the meeting Web page. On that page the slides will also be available as well as transcripts for this meeting.

So now I would like to introduce to you Dr. Alberto Gutierrez, the Director of the Office of In Vitro Diagnostics and Radiological Health who will discuss the purpose of our meeting today.

Thank you.

INTRODUCTION AND PURPOSE OF THE MEETING

DR. GUTIERREZ: Good morning and welcome all. Thank you for coming to this meeting.

My task really is just to give you an idea of why we are having this meeting. This one is somewhat of an unusual meeting for us. We had a very short time to put it together and the reason really is that the agency had been working on dealing with a lot of new or quickly moving issues in terms of health IT. There was a report last year in 2013 that detailed the areas where it was not clear where the Agency had jurisdiction or not and how it was going to deal with a lot of new technology that was coming on the market very quickly.

Earlier this year, May, the Agency had a public meeting in which we began to detail some of the issues and some of the places where the Agency at least was beginning to

make policy and what type of policy we are going to be making.

And we have issued some guidances, guidance in mobile Apps, guidances on data systems, actually rules on data systems. So we have begun to try to delineate where the Agency has jurisdiction and where it does where it is deciding to enforce the full fledge regulations or use enforcement discretion.

One of the areas that we are tackling currently is clinical decision support systems. And we are having lots of internal discussion as to what kind of decision support systems need to be regulated by the agency or if there are perhaps some area where the Agency can actually let the marketplace and let the other mechanisms that it is working on bringing to light with the 1C and others, maybe perhaps letting those mechanisms help regulate the marketplace.

So particularly an area that we have had a lot of discussion and perhaps need some light to be shed and that is why this meeting is here is in the area of insulin dose calculators. The Agency has thought that very simple calculators, perhaps is an area where people can actually make their own calculations and it is unclear whether regulating that area is a place the Agency wants to be. But one that is particularly difficult for us to actually be able to tell what the risks and benefits of regulation or not are insulin dose calculators in part because they are used not only by doctors but they are also used by patients.

So the meeting today is really to get the input from you as to exactly how insulin dose calculators are used and what are the risks of having a space that is regulated or not. The risks of too much regulation obviously is it slows down or it can slow down innovation. The risk of not regulating clearly is patient harm.

So it is the area that we want some advice. We want to understand how they

are used. We want to understand what the risks are and perhaps what is appropriate regulation in this area or not.

So that is your task.

We have added a session that is not an insulin dose calculator but it is also related in the sense that one of the areas that the Agency is looking to be involved if not in the regulatory part but in the more I say a partner and as a driver is interoperability. So that is the first session that you will have. And then you will get into the meat of what we really need some advice and that is insulin dose calculators.

I am unfortunately not going to be able to attend the meeting all day. I am double booked. I have another meeting that is going to be a lot of fun for me today. I have to go talk about laboratory developed tests at the AMP meeting which is going to be interesting.

But I hope you -- I leave you in good hands. Courtney will be here all day and the division. And I hope to get a lot of good advice from you as to how the center should move forward.

Thank you.

[Applause.]

DR. YANCY: Thank you Alberto.

Our first speaker will be Dr. Alain Silk who is one of our Scientific Reviewers in Chemistry and Toxicology. He received his Ph.D. from the University of California in San Diego. And today he will be discussing interoperability for diabetes diagnostic devices and diabetes management systems.

Please welcome Alain Silk.

Topic 1: Interoperability and FDA Update

INTEROPERABILITY FOR DIABETES DIAGNOSTIC DEVICES AND DIABETES MANAGEMENT

DR. SILK: Okay. Good morning everyone.

Thank you Jackie for the introduction.

And today what I'd like to do is introduce the idea of interoperability in diabetes devices and contribute to the conversation on this topic with the goal of encouraging future public discussion.

As an overview of what I'm going to talk to you about today first I'll provide a brief introduction into the concept of interoperability and discuss how it is an important part of health care in general and diabetes care specifically. And then I'll talk in greater detail about a few areas of diabetes care where we see particular benefits of enhancing interoperability including in remote monitoring, device consolidation, and the advancement of artificial pancreas systems.

So in broad terms interoperability involves making systems work together. And in the case of technology that we are exposed to everyday we've come to expect a great deal of interoperability. We generally take it for granted when systems are interoperable and we get frustrated when they are not. So for example I recently bought a set of network wireless speakers for my house and now I just take it for granted that from anywhere in the house I can control the sound on any one of these speakers just using my phone. And now that I've realized that this is possible that the sound system can work together with my phone I get really annoyed that at night I have to go downstairs to turn of the light in the kitchen. I mean why can't I just do that with my phone?

Interoperability is also an important part of health care. So for example if two doctors are caring for a single patient but they don't speak the same language then they can't

really cooperate to provide better care. And even if they speak the same language if they don't understand each other well then they can't work well together. So here we have one doctor talking Celsius, the other doctor is thinking Fahrenheit and we might actually expect the worst outcome for the patient in this case.

So really the better that these two systems, in this case the doctors, can work together the better the outcomes for the patient.

And it is the evolution of diabetes technology and the increasing adoption of new technology by people with diabetes that has led to a growing need for the interoperability of diabetes devices.

So formerly diabetes devices were operated primarily manually. They generated limited amounts of data. Those data could be difficult to access. And there were only a few devices that were used routinely for diabetes care, maybe insulin and syringes and then a glucometer with possibly some limited data storage and transfer capacity.

Now many diabetes devices are controlled electronically. They generate an incredible amount of data. Those data are more accessible than they ever have been before. And there are far more devices that are routinely used by people with diabetes. These devices include insulin pumps, continuous glucose monitors, sophisticated glucometers that might communicate wirelessly, various types of data analysis software and Apps running on phones and tablets. And so with all these devices it is reasonable to think that the better these devices can work together the better the outcomes for patients.

So interoperability of diabetes devices has many potential benefits. It allows for the integration of data from multiple devices and the easy interpretation of those data. Interoperability can improve the quality of life for people with diabetes by allowing the

consolidation of devices and allow for easier access to and analysis of data from those devices by consolidating software and applications. Enhancing interoperability can also allow for faster and more reliable data upload and download for sharing. And it can also improve interaction between patients and health care practitioners.

And so I've actually personally experienced how patient doctor interactions are inhibited when diabetes devices don't work well together. I have diabetes and when I go to the doctor I bring in my devices. I bring my meter, my CGM and my pump. And my doctor looks at the data from those devices to see if there are places where I can improve my self-management. But she doesn't currently look at those date in an integrated way and certainly not in a way that gets the most out of the data. So for example data download from my insulin pump involves me writing on a piece of paper my insulin settings. And clearly that is not the best way to try to correlate insulin delivery data with glucose patterns downloaded from CGM or meter. And so the fact that my devices aren't working well together in a way that provides really holistic view of how I am doing well or poorly in my self-management strategies is pretty inefficient and frankly not very helpful.

And so interoperability really can help patients get more out of existing technology and lack of interoperability can limit this and it can limit innovation and slow the development of new diabetes management tools.

One area of diabetes care in which enhanced interoperability has a big role to play is in remote monitoring. Diabetes care depends on data. And contributing to the care of someone with diabetes depends on access to their data. Remote monitoring is the real time monitoring of data produced by diabetes devices on satellite devices. And it gives better access to patient data to care givers so they can provide better care. And so with sub optimal

interoperability good data sharing is either not possible or data can be shared intermittently or incorrect data can be shared. And enabling the interoperability of diabetes devices can mean better data sharing which empowers care givers to provide better care.

Another area of diabetes care in which interoperability can make a big impact is in device consolidation. So currently people with diabetes often carry multiple devices. They'll carry a meter, a pump, continuous glucose monitor components, carry test strips, might have insulin syringes or insulin pen, they'll have it on a cell phone. And having all these devices can certainly help in the management of diabetes. But managing all these devices can itself be extremely frustrating. Further some patients may be hesitant to adopt new technologies simply because they don't want to carry around an extra device.

So here enhancing interoperability of these devices can speed the development of consolidated devices. And this can improve quality of life of people with diabetes by easing the burden of managing multiple independent devices. This will require coordination between companies in many instances and FDA is currently creating and communicating policies to encourage collaboration between medical device companies.

Finally enhanced interoperability is going to be a key component of the development of an artificial pancreas. And the development of an artificial pancreas that is a fully automated, closed-loop and all the steps towards that will help address many of the challenges faced every day by people with diabetes; challenges like struggling to maintain good glycemic control and avoiding nighttime hypoglycemia. An artificial pancreas system essentially integrates three separate subsystems, a continuous glucose monitor, a pump, and insulin dosing algorithms. And enhancing interoperability will break down barriers towards getting these different components together into an integrated system.

But because an artificial pancreas is a multi component system there is a major challenge in integrating components. So traditional artificial pancreas development involves a single company developing and marketing a whole AP device; the sensor, the pump and the algorithm.

An alternate pathway of artificial pancreas development involves different companies developing and selling the different components of the system. So for example one company would develop an algorithm that was maybe running on an App that would communicate with an insulin pump and sensor developed by two different companies. This second development pathway should provide more choices to patients regarding artificial pancreas system components and allow faster development and faster patient access to artificial pancreas technology.

Of course getting different devices from different companies to work together reliably poses certain problems that will require technical solutions like having defined device specifications to insure that each device performs as required. And this kind of effort will also need a way to insure that the component devices communicate together reliably and this might involve interoperability controls or standards.

And then, of course, there is the issue of responsibility; that someone will have to be responsible for investigating and resolving complaints and not just for each individual system component but for the system as a whole. And similarly someone will have to be responsible for investigating and reporting adverse events and insuring that any problems with the system are fixed and don't recur. And finally someone will need to be responsible for how modifications, upgrades or next generation versions of the individual components affect the system as a whole.

So at the end of the day the system essentially has to work reliably and someone needs to take responsibility to make sure that it does.

So in summary enhanced interoperability of diabetes devices had a lot of potential to benefit people with diabetes. It can result in a greater variety of available devices, more choices for patients, and faster development of new diabetes device technologies. It can provide for enhanced quality of life for people with diabetes in part by allowing them to draw enhanced benefits from existing technologies and increasing communication between patients and care givers.

Enhancing communications between diabetes devices is going to require enhancing communication between stakeholders, and the FDA looks forward to future public discussion on this topic.

Overall enhanced interoperability should lead to better care and better outcomes for patients.

And with that I'll stop so the next speaker can get into some more detail about the need for enhanced interoperability of diabetes devices.

[Applause.]

DR. YANCY: Thank you Alain for that talk.

Next we have Mr. Howard Look who is the founder and CEO of Tidepool, a non-profit open source effort for delivery of software platforms and applications that reduce the burden of managing Type I diabetes. Howard's career is now inspired by his teenage daughter, Katie, who was diagnosed with Type I diabetes in 2011. Today he will discuss with us the need for interoperability in diabetes devices.

Please welcome Howard.

NEED FOR INTEROPERABILITY OF DIABETES DEVICES

MR. LOOK: Good morning.

[Good morning.]

MR. LOOK: There we go. Thank you. Thank you for having me here. It is good to see everyone, some familiar faces in the crowd.

I was asked to talk about why interoperability is important. And so I am going to walk you through a bit of a journey of how I got into this. My background is not in diabetes; it wasn't until my daughter was diagnosed in 2011 that I started learning even what diabetes was and what insulin was and what diabetes devices could do. And that led me to this path of trying to make a difference to help people like my daughter with diabetes better manage their disease.

So I think of this as reducing the burden of Type I through access to data and interoperability.

I'll start by stating the obvious especially to a room like this which is Type I diabetes is a highly burdensome disease. I think everyone here knows that but I think it is worth reminding ourselves why this is so important. People with Type I diabetes and I should say I am mostly going to focus on Type I diabetes. I think everything I'm saying applies to anyone with diabetes whether Type I or Type II or other forms using devices to manage their disease. Type I is what I know best. I'm also going to often say when “I” have diabetes. I don't have diabetes, it is my daughter but it is easier to express these things in the first person.

So someone with diabetes makes 50 to 300 decisions a day. I didn't actually believe these numbers when someone first told me them until I actually started watching what my daughter, Katie, did. And some of the decisions are very simple ones like when did I last

check my blood sugar or kind of annoying ones like dah, where did I leave my blood glucose meter? Or do I have enough low supplies with me? Or how much insulin is left in my reservoir? And these are kind of the easier decisions that you encounter day-to-day. Then you get ones like well, how in the world should I bolus for that burrito; it is so complicated I can't weigh it, I can't tell what is in it, it gets hard. And sometimes it gets even harder, we have these devices that have settings that we need to change based on data, like what is the right basal insulin pattern for me? And what should my insulin to carb ratio be? Or ah I am going high for the entire day; it seems like I am doing everything right; did my insertion site go bad? And then it really gets tricky and again these could all happen in the course of one day. What do I do from keeping low when I exercise? Or what do I do when I get sick? How should I change my insulin dose when I am sick? Or I am over 450, maybe I have ketones, what do I do? These are all decisions that someone with diabetes encounters every single day.

So it is no wonder that there is such a great incidence of decision fatigue in people with diabetes. Sometimes that leads to depression or diabetes burn out which is really sad when you think about it because we can actually provide tools to make the decisions less burdensome.

And ultimately all of this leads to better -- if we can get this right, it leads to better outcomes, better safety and better health just like Alain said.

So I'd like to look at this reduction in burden with a very simple graph. The reduction in burden is on the Y axis, time is on the right and you are here now. So, far up into the right the ultimate reduction in burden clearly is a cure or a prevention of getting diabetes in the first place.

Now I am not a biologist, people I work with are not biologists. I am thrilled that

there are people working on this problem. I hope you all did the JDRF Walk and donated money to your favorite cause so that the people working on the cure can keep working on a cure. I hope it happens some day. It does make me sad sometimes. I have to remind my friends that my daughter is not a mouse and being cured in mice is not the same as curing my daughter.

The next best thing as Alain also described would be a closed loop system so automated insulin delivery, maybe insulin and glucagon together or some other form where software is making some of those decisions for you. That would reduce the burden.

If you read the testimonials of people who have done artificial pancreas trials the first thing they will say is I forgot what it was like to live a normal life to not have to think hard about what was in that food on the plate in front of me and to figure out how to dose for it. I could just eat and enjoy the meal and enjoy the conversation and enjoy my life. So clearly we want that to happen too. That will reduce the burden of managing Type I diabetes.

But there is a big open hole which is things that we can do now; things that will reduce the burden of managing Type I diabetes now when you start thinking about access to data and interoperability of devices. As a matter of fact there are so many things that can be done now that an entire movement has sprung up around it called "We Are Not Waiting". And companies like ours, Tidepool, efforts like Nightscout, CGM in the Cloud, the Do it Yourself Pancreas System. There are even people who feel like, you know what, I'm tired of waiting for a closed loop system, I'm going to think about building one myself because I know that is going to help my child live a better life. There are things we can do now when we have access to data and if we can make devices more interoperable.

So I apologize the formatting got screwed up a little here but I will tell you what

that bottom box says. What can we do now? Well I think of this as split it into two parts. One is access to data. And one is all about interoperability. And not just interoperability of devices which we are going to talk a lot about today but also interoperability of data; the ability to move data from one place to another and to put it into the system of your choice so that you can access the data however you choose. And when you increase choice you can reduce the burden of managing diabetes.

So I thought I'd take you through a brief thought experiment which is using digital cameras. This is circa 2000 or so when digital cameras first started emerging. And it was really exciting. Those of us that did a lot of photography on film were very excited at this notion of getting access to digital cameras. But in the beginning most of them, if not all of them, came with software and you pretty much had to use that software to get your pictures off the camera. That was a little bit annoying but it wasn't terrible because in general you only use one camera. Fortunately all the camera manufacturers settled on Jpeg as a format to view the pictures. So at least they all produced the same kind of picture. Imagine if they had not. Imagine if they had not only made you use their software to get photos off the camera but they'd also come up with their own image format. Hey, grandma, great news, I've got some new pictures of the kids I'm going to send you. Now I've got a Canon camera, I know my brother, Billy, has a Nikon camera, so you are going to have to install both pieces of software in order to view the pictures from all your grandkids. Fortunately that didn't happen.

But that kind of is what is happening right now with diabetes devices. We have separate software to access the data and yet again separate software to view it. Digital cameras got it right eventually; one piece of software to pull the data off the camera, another pieces of software, again your choice, in order to view it.

Now I didn't show the final consolidation here and I think that will probably come up at a future FDA workshop. Now nobody uses these digital cameras; right. We all use our cell phones. So cameras have all consolidated onto the cell phone. And I think that same consolidation is going to happen as well with diabetes devices where the interface happens here on one single pane of glass.

So we've got all these devices and it is much more complicated in the world of diabetes care because if I've got diabetes I'm probably using two or three or four devices. My daughter has a blood glucose meter in her purse, a blood glucose meter on her nightstand. We carry a blood glucose meter, we keep one at school. And then, of course, she has an insulin pump and a continuous glucose monitor. And every one of them comes with a different piece of software for getting the data off and for viewing the data. So you have to ask yourself, how are you going to do that? How are you going to access the data? How are you going to view the data? Well clearly I think the right answer is just like what happened with digital cameras. You should get to choose, it is your choice how to get that data. And it should be your choice how to view the data.

So let's take a look for a second at what happens when you can't get access to that data. And what happens when you don't have choice.

This is a screen from CareLink which as you know Medtronic pumps are the most popular insulin pumps. My daughter wears a Medtronic pump. And this is the screen that you see if you've upgraded your operating system and CareLink doesn't support it. Or you've upgraded your Browser and CareLink doesn't support it. And unfortunately this happens about every six months or so; every time a new release of MAC OS comes out. It takes a little while for CareLink to catch up. But maybe you can work through that, either they come out with an

upgrade or you can trick it and say no really I have an older browser even though you have a newer browser. But then maybe you are greeted with a screen like this which is hum, it is a Java plug in, maybe your Java is out of date or maybe there is this scary security warning.

Remember our job is to reduce the burden of Type I diabetes. I would argue strongly that this does not reduce the burden.

Here is a screen from another software management system, Diasend. In many cases this is the only way, the only thing available in order to access and view your data. This particular screen is a big spreadsheet of numbers and it may be a little hard to see on the screen but the numbers that are all out of range here are highlighted in bright, bright red. I may not want numbers that are out of range highlighted in bright red, throwing in my face that gosh, looks like you did something wrong here. That is not what diabetes is about. Numbers are numbers. I don't want to have to use this. I'd like to choose what software I get to use in order to look at my data.

Maybe I use a MAC; many pieces of diabetes software simply don't run on a MAC. Maybe I just upgraded to Windows 8 and the software that came with my device just doesn't run on the latest version of Windows operation system. It goes on and on and on.

When you have no access to data it means you have no choice. You can't choose to use a different piece of software to look at the data to help achieve more effective therapy. The data from the T1D exchange supports this. People simply don't upload their data. Fewer than 3% of people with a pump upload their data more than once a week. It is a little better with CGMs but not much. But a full 60% of people never upload their data when they have a pump.

Now some say that is just because people don't want to engage with their data.

And I disagree with that. There are plenty of people that want to engage with their data, who want to share the data with their doctor; they simply can't. I often say it is like crawling through broken glass. If you want to be an engaged patient, if you want to upload your data, it is just too hard. And as a diabetes industry we should be ashamed of that. This is already a burdensome disease and we just made it harder.

When you have no data you have no choice and no choice increases the burden of managing Type I diabetes. And that is not okay.

Now all of this is premised on a very simple belief which is if I have Type I diabetes that is my disease and that data; that is my data. I think this has mostly changed but within the last few years there have been people or device companies or software companies who have said no, no, that is our data. We are letting you have access to it. It changed recently but there was actually a software provider of diabetes data management software whose end user license agreement said by uploading your data you waive all right, title, and interest to that data. Now they changed it which I am very happy about; so I am not going to point a finger at them. They have said very clearly yes, we understand the patient owns their data. But it is my disease; it is my data.

And when it is my disease and my data I should get to choose. I should get to choose what tools I want to use to see that data. I should choose who else gets to see my data. Do I want to share it with my doctor? Do I want to share it with my friends? And I should choose what other devices and also what other software I use to manage my Type I diabetes.

Now this is not a role that is that far away. That is the good news. Remember I am talking about things that can be done now.

Let me give you an example of how this is playing out. My daughter, Katie, uses

a Medtronic insulin pump. It is a great, great insulin pump. We love it. She loves it. It is just the right form factor for her. It works really well. But she tried the Medtronic continuous glucose monitor and it didn't work for her. She didn't like the insertion of the Medtronic CGM and we found it wasn't that accurate. And so before too long we gave up. Now fortunately the Dexcom GCM came out not long after that. And so we gave that a try. And it worked really, really well. The insertion was more comfortable and the accuracy was much better in our experience. So that is great news.

We've got an insulin pump that we love and we've got a continuous glucose monitor that we love and works really well for Katie's therapy. The problem, of course, is the devices don't talk to each other. And worse the data cannot be integrated.

I talked to an endocrinologist last week who has many patients on Medtronic pump and a Dexcom CGM and she described to me how she has gotten really good at holding the printouts up just right to the light and laying them on top of each and lining them up just so. I am a software guy and I think really? We can do better. Well it turns out we can do better.

So fortunately Medtronic allows you to download your data from the CareLink back end. They don't yet give you access to the data directly from the device. Dexcom does. Dexcom should be applauded for being very progressive about making the data protocol for their device available and allowing other companies to access data directly from the Dexcom receiver.

So what that means is we've been able to write some software that integrates the two. So we have the Tidepool uploader which can easily upload data and we have an application called Blip that integrates that data in one place at one time and also lets us share that data with doctors and friends so that we can easily make therapy changes looking at

integrated data.

But it isn't all just about Tidepool. And it is definitely not just about getting one new application to view that data. When you have access to data and you have interoperability what you are really doing is you are creating an ecosystem. We don't know what all the good ideas for diabetes software are yet. But if you have access to data and interoperability of that data and even better interoperability of those devices an ecosystem of applications will emerge and better ideas will keep coming.

I've talked to athletes with Type I who say I just want an App that integrates my Strava or my Runkeeper or my Fitbit or Fuelband data with my Type 1 diabetes data. We should be doing that. We should be seeing new mobile Apps that make it easier to figure out dosing. I know we will talk much more about that this afternoon. We should be taking all this data, integrating it, and releasing it as a research database which will allow closed loop researchers and prevention and cure researchers to have much better access to data to help with their research.

And we should be doing things like remote monitoring so that people can have their loved ones keep an eye on them as well.

So back to what can you do now? Again I think about this as two parts. One is access to the data and one is interoperability of both the data and the devices.

I might need a new battery in this.

So again my apologies for the formatting. What can you do now? Well first and foremost if you are a device company you can release the data access protocols for your existing devices.

Joe is going to talk in a minute about standards. We are huge fans of the

standards, you should do that too but don't wait for that to release data protocols for your existing devices now.

Companies like Asante and Dexcom and Insulet have done that. And for that they should be applauded. That is making things better. That is reducing the burden for people managing diabetes.

If you have a Cloud service, you should be exposing access to the data using RESTful APIs that is just a term for a way for Cloud services to talk to each other. It is what all the kids do on in Silicon Valley these days. It is not hard. Downloading a CSV file is good, exposing RESTful APIs data is much, much better and it is not hard. And an open offer to any company out there that needs help, we are happy to help with that.

And then finally and Joe will be talking in much more detail about this, you should be adopting standards like IEEE 11073. Once you have standards we will then achieve interoperability of data and devices. And that will be a wonderful thing. But again you don't have to wait for that. We can do things now.

So this is not a choice. When the autoimmune system decides to go rogue and attack the beta cells in the pancreas and stop it from producing insulin that is not a choice we have. It happens and that leads to the burden of managing Type I diabetes and that kind of stinks.

This is a choice and it is a choice we are compelled to make. We can choose to give people access to their data. We can choose to make that data interoperable, both interoperability of data and interoperability of devices. And that will reduce the burden of managing.

Thank you.

[Applause.]

DR. YANCY: Thank you Howard for such a great talk.

Next we have Dr. Joseph Cafazzo who is the lead for the Center Global EHealth Innovation. He is an Associate Professor in the Health Policy and Biomedical Engineering at the University of Toronto.

Today he will discuss the current status of efforts to standardize interoperability of diabetes devices.

Dr. Cafazzo.

CURRENT STATUS OF EFFORTS TO STANDARDIZE INTEROPERABILITY OF DIABETES DEVICES

DR. CAFAZZO: Thank you. Thank you for having me.

So part of what I do in Toronto is my lab happens to be at Toronto General Hospital and I do have clinical responsibilities for all the medical technology. So part of the comments I am going to be making today is the state of technology that we see in our hospitals, part of the capital purchasing process, and how the marketplace doesn't always meet the needs of hospitals, providers and patients.

So the way we got into this was a prompt from JDRF about the state of the research that was happening around the artificial pancreas, the significant investments that they had been making and the pace of the work that was being done on the artificial pancreas, and the concern that there was a lot of wasted effort, a lot of burn, on the fact that these devices did not communicate with one another.

So we suggested that there needed to be a concerted effort to start the development of standards around this. And JDRF graciously provided us funding because the development of a standard is an ad hoc volunteer process. Many of these ISO, IEEE, AME

contributors, they are volunteers to the process. So they work at the pace of a volunteer committee. And to have dedicated resources towards the development of the standard greatly accelerated our ability to develop these standards.

And why are these standards so important. It has been articulated a few times. But really the world as we know it wouldn't exist without standards. We wouldn't be here without the transport industry, planes, trains and automobiles without the significant number of standards that have been developed over the years in that industry, not only for the components and the products but also the safety standards around them. All forms of construction have building codes, standards around materials and so on.

And let alone what we are talking about today is data interoperability; the internet and the data communications, the mobile phone that you use has hundreds of international standards that are all necessary in order for that phone to work properly on multiple networks of different vendors.

So really what we are trying to get rid of through these standards and you have to get into the mindset of an engineer, and being an engineer I can probably appreciate this, is that when you are tasked to build a new device and you have very clear timelines it is very difficult to start thinking about pulling a standard off a book shelf and trying to adopt that standard. It is daunting. It is much faster to build what I consider an arbitrary data format and that is what most products do is they start building these arbitrary data formats and arbitrary data transport systems. They might again grab any radio system that they find that is popular in total disregard to a standard and just start using that because it is fast and easy and it gets the product out the door.

And as I said in the context of the artificial pancreas what the researchers that

were funded by JDRF were really concerned about was this redundant wasteful effort, time, funding, personnel just to get data out of the device communicating with their algorithm.

Now the other amazing thing about standards is what happens at a systemic level is that once the data is liberated and that there are these interoperability standards it encourages these new entrants. Both researchers, more researchers can come in. They don't need to start from scratch. They don't need to establish all these detailed relationships with these companies. They can get going much more quickly. And let alone the companies that could start coming online because the data is liberated.

And this is really at the key is the sort of hidden secret around standards. This is not about building a specific product. It is really about creating a new market ecosystem of innovation. New entrants and ideas and products that you would not even have conceived of prior to the development of this ecosystem. I am going to speak to that.

First I want to go back to the dark side as to why this is not happening. Why could not industry or the marketplace just address this? I am going to be blunt about this part. These are the things I've heard in private, in the open, at meetings such as this. Our product is too sophisticated. It is too complicated. There is no way you can capture our product, our product, into a standard. Well that may be true. But standards are not meant to restrict a manufacturer in terms of all the nuances, the special sauce that they might have, in their product. There are, however, some basics that we can capture.

So the standards that we've had a hand in developing are robust as standards must be. It is not as if people have not considered the fact that there might be parameters that are very specific to a medical device and there is room for those parameters within any standard.

This is another one. No time, no resources. And I am sympathetic on this one. It is because a lot of people have the impression that there are these massive engineering teams in these diabetes companies when, in fact, the person responsible for the communication of these data might be a team of only one or two people. And they are under a lot of pressure to have a return on investment, get new products out the door, through the regulatory process. And we are very sympathetic to the fact that they may not have the expertise nor the people in order to adopt these standards. And we are going to address that in the end as well.

This is a bizarre one. No one has asked us for a standard; right. And I think again if you ask someone with diabetes what they want. I don't think they are going to say well we need the IEEE 11073 standard; right. They are not going to articulate it that way. The standard is a means to an end. I think Alain and Howard have both articulated very clearly the demand, the need for this. Let alone groups like JDRF and Helmsley Charitable Trust and the researchers and so on.

Now this may be a bit facetious but these are some of the unspoken reasons why manufacturers have articulated. They want to maintain a level of control over the data. And there are levels of this. They are concerned about liability. Who's taking that data? Are we going to be on the hook for the use of that data? Now that might be a valid concern.

Now this is a big one. The idea that a third party would come between them and their customer; that is a concern. I am going to address that. Let's face it; it is a protection against competition. So breaking into what they perceive, a company perceives, as a complete system end to end, all your needs provided by one company. So why would you want to break that and have a third party come in and snatch away a component and the revenue associated with that. I am going to address that as well.

And I think this is the one that disturbs me the most and I think Howard and I have shared this experience before is that what is their view of the patient's role in self-care, self-management. So unfortunately there are companies out there that have a bit of a paternalistic view on the view of the data and we have to get past that because as Howard already said it is patient data; it is not the company's data. And in many cases patients really need access to that data to properly self-manage.

Now obviously here we are at the FDA. This FDA is motivated -- I don't mean to speak for the FDA but this is what has already been articulated is that this is good for the regulatory process. This takes out a lot of variability in terms of having some sort of predicate devices that already use these standards that are well understood. There is more transparency. There is not this black box of a transport layer in how the data is formatted. It is something that is open that people are aware of and there are no surprises. It is built on an industry consensus, these standards. The industry has come together to come to an agreement on how these standards should be constructed and used. And to a certain extent like Bluetooth low energy the profiles have a level of security in them that again is transparent, that people understand that is universal. That if there is ever a breach in a standard like there was with Wi-Fi many years ago there is a quick reaction by industry to address it and a new standard is deployed.

And the FDA has gone to great lengths in terms of recognizing these IEEE 11073 standards for -- this happened more than a year ago and a recognition of many of the standards around temperature, ECG and a number of other -- 12 standards that were recognized by the FDA and we are right on the cusp of starting to release the diabetes standards. And I'll get to that.

And you know this is good for business because in the end there are jurisdictions that are starting to demand it. You cannot even consider putting in a proposal during an RFP process in Denmark unless you are Continua compliant. And Continua I'll get to but it is the body that has been facilitating the development of these standards. So the reason Denmark is so committed to this is that as you probably know albeit a small country they have very sophisticated electronic health record systems in that country. And they are going into sort of the second and third generation systems where there is considerable amount of tele-monitoring, a lot of patient self-care devices, home devices and they realize that they are not going down the path that they've already gone down with EHRs. They want to make sure that everything they are buying is standards based.

And a lot of people say well you know to a certain extent isn't the consumer market addressing this; right. So there are these Bluetooth enabled weight scales and activity monitors such as Fitbit and lots of Apps right there. But I don't think this is enough for diabetes. The reason being is that and I think many of you experience this is that yes, there are standards such as Bluetooth and you can instantly very easily now even with Bluetooth LE start using your device quite quickly on your mobile phone but that is where it ends. It really stops there in terms of the lack of standards beyond the transport layer. All the data now is to a certain extent trapped amongst these little Apps or other smaller ecosystems.

And a lot of people -- I've been getting this question a lot over the last few months, Joe, hasn't Healthkit solved all our problems, it is aggregating data; right. It is aggregating all this data together. And hasn't Apple sort of addressed this. And you know what, they are thinking about not siloing this. They are thinking about how it is going to get to the clinic as well, which again is an important aspect. It is not enough just to get the data off

the device onto a mobile phone for transport but it is important to get it to the provider as well. And Apple has done that.

And you know I think Apple is very good and I have to give them credit for being the first to drop Bluetooth low energy which is a very popular standard. They've done a lot. Remember that they are the ones who sort of first even started adopting USB back in the late 90's, they were the first. But in terms of data Apple wants to somewhat control this. They want a *de facto* standard around health. And it is a noble effort. And they are making lots of deals with a lot of -- Epic and perhaps even Cerner. But the notion of *de facto* standards are not necessarily a good one for industry.

The *de facto* standard is not necessarily an open standard. It is the standard that has occurred just because of the accumulation of market share. And every company wants to achieve this. They want to become the *de facto* standard, of course. They want to be a Microsoft that Windows is on 95% of personal computers around the world. That is an incredible standard. It is a standard; let's face it. 95% of all personal computers. And this is another one that we've been living with for 25 years. Word as a standard, it is a *de facto* standard for documents. There are others like PDF but let's face it most of us in order to get the work done even whether we like it or not we are stuck with Word. And it doesn't necessarily allow for a lot of innovation when it is tied to a single company.

So HealthKit is there. And a lot of people are talking about it in a context of diabetes. But there is another real reality here. It is a different place. It is not Microsoft versus Apple anymore like in the 80's and 90's because and we don't talk enough about this but if we are really trying to get people to access their own data we have to be cognizant of these figures. As popular as the iPhone is as it steals headlines everywhere they still only have about

a third of the market share and it is dropping. It is dropping. That is the US market share. And this is the global market share for iPhones. People are not cognizant of it and it is dropping. And yes there are like lots of android phones out there and maybe Google can do something about it but literally there are hundreds of different combinations and permutations. So this is not something necessarily that even a company as large as Apple can solve because I don't think we want products that can only work on about 10% of people's mobile phones.

I also have to point out that there is a lot of confusion that the standards I am going to be talking about are not about performance; right. There are lots of standards around the performance of BGM and so on. This is what these standards are not.

Now I want to talk about some successes of standards within the context of the medical device industry. So I have a -- you know my career now is 20 years and at the beginning of my career I was introduced to -- this was just coming out is this DICOM standard, the Digital Imaging and Communication in Medicine Standard. And I can't imagine what medical imaging would be today if it wasn't for this particular standard.

This is what it was like early 90's before DICOM. You've got these major players in the medical imaging space, GE, Siemens, Hitachi, Philips, many others; right. And this was the siloing. If you wanted to look at these images in a soft copy review and that is what people were expecting now that all these imaging systems were now digital and we were dropping and trying to drop film as much as possible. So these picture archiving communications systems you had to buy a GE system, you had to buy a Siemens system, you had to buy Hitachi and Philips.

And having worked in a hospital and being at the early part of my career involved in the purchasing decisions and seeing what other hospitals were doing around North America a paralysis set in. People did not know what to do here.

Everybody wanted to be the *de facto* standard. You know buy Hitachi, all Hitachi and you'll be fine. Buy GE and all GE, create a GE hospital and you will be fine. And you know with a large teaching institution such as Toronto General, Mass General, all these large teaching centers across North America and around the world it was an impossibility. And you know what, what was starting to happen were decisions around this were starting to become deferred. The paralysis set in. We were buying nothing instead of buying something because we could not deal with the intransigence of these companies in terms of not being able to have these images being communicated.

Just like Howard said this is the scenario where a GE imaging system, an MRI or CT would create a GE image that had to be run on GE software. You could not see those images on anything else. It is sort of a worse scenario than with the cameras.

Now this is what happened after DICOM. DICOM became the standardized data exchange. I don't know exactly what the tipping point is that these companies decided they had to do something. Perhaps they realized that they were limiting the marketplace by the fact that they could not move product because their systems were incompatible with one another. And what ended up happening was a renaissance. There were PACS systems by third party companies that started popping up and the incredible number of applications that started coming up and novel applications. And you know what; this did not hurt any of these companies. This started driving the sales of those imagers, MRI, CT, Ultrasounds, X-rays, nuclear medicine; started driving the sales because now the data was liberated. And there were new applications that people could not even have conceived of before. And you know what these companies shouldn't be alarmed. For one thing they were driving the hardware sales.

But you know whenever one of these very novel applications would pop up that

they felt that would complement their portfolio they would acquire them and roll them into their portfolio. There is nothing wrong with that. This is a true market ecosystem that was created. So PACS just took off. Where would your hospital be without PACS and again all these novel imaging especially in cardiology and areas of cancer, the imaging systems, the data fusion that was possible as a result of that standard.

So again this is what it was before and this is diabetes today. I haven't included all the companies but this is sort of where we are. We are like imaging was 20 years ago.

And what I am saying to these companies is that there is pent up demand. There is an ecosystem to be had if we just adopt a standard. There are -- you know what is possible is unleashing the marketplace in terms of developing applications that could benefit and drive the sale of diabetes devices.

Now we come back as to the main reason we wanted to do this was to facilitate the work around the artificial pancreas as Alain referred to it as the alternate pathway. And not only just at the local, the PAN, Personal Area Network, aspect but also extending that data off to the EHR, the PHR and tele-monitoring applications. So we turned to Continua. We felt that this was the best route. This is an industry consortium of hundreds of companies. And this is not a unique problem. They were looking at all these personal health devices, pulse oximetry, pedometers, weight scales, fitness equipment, medication tracking and glucose monitors, all these devices in the home and how is this going to get to other family care givers, disease management providers and their personal health record. So this has again been going on now for about eight years.

And what Continua is going to do is bring the best of these standards together under one umbrella working with ISO, IEEE, Bluetooth, USB and not just at the Personal Area

Network, not simply getting the data off the device to a local manager but insuring that it can get into the clinic and to other providers and other novel applications; so working together with HL7, IHE and so on.

And you know there are a lot of big players in this. And companies that you might not seem -- obviously there are companies that are medical device companies you see here at the board members such as Philips, and Roche, some big health care organizations such as Partners out of Boston, United Health, but also consumer companies, Samsung and so on, Orange which is a distributor. And you know JDRF decided to join as a promoter member because it was so important that they feel that diabetes data become interoperable. And there are literally hundreds of companies including some diabetes companies that are members of Continua. This is just a short list of some of them.

Again partnerships are so important in industry liaisons with again as I said the Bluetooth working group, IHE, HL7 and this is truly a global standard. These groups crisscross the globe, Asia, U.S., North America, and Europe. And they've been crisscrossing the world for the last six or eight years in developing these standards over time.

Now the Bluetooth standard is becoming quite mature. It is built off of -- everybody is very familiar with this is perhaps the most popular transport standard in existence. There are more of these Bluetooth radios built than any other form of wireless transport largely because they are built into almost every single phone is Bluetooth low energy. And now the Bluetooth working group has worked on specific profiles for medical devices including a standard on a blood glucose monitoring and very close to completing the CGM standard. And the reason they are very close is that it was dependent on the IEEE 11073 standard which extends the standard back from the transport all the way into the clinic.

And this is what the IEEE standards looks like. Down at the base level are the communication protocols, what we call the transport and including Bluetooth all the way up to these device specializations and you can see there is pulse oximetry and blood pressure, thermometers, weight scales, and the glucose meter standard which is complete, cardio and you can see insulin pump there and CGM which were added as a result of our efforts.

So this is how it sort of maps to the artificial pancreas is that you can see the BGM there with the Bluetooth low energy glucose meter profile which again is already complete and it is actually going into its second revision and as well the IEEE standard 11073 10417 standard again going into the second revision. The CGM standard, there is the CGM profile and the specific IEEE standard for that device as well as the pump. And that is how those map. And you can see that -- you can't really see it here but they work in tandem. The Bluetooth low energy standard works around the transport, the wireless transport of the data from the device to the manager or in this case we call it control. And the IEEE standard extends that data set all the way back into the electronic health record, the personal health record, and any tele-monitoring system.

This is the entire standards development process. You can see that the second version of the blood glucose monitor is now in drafting the second version of the standard. The first version is already out there. You can see now that the -- we are in the third revision -- the third balloting of the insulin pump, so it is getting very close to being completed. And you can see just recently the IEEE 10425 standard, the continuous glucose monitor standard, just recently published. And here it is. It is available now. It is on the IEEE Website. And we are going to be working very closely with manufacturers to get this into use.

And you know I have to acknowledge the team, my colleague, Nate Hamming,

who led the tiger team and all the contributions in order to get that CGM standard out in a very short period of time, less than two years in order to develop the standard and get it published. And you can see it is a mix of academics, people in industry, people in start-ups, widespread participation. Melanie Yeung who is in the audience today working on the insulin pump standard, again, a good cross section of participants on the tiger team.

So what is next for us? We are very fortunate that JDRF and the Helmsley Charitable Trust want us to continue finishing off these standards. But we realize that barriers to this still exists for the manufacturers. We really want them to embrace it. They are resource constrained. They don't have necessarily the expertise to take a document, a standards document and create a product out of it. So we are going to be assisting them, these industry partners, with facilitating workshops around the use of the standards, demonstrating the use of the standards, and actually developing and designing code for them to use in their product that they can freely use.

So really this is where we are at today. And what I am hoping is that we have a transformative moment, this tipping point that allows us to follow suit on another very difficult industry which was imaging 20 years ago. And have this; right, an ecosystem of companies and applications that we could not even have conceived of now. And so it goes and goes and goes.

I hope that within a very short period of time we have a thriving ecosystem of products and not just a handful of products to choose from.

Thank you very much.

[Applause.]

DR. YANCY: Thank you Dr. Cafazzo.

And at this time we will open it up to the audience for any questions that you

may have for our panel of speakers today. If you could just come to the aisle to the microphones and again introduce yourself, tell us where you are from and then ask your question.

Q & A

DR. KLONOFF: David Klonoff, Diabetes Technology Society. Thank you. And clearly there are benefits for patients. I want to tell an anecdote because we have industry here and it is helpful if industry buys into what you are all saying especially with what I heard you say, Joe. At the Diabetes Technology meeting about ten years ago we invited a speaker from Atheros which was later acquired by Qualcomm and he got up and said I don't know anything about diabetes but I know about flat screen televisions and when we introduced standards in flat screen televisions sales increased. And he said so I urge all of you diabetes product manufacturers to get some standards because then your sales will increase; people will find your products more attractive, they will use them more, and it is good for companies. So I think the benefits for patients that you described, all of you, are very real and for people from industry in the audience it is going to be good for them too.

DR. CAFAZZO: Yeah. Thanks, David. It is interesting because when I talk to a lot of diabetes device manufacturers I almost get the impression that the software is an afterthought, very secondary. I am not even sure they think of it as the source of significant revenue. And that is like again I am talking strictly dollars and cents from a business perspective is they are dead wrong. They are dead wrong and again they may not necessarily reap a direct revenue line from software but the driving of software, the driving of hardware sales from good software has clearly been established in other industries. I think I've demonstrated that. I don't know where companies like GE, Hitachi and Siemens would be

without the thriving ecosystem of PACS and applications that are driving the sales of the multimillion dollar imaging systems. The same can happen in diabetes.

MR. FLIS: Good morning my name is Mike Flis. I'm from Roche Diagnostics. I'd like to ask a question to Dr. Silk. Following up this idea of Continua being a method to demonstrate that your product can interoperate with several other devices; historically FDA has asked a manufacturer to provide data demonstrating that our device communicates reliably with a specific other device or several other devices. Are you about ready to allow us to say that we comply with the standards that are identified by Continua and make simply the claim that our product is Continua compliant?

DR. SILK: Actually I think I am going to hand this one off. Courtney?

DR. LIAS: Courtney Lias, FDA. So you know we have a long history of recognizing standards. So that is why we think that the development of the standards that Joe is mentioning is a good thing. So if there are standards out there and the companies are actually willing to adopt them and they become something that FDA recognizes you can say simply we conform to this data transfer standard and there is actually very little that we ask for in terms of pre-market review or anything like that for those types of things.

We believe it is a good thing to develop these types of processes. So I think that there would be no reason why we wouldn't be able to take a well developed standard, assess it, and hopefully recognize it for people to use.

MR. FLIS: May we take this one step forward. Imagine electrical safety we all put our underwriter laboratory symbol; that is what the public looks for. They don't know the standards that are involved with that, that just want to see the UL symbol. The Continua symbol could act in the same manner. So we'll comply with the standards. We wish to put a

Continua symbol on our device.

DR. CAFAZZO: I see your point. I think there has got to be sort of an evolution because we know what Continua represents is an adoption of a number of like in the case here we are talking about Bluetooth LE as well as the IEEE standards. So -- and I know Continua talks to the FDA and there has been recognition of the IEEE standards, and so on. Whether that is going to be almost like a building code or a level like a UL standard or CSA standard, that remains to be seen. And it is really sort of an evolution as the standards become more adopted and Continua gets their certification process more well established as well.

DR. LIAS: So I have a question. It was very helpful to see sort of the status of all these different standards that are under development and where they are. I was wondering if you could give your opinion, Joe, on the different industries so for example glucose meters, CGMs and insulin pumps and you can comment on third party software as well though I suspect they are all for this; sort of where they are in this space in terms of overall industry engagement.

DR. CAFAZZO: I have to call out Roche as being very instrumental in the development of these standards. They have been very engaged. Everybody did comment; we did have communication with Animas, Insulet, Dexcom. Dexcom has been supportive if not necessarily active. And Medtronic. It is one thing to be participating in the development of standards and another entirely in terms of the adoption. And we are working on that part. And you know we've been working at this for more than two years and we do see a shifting of the sand and understanding of this. And we are hoping that the tipping point is when one of the major manufacturers does this. Then -- and this happened in imagining as well, is that then everybody feels it has to be -- it becomes a cost of admission, price of admission in order to be

able to sell into the marketplace. So we are actively now we are with the help of JDRF and Helmsley speaking to these companies and facilitating conversations about the next generation of the next iteration of their product adopting these standards.

Again we are providing them everything they need from a CGM perspective. CGM is done. It is ready to go. Insulin pump and Melanie will probably comment on this later is because it is a therapeutic device it is a little bit more complicated. The read only version should be probably done within six months. Melanie is nodding to me. It is the command and control aspect which is a little bit more contentious that is actually something that even IEEE Continua has not contemplated something for a therapeutic device of such -- something that is potentially dangerous as insulin. But we will get through that. There is consensus that there is a need for it. It is important. And that aspect of the standard will follow within a year. She is not nodding anymore.

But that is the current status.

DR. LIAS: Thank you. I think we talked to you about this but we are interested in further public discussion to find out how FDA might be able to help in this area both finding out from you all who are working on developing standards and also from industry how FDA could facilitate this.

DR. CAFAZZO: So the fact that you recognized the first 12 standards for 11073 now CGM now joins those 12. So the conversation needs to be had in terms of an acknowledgement of recognition of that CGM standard.

DR. LIAS: Thanks.

MR. DUNLAP: I should give Courtney thanks for offering up the idea of how do we feel about it as patients are very interested in this. I think Howard you said earlier you give

a shout out to Dexcom for opening up their API or their standards and thanks goes beyond just Dexcom for that. I think that Dexcom came here and asked for that to be approved and FDA is working with Dexcom on an open area; so thanks to FDA for that. I think that the burden of diabetes to some extent falls on everybody. It falls on industry. It falls on FDA. FDA certainly spends a lot of time reviewing documents. Industry spends an awful lot of time making them. So thanks to Roche for working with Dexcom and Joe and other companies to have standards. Those standards will lower the cost for industry to produce tools for us. It will lower the burden for FDA to review those tools. And ultimately they'll give us the tools that we have been clamoring for.

I can tell you first hand this isn't academic; this isn't about an article in a journal or an end number or whatever. I have N of two, I have two kids with Type I diabetes, they were extremely reluctant to wear continuous glucose meters because it was one more thing they had to deal with and I can tell you that it has been 11 years and 14 days since my son was released from Children's Hospital Philadelphia with Type 1 Diabetes, not that I'm counting. I don't think that he has ever downloaded anything. And I'm sure that impacts his care. The reason I want him on a CGM is his A1Cs are so low the only way he is getting there is nocturnal lows.

So we need this for safety in a very real world patient centric way and we need you all to save money to get there. So everyone's interest should be aligned.

MR. LOOK: If I can just amplify one of the things that you touched on. So first Asanti should get credit for having been the first to say yep, we understand the value in giving access to the data. Dexcom and Insulet have done the same. We hope more will follow suit soon. We as a small company, as a start up, we also found -- we were actually here in Silver Springs three weeks ago I think it was and Courtney and Stacey and team made it very clear to

us that they see how valuable this is to patients and how getting access to the data and making the data available in a way that gives patients choice is not only a low risk activity but it is a very high benefit. But it can only happen when we've got access to the data. And so the FDA is totally supportive of this. I mean people are always going ah, the FDA must be slowing you down. No, it is not the FDA that is slowing us down. It is getting access to data from the devices that is preventing this from happening. And it is ultimately interoperability and standards that will allow it to happen even more and allow that ecosystem to flourish.

MR. PETRICK: Hi, my name is Nick Petrick. I'm from the FDA. And just I guess a little more information on that DICOM standard. The person from Roche asked about how the standard was recognized and, of course, the agency will recognize the standards for that and the companies will claim they meet those standards. DICOM is probably you are well aware, some people are well aware, it is very complicated. And these systems aren't trivial to make sure that they work with each other; that the software can actually interact with the imaging format; and the data that comes through. And there is also individualized company information contained within DICOM. So there is a lot of complexity to the systems. What DICOM does is run, typically at RSNA, Radiological Society of North America, meetings, connectathons and other interaction events where companies will come in in order to sort of meet the standards you need to go through these connectathons and determine that your format will interact with other companies and so forth and so on. And so that may be something that your group might think about doing or running as a group when this comes on line to determine -- because my guess is it is going to have the same problems. There is going to be a lot of complexity and variation of how things can be implemented, it is not completely fixed.

DR. CAFAZZO: No, it is already in place; that is what Continua does. They have

their connectathons and they are done quarterly all around the world for the Asian manufacturers in North America. So Continua again being an industry consortium thought through this and they again there is lots of precedents. And I agree DICOM is perhaps and in fact I think it is more complicated than diabetes. And yes the whole issue of DICOM conformance and so on. But the companies got through that and they reaped the benefits. And I would say it is not even that complicated within the context of diabetes. And so the certification processes are all in place. It is all there. There are opportunities on a quarterly basis to test the interoperability of your devices through these connectathons.

MS. YEUNG: Can I add just one more thing to that, Joe.

DR. CAFAZZO: This is Melanie Yeung from UHN.

MS. YEUNG: Yeah, so the IEEE and the Continua certification does have a testing process similar to DICOM where you have Plugfest. So these Plugfests are happening quarterly and around the world so that you can actually test, come to Continua and actually test for your device to be interoperable and go through a test tool. And manufacturers can download these test tools to practice or to test beforehand before going to these Plugfests.

On the Bluetooth low energy or now they call it Bluetooth Smart before actually publishing the 1.0 version or the full version of the publication of the standard what we have to prove is actually it gets tested and test cases are written even during the process of writing the standard. And so they've gone to the extent of you have to actually prove that there is an actual physical even though it is a black box somewhat of a tool that it is testable so that when products or when the standard does come online that all those glitches, all those minor things that you might find out when implementing those standard has been addressed. So both Bluetooth low energy and the IEEE group have this testing and certification process built in.

MR. JARRIN: Robert Jarrin with Qualcomm Incorporated. I am heartened to see Qualcomm mentioned in one of your slides, Dr. Cafazzo. We are also members of the Continua, obviously Continua Health Alliance.

We have a medical device subsidiary that is mostly predicated on medical device data systems. However we are partners with a number of blood glucose companies including some of those that have been mentioned here today. We have an investment fund that is invested in a company which has produced the first mobile blood glucose meter called Telcare. They are a local company.

As being members of Continua the last speaker just basically stated what I was going to state about the Plugfest. You know Continua really does do a lot of work in developing use cases, testing the protocols, using reliable standards, identify those publicly available standards and then working within the membership to insure that we can all use these standards in the most appropriate way. You know bench testing them et cetera, et cetera.

Michael Flis from Roche who spoke earlier I think he was trying to make the point and I would like to underscore that point that if we are using these available standards that have been recognized some of which have been recognized by the FDA the available next step for us is to insure that as a group they are working and working reliably. I think that would be wonderful if the FDA could consider giving a nod or a blessing to that as well.

Thank you.

DR. CAFAZZO: Yeah, and Qualcomm has been an amazing supporter of these standards and a major player within Continua. And I guess the bottom line is the message to that -- those one or two engineers who are working in the bowels of Medtronic and Dexcom and Insulet that there is lots of help out there in order to get this working within your system.

MS. YEUNG: I just wanted to ask a question but go ahead.

MR. BROWN: Okay. Adam Brown from diaTribe. Joe, I had a question on you said it is the second blood glucose meter standard. So there was one published it sounds like and then what happened, was it adopted, was it not? How did all of that work?

DR. CAFAZZO: Yeah, I can't say that we're thrilled about the adoption of the BGM standard. Roche I believe used the standard on a meter that was marketed in Europe. It is now going through a second revision. I think also timing has a lot to do with this is that that standard was released I guess prior or around the time when Smart phone technology started taking off so in some sense the adoption of standards has to have this critical mass, this confluence of events. And perhaps that standard happened during a cycle such that there maybe was not as much of a need for a standard. But now given the proliferation of Smart phones I think the timing is good.

There was acknowledgement that the standard needed some revisions. And now it is going into its second revision. I think this is also acknowledgement how the level of flexibility around this is that if, in fact, industry is seeing some shortcomings to the standard they can be revised and amended. It is not as if this is a static document either.

MR. BROWN: And then just a quick follow up on that, maybe more for the FDA is the standard gets published and then what does FDA need to do to I guess recognize the standard is the terminology? Is that rulemaking? Is that -- what does that process look like so that we insure that what happened with the first BGM standard may be --

DR. CAFAZZO: And maybe Courtney can speak to that.

MR. BROWN: Cool.

DR. LIAS: Sure. We typically will review the standard; determine whether or not

it may be helpful for regulatory purposes, whether it meets our needs. And we can recognize an entire standard or we can also recognize parts of the standard. So that process goes that way.

It is also most helpful if we are informed or involved through the development center, so we also try to get involved in a lot of standards development processes. So if we are involved the whole way in we don't need to review it as much on the back end because we've been involved in the development. The ones that are developed then we have teams to review it and sort of decide to recognize.

MR. FLIS: Mike Flis again from Roche Diagnostics. That kind of gets to my next question. FDA doesn't publish standards, they acknowledge standards, they publish guidance documents and regulations which explain how we use those standards and bring products to market. So there are some guidance documents I have an interest in, the MDDS guidance was issued as a draft. Can we get a sense of when that particular document will be finalized? And will it make it clear for those of us in the diabetes community that CGM, a class III device, when the data makes its way into the software the software remains eligible for enforcement discretion?

DR. LIAS: Mike I am not sure I understand your second part. The first part I can't comment on timing for the MDDS finalization but basically the process is we get comments from industry, those comments are analyzed and I know that people are working very hard on that revision so there is an intention to finalize that guidance document.

With respect to CGM guidance can you clarify what you are asking for?

MR. FLIS: Sure. CGM is considered a Class III device now subject to the PMA rules. We anticipate the MDDS guidance is going to say that software that is used for tracking

and trending functionality is eligible for enforcement discretion. That implies that CGM data that makes its way to software that that software although it is capturing Class III data is eligible for enforcement discretion; will that be true?

DR. LIAS: So the MDDS guidance document, the draft guidance document doesn't directly address any particular type of device. It gives a definition of what an MDDS is or isn't. I do recommend you wait on the final guidance to see if it provides any clarity around that.

In the preamble to the MDDS rule it is very clear that active patient monitoring is not MDDS. Also products that do a lot of analysis are not MDDS. There is a mixture. We did recently though down classify software that does analyze CGM data to Class I exempt. So there are a couple of different pathways. Some products may be MDDS, some products may fall under this Class I exempt pathway which still is a very sort of straight forward pathway to market for that type of software.

MS. YEUNG: Melanie Yeung from the University Health Network. Question for you Howard. You mentioned about your issues with Katie's upload to the MAC OS or every six months there is always an upload error because of the OS upgrade itself but CareLink hasn't necessarily, their software hasn't necessarily been upgraded. And so we've heard from a lot of manufacturers about this maintenance mode and the issues with being able to keep up-to-date with some of the safeguards that the OS are doing, new operating systems, and so forth. I just wanted to see if your comments on how you foresee this maintenance of software happening in the future?

MR. LOOK: So the ability to keep software up-to-date gets much much easier if lots of people are working on software. When only one small team as Joe said in the bowels of

Microsoft is doing it I can understand why it is hard. If a company like Medtronic were to publish the data protocols to read data out of its device or support standards like Joe talked about then many many companies can be working on software to read that data and display it.

There are lots of ways to write software so that it doesn't become inoperable when an OS upgrade happens. Web software in particular should not be made inoperable. So it is actually a decision that Medtronic is making to say oh, you have a new browser that we have not seen before so we are not going to support it. It turns out if they actually for example supported HTML standards they would keep working. And it turns out, in fact, the decision to not let CareLink work when a browser upgrade occurs is a semi-arbitrary decision. It actually does continue to work; they are just choosing to say oh, the version number is bigger than I've seen before so until we know for sure I'm going to shut it off. But if they allow other people to write software, then lots of people can work on the problem and that ecosystem emerges. And that is what makes it better for everyone.

DR. CAFAZZO: Just to add it is again astonishing how few people are working on these software systems that so many people are dependent on. And it is not as if there were pre-release versions of Windows 8 and Yosemite that weren't available six to eight months or maybe longer before launch. But again when you are talking about a handful of people who have many priorities in terms of -- and again it is just an indication of the level of priority that software is for many of these medical device manufacturers; it is just not there.

MR. DUNLAP: Hi, Bennet Dunlap again. Maybe we should all just sit together at lunch and talk. Anyway in response to the MDDS docket Courtney had mentioned that industry had an opportunity to comment. My understanding is that the vast majority of the comments in that docket were from patients. I can only speak to the comment that I wrote

although I have a feeling that what I wrote was copy and pasted by a couple of hundred other people. And that was a comment about patient interpretation of risk and the differentiation of active patient monitoring which if we are a patient in the ER that is active patient monitoring; if we are at home with our CGM we don't see that as a risk that is not active patient monitoring. So in response to your comment I know that there were at least a few hundred comments to that effect on the docket.

DR. LIAS: Just real quickly on that one though I do want to clarify that the comment that active patient monitoring may not be MDDS does not mean it is Class III necessarily.

MR. DUNLAP: Right.

DR. LIAS: The other thing I wanted to follow up on was there may be several people in industry sitting out here thinking to Melanie's comment oh, well FDA would never let us just do those things, we have to check version control, or we won't have followed our software validation processes.

I do want to encourage industry to talk to us and we've talked to a lot of companies about this. One, typically even PMA supplements aren't necessary for operating system upgrades. And so there is no sort of regulatory submission burden on that type of upgrade. Two, we are very happy to talk to companies in the diabetes arena about processes that might be cleared or approved for them to do it on their own.

So even if there is some sort of an expectation that you meet FDA standards for software validation does not necessarily mean FDA has to pre-review it before those things are done. So I did want to mention that and encourage companies to talk with us if they have proposals on how to make that process easier for them to deal with.

MR. STEIL: Gary Steil, Boston Children's Hospital. I had just a quick follow up with Howard on this last comment about the browser update, the company checking the browsers; I don't know if we've validated this yet. And it came up earlier I think in Joe's talk about companies saying liability is potentially a reason they might not want to do some of this stuff. Where does the liability go in sort of a open source software that as we move data from a device to another device and then back let's say to a clinical decision making process and the new browser provided the wrong glucose information, who now becomes responsible in a kind of an open source world for that data, the actual number showing up in the clinician's hand being correct?

MR. LOOK: So I am actually going to restate your question because I think I know what you are getting at but to clarify just because software is open source doesn't inherently mean that no one is responsible or takes responsibility for that software. Like Apple publishes open source software. Google publishes open source software. Open source just means that your source code happens to be out there where other people can access it and see it.

So I suspect what your actually asking is what happens when it is a community led open source effort as opposed to a company led open source effort. Where does the responsibility go? And I think that is a good question and I think it is an open question. So there are some interesting examples going on right now.

Tidepool as an open source effort where we are an established entity and we have employees and we are a corporation that we have made the decision that we are going to in all other ways act like a company we just happened to have make the decision to be non-profit and open source. And then there is the Nightscout effort also a wonderful effort, also

open source but mostly led by volunteers. Actually I think only led by volunteers, there are no full time employees, no one getting paid by an entity, by a corporation to work on the Nightscout effort.

I think it is a good question. And I think it is an open question. I do think that we need to find ways to allow efforts like Nightscout to flourish. That is part of that ecosystem. We need to do it in a way that insures patient safety and efficacy. We need to do it in a way that allows patient choice. So I actually think it is not any different. I think a community led effort could deliver regulated software just as easily as an industry led effort can deliver open source software. And I think it is up to us to decide what is the most effective way to allow that delivery to happen. But I don't think it is any different at the end of the day.

DR. YANCY: Are there any other questions? Seeing none we are going to have a 15 minute break and then we will come back in 15 minutes and start our second session.

BREAK

DR. YANCY: If everyone can please take your seat so that we can get started with the next session.

So we are going to switch gears just a little bit and begin talking about Insulin bolus calculators. And our first speaker is Dr. James Mullally. He has his Ph.D. in Medicinal Chemistry from the University of Utah. He is currently a Medical Device Reviewer in the Division of Chemistry and Toxicology. And today he will be talking about what exactly does FDA do.

So please welcome James Mullally.

TOPIC 2: Insulin Bolus Calculators - Basics and Use

WHAT DOES FDA DO?

DR. MULLALLY: Thank you Jackie.

So yes I will not be speaking about Insulin bolus calculators myself but those talks will follow. Today I'm going to give you a very basic understanding of what it is FDA does and how we contribute to a healthy device marketplace.

So when most people think about what FDA does they tend to think about our role in the pre-market; that is our regulation of devices that are entering into the marketplace. But FDA plays in equally important role in regulation of devices that are already on the market. This is probably less well known because a lot of it takes place behind the scenes whether at the manufacturer, within the manufacturer or within FDA.

So I'll give you a little bit of insight into what is going on in terms of regulation. Some other questions that often come up are what is the value that is added to regulation? And so I'll speak to you a little bit about how we add value to the pre-market and post market again spending most of the time in the post market. And what is the right balance? As Alberto Gutierrez mentioned one of our major concerns is innovation in the marketplace. And the last thing FDA wants to do is be a road bump in the path of innovation. So we have to try to strike the right balance.

So how do we do that? Well a major consideration is that we strive to have the regulatory bar that is applied to a particular device to be proportional to its purpose and risk. So there are devices that we consider low risk such as data analysis software that are looking at retrospective data in which we feel patients are not going to be acting on that data. These types of devices do not require pre-market review but they are subject to device design controls and good manufacturing practices and certain reporting. I'll speak to you a little bit more about some of these elements later in my talk.

In addition devices that are of moderate risk such as glucose meters where patients actually do use the data that is produce by them to make treatment decisions and insulin pumps. In addition to requiring design controls and good manufacturing practices, et cetera, they also come in for a pre-market review.

High risk devices like AP systems require a more stringent level of pre-market review called the pre-market approval process which also includes inspection of the manufacturing facility and inspection of change control processes.

One further level I'd like to speak about which I'll bring back later in my talk as well is that of enforcement discretion. So devices that are under enforcement discretion are legally devices, however, FDA is choosing in this case to not regulate -- to not regulate the device regulations under the law.

But ultimately the goal that we have is to achieve that balance.

So what is pre-market review? Well it is an independent assessment of the analytical and clinical validity of the studies that are used to support claims that a manufacturer makes for its device. It allows us to understand how that device works and what its intended purpose is. And one of the common misconceptions is that perfection is required. But this is not the case, benefit versus risk is also considered. One of the elements that we look at that is going on behind the scenes at the manufacturer is design control. And I'll speak to you a little bit more about this in detail.

And so design control allows for a process that insures quality and safety in the device and that changes that the manufacturer makes to the device are deliberate and considered and that manufacturers are also following good manufacturing processes and that their labeling is truthful and accurate. So in a nutshell the pre-market adds a value that we

insure that devices that come on the market are safe and effective.

So what value does the post market add? Well in a nutshell post-market assures that someone is and must be held responsible for or accountable for the device. So manufacturers in order to do this employ manufacturing and design controls and again I'll speak more about these elements. But there are design control and risk assessment that are involved. Manufacturers employ complaint handling and adopt Corrective And Preventative Actions, also known as CAPA. And together working with FDA manufacturers also and others insure that proper reporting takes place and that corrective actions take place when necessary. And I'll speak to you about all of these elements.

And finally FDA has within its authority and when necessary to conduct inspections and have other processes which I'll talk about more.

So about design control there are multiple elements to design control. It applies to low, medium and high risk devices. And it takes place both in the pre-market and post-market. Some of the elements are that a manufacturer has to establish what their design requirements are going to be. So what will the device be? And what is the output? And verification is, does that output match up with our design requirements? And finally validation is insuring that the device, that output meets the needs of the user and the intended use of the device.

In addition there is software validation that takes place. And all of this is done in the context of a robust risk analysis. So that way during device development, or when changes are made to the device, the manufacturer can insure that the device remains within an acceptable risk. In a nutshell design control allows for the manufacturer to construct and change a device with an acceptable risk.

So what do manufacturers do to keep abreast of device issues? So I'll talk to you about complaint handling and CAPA processes.

So with regard to complaints manufacturers must maintain complaint files. And they have to evaluate complaints when they come in to decide whether or not they should be reported to FDA. And any complaints that involve device defects must be investigated.

As far as Corrective And Preventative Actions or CAPA is concerned complaints and other data sources whether they be internal or external regarding devices that might identify potential issues have to be documented. And when these issues are identified they have to be investigated down to their root cause. In addition actions have to be put in place that allow for addressing these issues and preventing recurrence.

So what these processes insure is that manufacturers are aware of device issues.

So what do they do in order to report device issues to FDA? And I'll talk to you about reporting and corrective actions. Medical device reporting is a process where manufacturers and others, because it also applies to user facilities and importers, can report the adverse events such as injuries and deaths. And when issues are encountered manufacturer can take corrective actions. This is often done in conjunction with FDA so corrective actions and product recall can happen. Those actions can take place with either fixing the device in place in the marketplace or they can result in product removal from the marketplace. But either way the decision and the timing of that decision is a risk based approach.

And so these two controls are in place to allow FDA to understand what is going on with devices in the marketplace.

So what other actions can FDA take?

So I'll talk to you about some of the other actions, inspections, et cetera.

So should FDA become concerned about signals it is receiving about a particular device, inspections are a tool that can be used to dig a little deeper into the manufacturers processes and documentation to understand what is going on. I should also note that inspections are a normal part of the pre-market approval process as well as periodic inspections take place for device manufacturers. So that is a normal part of the process. But in the case of device issues it allows us to dig a little deeper into what that issue might be. It means that there is a physical presence of FDA at the manufacturing site regardless of where that site is in the world.

And depending on the nature of the issue that is uncovered this may result in warning letters or other types of letters which are a mechanism for allowing the manufacturer to address any of those issues. In cases where FDA really feels the need to prevent product distribution in the marketplace there are also tools such as injunctions and seizures. And some money penalties are also a tool that can be used.

So again FDA really tries to maintain a balance between the benefits and risks of a device in their regulatory oversight that is applied to a device. And in that way devices of high, medium, or low risk can be balanced by the high, medium, or low level of regulatory oversight.

In certain circumstances enforcement discretion can be used. And enforcement discretion is a special case in which we strongly believe that none of the benefits of regulatory oversight such as design control, reporting, et cetera are required to insure public safety for that particular device.

So how can the public help?

So patients, health care professionals and consumers who identify problems can report those problems in several different ways. One of which is you can download the Mobile App, MedWatcher Mobile App and submit reports. Other way is to go to the MedWatch online reporting form and the address is indicated here and you can enter in device reports that way.

I'd like to thank you for your attention and hope you enjoy the rest of the meeting.

[Applause.]

DR. YANCY: Thanks, Jim.

Next we have Mr. Steven Scott who is a Divisional Vice President of Research and Development at Abbott Diabetes Care. He is leading the team that is researching and developing sensor based technologies. Today Steve will discuss manufacturer's responsibility in implementing insulin calculators.

Please welcome Steve.

MANUFACTURER'S RESPONSIBILITY IN IMPLEMENTING INSULIN CALCULATORS.

MR. SCOTT: Good morning all.

So I'm going to go through how as the manufacturer we designed what we have as a product that is actually not available here in the U.S. but a product that contains a bolus calculator within the blood glucose meter. I'm going to go through the design process, the risk management, the setup and use of the meter, bolus calculator, and the dose calculation, example dose calculation on the meter and then some field experience that we find with our calculator.

So basically need for a blood glucose calculator that can assist patients with Bolus insulin dosing. So basically there is evidence out there that people with diabetes are not

meeting their glycemic targets. People with Type II diabetes are not often advanced quickly enough on to insulin therapy to improve their diabetes. And health care providers will stick with a fixed dose of pre-mixed insulin because it is easier for patients to use rather than going into the more complicated insulin dose and regimes.

Here is what the problem we have. This is what a patient may receive if they are going on to a meal dosing regime and then they can see that here we have it split where your carb ratio. This is where the carb ratio is differential between breakfast, lunch and dinner. So you can see that one unit of insulin for every 12 grams of carbs, one unit of insulin for every 12 grams of carbs at lunch and then one unit of insulin for every ten grams of carbs at the evening meal. And then dose before the meal.

So insulin dosing is challenging and it is hard to learn , faces challenges in teaching the dosing, it is difficult and it is time consuming. There is also the patient numerous challenges for the patient; there is knowledge challenges, skill and time for the patient to be able to calculate their dose.

So here we see some studies of low numeracy skills and upon this only 41% of diabetic patients could calculate an insulin dose that required an adjustment for both carbohydrates intake and blood glucose level.

So do bolus calculators help? People have difficulty calculating the required dose for adjustment which results in dosing errors or suboptimal doses. And then there is evidence the bolus calculators can facilitate adjustable dose calculations which can result in better glycemic control.

So creating a bolus calculator? Let's build a calculator into a blood glucose meter that will perform the math that a patient would normally have to do on their own to calculate

the dose that the patient needs. So what does the patient have to think about when they calculate their dose? How much insulin do I need to cover my meal? Do I need to adjust my insulin for my blood glucose level? I took insulin some time ago, is this insulin still active in my body? Do I need to adjust my insulin for anything I'm about to do such as exercise?

So having established the need for a bolus calculator what would an organization have to do to when they go about designing such a calculator? So just to show at Abbott what we did this shows you that we started this process back in 2009 and we took input from over five and a half thousand patients in 1500 HCPs in 11 different countries around the world to understand the process for designing this calculator. So you can see starting back here in preliminary concept research we did some interfacing design research, couple of rounds of that. And then we did some human factors pre-work as well. Eventually we got through that into what we then in 2011 we started a formative human factors research and then we went on to our formal human factors research. And then we followed it up and I'll come back to this for the numeracy study using our calculator.

So when we design an insulin calculator we've got to deal with potential hazards and come up with design mitigations for these potential hazards. So through that process I just showed you where we have five and a half thousand patient input, 1500 HCP input we come up with the fact that there were some unique features needed in the design of our calculator. We need two setup options, there needed to be an easy setup option which was just a fixed meal dose and that can be with or without adjustment for glucose level. And we needed an advanced mode for carb counters.

So then it also contained that we needed as you saw earlier an option for variable meal, time of day correction factor. So change is a correction factor based on the time

of day. There was a need for manual insulin logging to be available on the system. And we also found the set on the calculator needed to be restricted to a health care professional.

What we did find is patients liked the idea of a suggested dose and calculated based on HCP instructions and settings. So there was a comfort level that we found when we spoke with patients that they liked the idea that they have a system that would give them a suggested dose that was based on input that the HCP input into their system. So the studies showed that HCPs were capable of setting up the calculator by the design we did and that patients were able to obtain and fully understand the suggested dose that the calculator would give.

So here is the basic understanding and comprehension. Okay. We offer different modes to suit the patient needs. The mode in the calculator was easier advanced. Meal marking carbohydrates so we could -- we have systems that have in terms of grams of carbs and we have systems that are designed in terms of servings and we have this setting which is just time of day setting that you can see here which allows you to adjust the carb to insulin ratio based on the time of day.

So we have general label mitigations that we put into the labeling for our calculator. We explain the use of the rapid acting insulin calculator so this is for Bolus insulin dosing. We explain that it is an optional feature and that basically the feature should be set up by the HCP.

So we have also labeling that is built into the calculator itself. So it doesn't show very clearly here but there is an instruction screen shown on the slide that basically says when a patient gets to a certain screen they can get contextual help by pressing the question mark, then they'll get a description of what that screen they are inputting actually does.

Then we have HCP phase in labeling which describes the HCP how they would go about setting up the calculator. So here you can see first screen the HCP see it says enter patient's meal, two parts to the set up, and other patient's meal time, insulin settings and then enter patient corrections settings. And again contextual screens that will assist the HCP during the set up process of the calculator.

So we have to think about errors that could occur during insulin dosing. So what are these errors? We could have carb counting errors directly influencing suggested dose; incorrect logging such as meal selection influencing suggested dose; and double logging can result in overdose. So again we build in mitigations to deal with this.

Again meal entry on the screen has instructions, a patient can see instructions. Here are two examples here with carbohydrates and the serving example. Prevent double dosing. So if a patient goes in and says I am about to take dinner and they already logged dinner that evening a warning will come up saying you've already logged the insulin for that dinner today and do you really want to log additional insulin within the device.

Use and dose adjustment. So there is a dose adjustment; a user can make a change to this. And you can see that when the insulin dose is given you can see there is a rate how the dose was calculated. So in this example here you can see the dose was calculated in terms of the amount of insulin for the carbs we are going to take, the amount of insulin for the adjustment of glucose back to target, and adjustment for active insulin on board, and then a user change. And if the user change is making a positive change there would be a warning that suggests that to be careful there because they could be using excess insulin and insulin could push them into a hyperglycemic level.

So other errors that could occur: if rapid acting insulin is not logged consistently

enough, user forgot to log the previous one or incorrect dose amounts are logged compared to what was administered. Again design mitigations. So we provide ability for the user to log a forgotten dose. So when the user -- so this is how the user tests their blood glucose, they get a result here, 143 milligram per deciliter, they'd hit the calculator button, the first thing the calculator would say is have you taken a dose since the last known dose within the system? And if they say yes it would take them through the ability to log that dose. So they can say how much that dose was and then how long ago did they take that dose. Appropriate cautions in the labeling it is important to log all your rapid acting insulin doses so your reader can account for active insulin when calculating your suggested doses. So it is stressing the point that failure to log the rapid acting may result in a suggested dose that could be too high. So if the meter is unaware of a dose of insulin that has been taken it cannot compensate for that.

And then also in the calculator we allow for appropriate dose resolution, the dose resolution could be to a single unit or up to half unit increments.

So preventing erroneous dose recommendations due to the incorrect calculator set up it is really key that the HCP setting such as correction factor, carbohydrate ratio and insulin duration are all set appropriately and that, therefore, the dose recommendations will be correct.

So the design mitigations we build in. We restrict the access to the calculator with a professional code that is assigned out to health care professionals and that it is stressed that it is only the health care professional that should be using this code and access the set up of the bolus calculator.

We provide step-by-step instructions on the screen for set up of the calculator. You can see you can either have the easy set up mode or you can tap to go to the advanced

mode and then the next screen will tell the HCP there is going to be a two-part setup for the calculator.

At the end set up complete and then we reinforced the description of the settings that have been used in the calculator so you can see here this is a calculator being set up in advanced mode, it has got a four hour insulin duration, the active insulin, BOB as we like to call them, bolus on board, active insulin is switched on, the carb ratio, one unit of insulin for ten grams of carbs, the correction target is in this case 70 to 130 mg per deciliter and the correction factor is 1 unit for every ten milligram per deciliter.

We provide the contextual help screens on this as well at each part of the setup. HCP can go in and seek contextual help screens on there. For example there are insulin calculator estimates the amount of rapid acting insulin still in your body. If you select yes, this estimate will be shown. The home screen has a symbol and then you can see our man BOB at the bottom of that contextual screen.

Other mitigations that we put in are under the hood as it were that we like to say in the calculator. If the time is set incorrectly, a change due to daylight savings time, we use relative time for insulin on board calculations so there is no direct impact. So if I was to put the clocks back, put the clocks forward an hour it is not going to calculate that I've used an hour more of insulin within my body. The insulin calculator uses the relative time.

To be safe we always round down the insulin units. Within two hours of another dose we do not allow the calculator to calculate a correction insulin. Below 60 mg per deciliter glucose levels we do not calculate an insulin -- give a suggested insulin dose. If the user actively changes a dose we provide contextual warnings as I showed earlier that this may cause an issue.

And then old blood glucose readings, basically there is a lock out on the calculator after 50 minutes. So you can take your blood glucose if something has caught your eye during the insulin calculator button was available on the screen, the screen switches off, you switch on the device, you can get back into the calculator and get your suggested dose but that locks out after a 50 minute period.

So the input to the insulin calculator is blood glucose level, correction factor, carbohydrate ratio and insulin duration. The meter input is the current BG result and the user input will be the carbohydrate amount in the advanced mode only and any user change.

Just to walk you through the set up in the advanced mode of the calculator. We go to the first screen, we select the advanced mode. Grams or carbs, we select grams. Then the question: what is the carbohydrate ratio, so in this case one unit of insulin for every 50 grams of carbs, we've selected -- I'm showing an example where this is allowed to be selected in terms of the time of day so I can have different gram to carb ratios for time of day.

How does the patient target their glucose to a single target or to a target range? So you can go to a target range or you can just say you want to go to a single target. It allows you four different setting of that by time of day. So in certain cases our research showed that the target range may be high in the evening because of concern over nocturnal hypoglycemia, so they might go for a slightly higher target in the evening. So we built that into it.

Then we next built in the correction factor. Again here we show an example of one unit of insulin will be given for every 50 mg per deciliter off of the patient target. Then we have the insulin duration a dial up insulin duration and then a selection as to whether you want the patient to see an active insulin symbol on the screen.

So basically the advanced mode, the suggested dose is made up of the meal

bolus, the correction bolus, then it is the active insulin is subtracted from that suggested bolus and then any user change that the user wants to make to the bolus because they themselves understand their disease and feel like I'm going to take slightly less insulin this time because I am going to do some exercise after I've eaten my meal.

Here is a work through example, you can see carb ratio here is one unit for ten grams of carbs, correction factor one unit for 50 milligram per deciliter. The target blood glucose is 100 mg per deciliter and the insulin generation is six hours. So blood glucose test is performed, a result of 204 occurs, a meal is going to be 20 grams, and active insulin you can see here is two units, time left three hours 24 on it. So we've got the calculation that says we've entered 20 grams of carbs, one unit per ten grams, we are going to take two units of insulin for the meal. The blood glucose reading is 204, target is 100 mg per deciliter, we are to adjust by one unit for every 50 mg. per deciliter, the correction dose would be two units of insulin. So now we've got the meal plus the correction dose, it comes to four units. In this case we've got two units still left in the body active so we take away the two units that are still active and the suggested dose that will be shown on the screen would be two units of insulin.

We got some usage statistics from our field experience of the bolus calculator. So we've had the bolus calculator in operation outside the U.S. since 2011. We estimate somewhere around about 600,000 users of devices that have the ability to have a Bolus calculator. Our analysis of meter systems and return meters and things like that show us about 60% of all these devices have the bolus calculator activated. So about 400 -- greater than 400,000 people on a worldwide basis using the bolus calculator.

We did a user study of 409 insulin using patients that showed 63% of those made an error when they were manually calculating their insulin whereas the error rate with the

calculator was 6%; those errors were due to patients making an error following the protocol rather than any error with the device itself. Whereas 83% of those people expressed confidence in their calculator and 87% said they would prefer to use the calculator to their manual method of calculating insulin.

As just as a complaint summary, looking at all this, you know one of the things we are happy to say because I was interested to hear the speaker before talking about the risk benefit. When we produced this device that is basically what we have to go through is we look at the risk versus the benefit and without the experience in hand you have to do your best to estimate what the risks are likely to be versus the obvious benefit of the device. And so we are happy to say that we have not actually seen a serious adverse event occur through the use of our bolus calculator in this field experience. So we have three years plus of field experience, approaching half a million users of the device and we have not seen any adverse event occur due to use of the device.

Okay. Thank you.

[Applause.]

DR. YANCY: Thank you Steve.

Next we have Adam Brown who is Senior Editor at diaTribe and the Head of Diabetes Technology at Close Concerns. Adam was diagnosed with Type I diabetes at the age of 12 and has worn an insulin pump for the past 12 years and a CGM for the past four years. Today he is going to discuss with us the clinical aspects and how patients use insulin bolus calculators.

Please welcome Adam Brown.

CLINICAL ASPECT AND HOW PATIENTS USE IBCs

MR. BROWN: Thank you. I really appreciate it and it is an honor to be here and to represent the diaTribe foundations. We are a non-profit organization and we are committed to improving the lives of people with diabetes and pre-diabetes and advocating for action.

By way of disclosure I am also an employee with Close Concerns. We are a health care information company. We only focus on diabetes and obesity. Some of the organizations that will be discussed today subscribe to a new service that we produce called Closer Look, that is both non-profit and for profit organization subscribed.

So and as was said I have had Type I for 13 years and also get to work with many patients in my work at diaTribe, so it is great to bring a patient perspective.

And just to start out I want to thank Courtney and Alberto and the whole team here for inviting patient input. That in itself is a huge, huge win and should be celebrated and acknowledged and it is noted and appreciated.

And I'd like to and all of us at diaTribe and patients in general want to be partners and we want to help the FDA do your jobs better and make them easier and help you understand risk benefits and we are absolutely your partners in that effort.

So to give sort of a brief outline, talk a little bit about how patients use bolus calculators, some of the risk of bolus calculators from a patient perspective and how those compare with maybe some of the other risks patients are taking on; discuss a few regulatory considerations and suggestions. And then close with some needed innovation in insulin bolus calculators.

So to prepare for this presentation since the topic is so complex we asked a lot of people in the diabetes community their opinion on bolus calculators; care givers, people who work in the industry, manufacturers and this is what one person said which I thought was really

important to start the presentation off. "I believe that the bolus calculator is one of the biggest leaps pump technology has ever made." And that is a driving crux of the beginning part of this presentation is that these are really, really valuable for people with diabetes. What is -- there is one important word on this slide though and that is pump technology which is where bolus calculators have to date been largely relegated to.

But this is why they are such a huge advance for patients and you heard about it from Steve just now. It is the math. It is simplifying the math that patients are doing at every meal when they are correcting their glucose trying to figure how to balance all these different factors. And just to run through a couple example scenarios we will see a lot of these in the afternoon so I'll go through it fast. But this is a simple calculation; right. So only a correction a glucose of 165, a target of 100, a sensitivity factor of 35, results in 1.86 units is the amount that a patient would get for that dose. This is a more medium calculation so you have correction for high plus you are eating carbs so add in 45 carbs, add in an insulin to carb ratio of 1:12 and you have not only the correction dose, you have to remember 1.86 units but then also the carb dose 3.75 units giving you a total dose of 5.6 units. And then here is more of a hard calculation right. So you have correction from the first example, carbs from the second example and insulin on board so adding in last bolus taken 3 units three hours ago, duration of insulin action, let's say it is set at four hours, that is a controversial point in the community but let's say it is four hours in this scenario, so add in the correction dose, add in the carb dose, subtract off the insulin on board and it is 4.86 units. So this is a lot of math to ask people to do in their head. Even if they are not carrying it to two decimal points it is three equations, remembering the answers from each and adding them up together.

And so this is why bolus calculators are a big advance for patients. They make

the math easier. And when we are talking about insulin which is one of the world's most dangerous drugs puts people into the ER at rates almost higher than any other medicine out there and we are giving patients insulin to dose and take themselves, it is really important that we get the math right. And the fact that bolus calculators help patients do that is really, really important.

The problem however and it goes back to the word I highlighted on that slide is that right now most patients don't have access to this technology. This takes CDC data, the 2014 fact sheet, it is also some internal estimates that we've done at Close Concerns and the estimates are about 30% of people with Type 1 in the U.S. are on an insulin pump, so that is about 70% that aren't on a pump with Type 1 who don't have access to a bolus calculator and I'll touch on meters in the next slide. And for Type IIs on basal-bolus therapy it is even worse 90 to 95% who aren't on a pump who don't have access to bolus calculator software to help them take the proper insulin dose.

And there is one meter in the U.S. that is the Roche Accu-Chek Aviva Expert; that is the only stand-alone meter with a built in bolus calculator. It was launched a couple of months ago. Definitely an important advance for patients. We'd love to see more meters with bolus calculators. It is really important from a patient perspective.

Close Concern's sister company dQ&A surveys over 10,000 patients a quarter. Right now there is only one patient in the panel on this meter so it is not to say that this meter is not an important advance, it absolutely is, but it is to say that we need many more like it.

So to touch a little bit on the risks of bolus calculators. I want to flip that on its head actually and say that bolus calculators reduce risk for patients, they don't increase it. And so it is probably the case that an average to bad bolus calculator is better than no bolus

calculator at all. And the reason is because a lot of patients are guessing and ball-parking which is something I'll touch on in the next slide which can have pretty important implications for the safety of taking an insulin dose. Using mental math as I showed in those three examples, trying to remember all the equations and add it up correctly is pretty tough even for people who have good literacy and numeracy.

A major, major safety mitigation in bolus calculators is insulin on board. That is what keeps patients out of trouble and when people don't have access to a bolus calculator it is hard to remember insulin on board. And you know keeping that in mind helps reduce the risk for patients.

And then you know some patients might just say forget it, I'm just going to each the same exact meal, I'll take the same exact dose every day and so if bolus calculators can make people's therapy and eating style a little bit more flexible that is an improvement in quality of life that is significant from a patient perspective.

And so this is what I'd like to say is sort of a real world scenario; the real world impact of ball-parking. So this is all the same data as the first scenario with one important change. There are six units of insulin was the last bolus and it was taken three hours ago. So there is one and a half units of insulin on board remaining. And so on the left side is the dose that you would get in a bolus calculator. And on the right side is what I would say is a ball-park or a more real world scenario, factoring in a slight error in carbs, say from 45 say you count 60 carbs which is pretty easy to do as I'll touch on later, correction feels like about 2 units, 165, my target is 100, 35 is sort of my factor. And it is hard to remember the IOB because you took the dose a few hours ago. And so there is a pretty dramatic difference when you ball-park between when you ball-park and when you actually put the calculation through the software.

So the second important point about the risk of bolus calculators is that risky calculations are often driven by bad settings, not the calculator itself. And the settings are often suboptimal, the feedback loops to improve them and optimize them are slow or they are non-existent. And we can do a lot better to improve these settings. So when you take people's pumps and John Walsh has done work on this, you take people's pumps and you look at the settings a lot of them end in five or zero just because the math is easier that way. They are not actually based on the sensitivity and the factors that patients need.

Often the initial setup is based on very general formulas, you know, 1800, 1200 but they don't account for the individual variance that a lot of patients will face. And then there is a certain aspect of clinical inertia where whatever was set in there initially will just kind of stay there.

And a lot of patients need varying formulas over the course of the day so people with Type I often have dawn phenomenon, they are more insulin resistant in the morning and they need more insulin in the morning to cover carbs and the lower correction factors and often it is easier just to have it throughout the day. So this is just to sort of add a point of nuance to bolus calculators and say that the risks of them can often be driven by bad settings and settings that we need improvement on and I'll touch on that in the last section.

So the third area is carb counting. I won't spend a lot of time on this but carb counting has a huge, huge impact input into bolus calculators. And it is really hard to count carbs accurately let alone factoring in fat and protein. So this is a cup of oatmeal measured in a measuring cup and then this is the exact same cup poured out on a plate. And it is really hard to figure out how many carbs are in the amount on the plate versus the amount in the cup. And it is just to say that carb counting is an important input into bolus calculators and that is

often where a lot of the risk stems from because patients are just misestimating carbs because honestly it is pretty hard to do this in the real world.

And so not washing hands is another big input to bolus calculators. This is a quote from a piece Gary Ginsberg wrote in the Journal of Diabetes Science and Technology. He said with a sample of .3 micro liters which is what is used in the Abbott Free Style strips for instance one micro gram of glucose which is the weight of a dust particle will increase the blood glucose by 300 milligrams per deciliter. So again a very risky bolus calculation might be where someone tests their blood sugar, gets a glucose of 300, enters in the bolus calculator they are actually at 100 and that is when the patient gets in trouble. And that is again to say that insulin is a dangerous drug to dose and bolus calculations that end up being risky may not be driven by the calculator itself.

So another key point that we really like to harp on is that diabetes is just so complicated and there are so many variables that affect blood sugar that it is actually completely impossible to make a perfect bolus calculator because at any given point in time there is something upcoming or something that has happened in the past that will impact the calculation that is going to be made and so whether it is carbs or exercise or medication or caffeine or glucose toxicity, being high makes you more insulin resistant. There are so many variables that are in this game that trying to drive to a perfect bolus calculator is actually an unreasonable standard.

So this isn't at all, at all to say that bolus calculators aren't useful. They are incredibly useful. It is actually the opposite, it is to say that one we need a lot more innovation in bolus calculators to account for all this variability and two we won't get to a fool proof bolus calculator because there are just too many variables to account for.

And so this is really an illustrative calculation; right. So all the same factors as before but add in you know I didn't get as much sleep last night, most people need more insulin when they don't sleep as much. I had a less than normal amount of activity yesterday, the morning bolus is a morning bolus so it includes carbs and fat, the CGM arrow is rising. So I mean what dose do you five in this case; right. So this is again to say there are so many variables here a calculator is going to be incredibly useful but it is never going to be perfect. And we have to be okay with that because we are asking people to take doses out there in the real world.

This is a quote that a Type I parent, an engineer, wrote and I think it is pretty great. "Insulin pumps precisely deliver inaccurate amounts of insulin" which is to say that when we are figuring out how much insulin to take there are these huge variables that are, you know carb counting and that are driving what amount to take. And often it results in an inaccurate amount of insulin but our pumps can dose at very, very precise intervals like .05 units or .025 units. But when the bolus is off by three units the clinical relevance of pump accuracy becomes a little bit less important.

So and then this is something you can see where I took the camera picture reflected off the CGM but this is a picture of my CGM from a couple of weeks ago and I was traveling and trying to manage insulin like every other day with Type I diabetes. And this is just to say that the risk of bolus calculation are a lot lower than just going to bed with diabetes; right. So I went into bed at range and woke up, spent four hours low and woke up. Didn't wake up to the CGM alarms because I put it on vibrate and just forgot to turn it back to loud. So I mean just patient real world errors. But it is just to say that when we are thinking about how risky our bolus calculators let's also remember how risky are the things patients are doing every

day.

So some regulatory considerations and suggestions. The first is that we'd love for the FDA to focus on presence versus absence of a bolus calculator; right. So a device that contains a bolus calculator carries addressable risk. There are devices on the market, they have bolus calculators, we have experience with bolus calculators. However a device with no bolus calculator carries clear risk as I talked about in the examples on ball-parking and mental math, you know, that is a real world issue for patients that we need to think about; so when FDA is evaluating devices that is an important consideration.

I think Steve really did a great job of showing what Abbott has done. I think Abbott with the Insulinx and showing the labeling and showing all the risk mitigations has really sort of paved the way for what we are saying on this slide which is just let's give patients access to clear labeling. How does this bolus calculator work? It should fit on one page or half a page or a note card. And it should be available online and easy to find. And the manufacturers should need to do simple software validation and some very basic human factors just to make sure that the dose that is being recommended is the actual one that it should be.

Going a little bit beyond that to say that clinical trials of calculators are needed or we should standardize calculators and they should all work this way is a little bit more tricky because when you start requiring clinical trials which are pretty tough to do in the area of bolus calculators and when you start standardizing things that is when innovation starts to get hampered. And so this is at a time when the community needs innovation the most. And I think the morning talked about how standards can really lay kind of railroad tracks for everyone to innovate in a really big way. And in bolus calculators I'm not trying to discount what was said in the morning but it is to say that if we want to incorporate CGM trend data and we

standardize Bolus calculators and say here is how a bolus calculator should work adding CGM trending data into a bolus calculator is really valuable. And we don't want to inhibit the innovation in calculators just by making them one size fits all.

So shared responsibility I think is another important point and it goes back to the idea that these things are never going to be perfect. And to add on to that no single party needs to be held liable for 100% safe operation. So patients shouldn't be held liable for that. FDA -- it is not on FDA to make sure that this is 100% foolproof and perfect and will be used perfectly in the real world. Industry also can't be expected to design a product that will be 100% safe and foolproof. So having all of the parties here share the responsibility so FDA making sure that some simple requirements are met, industry meeting those requirements, patients having access to clear labeling, HCPs being trained and familiar with the devices. Zero risk is probably impossible but if we share responsibility a lot of the risk can be mitigated.

And so to conclude the last part of the presentation and to discuss what we believe are some needed innovation in bolus calculators. The first goes back to the early part of the presentation. Only 30% of Type I's are on pumps. Only 5% to 10% of Type II on Basal-bolus are on pumps. Not enough people have access to this very simple software that can really help mitigate mealtime dosing errors. And so making sure that more standalone meters have bolus calculators, more validated Apps have bolus calculators, more Web based software have bolus calculators would be really, really beneficial for people with Type I and people with Type II who just aren't on a pump right now.

And striking the right balance between safety innovation can really insure that happens. So if you think about App makers historically are not experienced with going through the FDA processes. And they have maybe a different fresh mindset coming from an area that is

not laser focused on diabetes, maybe focused on user interface or other issues. But they don't have the experience going through the FDA process. And so making sure that the innovation and safety line is clear in the sand and appropriate so that people who don't have the experience in the space can come in and bring cool innovations to help people with diabetes. Apps is really important.

And then building meters with standalone calculators and Abbott has done this outside the U.S. and Roche has done it in the U.S. But getting more meter companies to do this just seems like a no brainer to us.

Another big one goes back to the risk of bad settings and bringing software that can help patients optimize bolus calculator settings, so ending in fives and zeros just for easy math, you know, we can run algorithms and analytics to optimize these and figure out what patients need. And it is hard to do this in the real world because there is again so many factors to consider. It is hard to do like a perfectly timed standardized test. You might be more insulin sensitive or resistant on one day versus another. So running algorithms over the long term in really good software to help patients optimize these settings would be really beneficial.

The third part and I mentioned this earlier is adding CGM trend information to insulin bolus calculators. So this is some really interesting work from Dr. Steve Edelman and Jeremy Pettus, they are at UCSD and what they did is they surveyed a bunch of Dexcom users and they said here is a case study, here is a scenario, here is the dose, here is what your CGM said, here is what your blood glucose meter says. How would you change the dose based on one trend arrow up? How would you change it based on two trend arrows up; one arrow down, two arrows down. And what they found is that people in the real world who are on CGM are making some pretty profound changes to the way that they deal with trend arrows and the

calculated dose that they get. So often you'll hear thrown around 10% to 20% adjustments based on the arrows but one arrow up people were taking double the dose, 111% increase in the three unit dose they would increase it to 6.3 units on average, 140% increase for two trend arrows up and about a 50% decrease for trend arrows down. So this is to say we have pumps that are integrated with CGM; they have bolus calculators in them, why can't there be a setting in the bolus calculator where I can set the percentage increase or decrease I want in my calculated insulin dose based on the trend arrow that the CGM is showing at the time. So I could say whenever there is a trend arrow up I want a 50% or I want a100% increase in the calculated dose and that way patients aren't having to make this manually. And oftentimes you might forget, you might be running through the bolus calculator and forget to look at your CGM trend and then that has a real impact. So the conclusion of this study was that people are making pretty significant changes. And I think it also speaks to the fact that real time CGM has a pretty big impact on calculated insulin dose. And if we can start to think about how to incorporate that into bolus calculators, that would be really useful especially as we move to artificial pancreas.

And then thinking on that point getting treat to range control after meals, providing a patient safety net, these are two examples from my own experience. The one on the left is going to bed in range, waking up at 2:00 a.m. low and then just completely overeating and starting the day at 265. And it would have been safer to have a very conservative range controller that kept me at 160 or kept me at 140 for the whole night instead of waking up at 265. And on the other side of the spectrum stacking insulin and going too low because nothing seemed to be working, having a mitigation system on the low end to prevent that would be really great.

So key take away considerations. As I talked about earlier bolus calculation is filled with complexity, it is filled with math even for people who are really engaged. For people that don't have a lot of fluency with numbers and don't have a lot of fluency with how dose calculation works bolus calculators are even more beneficial. And most patients though unfortunately don't have access to bolus calculators right now either to a pump or to a meter with a calculator. We believe that they reduce risk for patients especially those with literacy problems and are probably a lot less risky than things patients are doing on a daily basis. And when you think about all the variables involved in bolus calculation and all the variables involved in diabetes we are never going to make a perfectly safe bolus calculator, a zero risk bolus calculator and that is perfectly okay because the benefits of a bolus calculator probably in most cases outweigh the risk they are going to bring.

So ideally from a patient perspective we'd like to see that bolus calculators have clear labeling, have some human factors to verify that the system performs as it is intended to perform. But there is a lot of innovation we can do to make these things a lot better so we can get software to figure out how to improve the settings, we can get bolus calculators into the hand of more patients through meters, through Apps, through software. And ultimately adding in CGM trend information, adding in some treat to range control would be really beneficial.

So thank you very much for the opportunity to present. Really glad to be here and thanks to the FDA for holding an important meeting. And really excited and look forward to the panel discussion. Thank you.

[Applause.]

DR. YANCY: Thank you, Adam.

At this moment we are actually scheduled for lunch. So if you guys could table

your questions until this afternoon's session; that would be great. We are going to go to lunch now and return about let's see what time the schedule says; around 12:30. If you guys would come back around 12:30 that would be great. Thank you.

LUNCH

WELCOME BACK/ANNOUNCEMENTS

DR. YANCY: So, welcome back. Just another few announcements. This afternoon's session is going to be on Insulin bolus calculators Benefits and Risks.

We remind you that there is a kiosk outside of this room that will be open during our breaks.

If you have any questions, please come to the microphones in the aisles and speak clearly. Please try to speak into the microphone because we have people on the Webcast that may have difficulty hearing you if you are a little bit away from the microphone and also for the transcriber.

All right. So let's get started.

Our next speaker is Howard Wolpert. He is a Senior Physician and Director at Joslin Institute for Technology Translation. His professional focus is in Type I diabetes and the use of technology and intensive management. Dr. Wolpert divides his time between patient care, teaching, and research. And today he will be discussing the clinical validity of insulin bolus calculators.

Please welcome Dr. Wolpert.

[Applause.]

CLINICAL VALIDITY OF IBCs

DR. WOLPERT: I'd like to thank the FDA for giving me this opportunity to present

my perspective on the clinical validity of insulin bolus calculators.

So just my disclosures. I work with Abbott Diabetes Care in developing decision support software. I am involved in collaboration with Glooko around developing an App for hypoglycemia management. And I've also consulted with Tidepool around their platform design and system functionality.

So the agency has asked us to address four different questions which I am going to go through in turn.

The first question is how can patients and providers be confident that the insulin bolus values obtained from the calculators are accurate and appropriate for their use? And before diving into this I think it is worthwhile to really look at how insulin is actually used in practice. And I am going to illustrate that with an example of a patient of mine, Carl Smith, who died in 2006 and when I wrote the public media I dedicated it to him and he had a really interesting fascinating life story with diabetes which I think is pretty instructive in terms of the whole issues or how we dose insulin, the potential place of bolus calculators. He was actually diagnosed in 1922; this is same year that insulin was first isolated. And when he was diagnosed in the summer there was actually an insulin famine and this is before Lilly got involved in insulin production. And so he started insulin in December of that year and he lived a long and vigorous life. He actually died three weeks before his 90th birthday. He went out to play tennis in the morning and after his lunch didn't wake up from his afternoon siesta.

And I think the question is really why was he so successful with his diabetes. One issue is that he clearly knew his body's physiology and his glucose metabolism. The other thing I would say is that he was very independently minded and he ignored most of the recommendations he got from his physicians. And just when he first came under my care

which was in the mid-90s he was still taking doses of animal regular insulin three times a day before meals. He got up at 2:00 in the morning to take two units. And I dug into the paper charts which we had at the time. And in the 1950s he was seeing Alexander Marble who was Elliott Joslin's right hand man. And there were these letters telling him he should go on one shot a day of insulin, Lente insulin because it would be better for him than multiple injections. And he was an engineer who obviously this is a time before blood glucose monitoring was checking his urine glucose obsessively six to eight times a day. He knew that MDI was better than long acting insulin so he ignored the advice that he got from all of the leading diabetologists of the day.

So I think really what it comes down to is personal experience in the patient influence what is best for them. And really the patient is the ultimate decision maker in their day-to-day diabetes management.

And I think this is important context in terms of thinking about how we use bolus calculators or how we can expect patients to use bolus calculators. And that is I don't think my role is not just simply to prescribe insulin doses; it is really to guide the patient in making informed dosing decisions and managing their diabetes appropriately.

So I think this sort of collaborative approach to diabetes care, not just simply prescribing a carb to insulin ratio or a sensitivity factor. Really it is something that needs to be considered in terms of the way we look at the use of these devices and even when it comes down to potential testing or regulation from that standpoint.

So if you go back about two decades ago this is about the time when I was finishing my fellowship. This is through the standard insulin replacement regimen, regular in the morning, at dinner time, using MPH to cover lunch. As you can see there the challenges with

this type of program is that eating had to be organized around the insulin profiles. Insulin dosing was relatively fixed. From a standpoint of patient engagement obviously a program like this which doesn't provide much flexibility in a person's life is not something that promotes adherence and engagement in self-care because essentially if people want good glucose control they really need to let the diabetes and their insulin profiles and their eating patterns to dominate their life.

So where we shifted in the past two decades as shown here is to a more flexible approach to insulin therapy so called basal-bolus therapy. A couple of milestones along the way which I've outlined. I think obviously the DCCT was a huge impetus to the shift towards this approach to insulin replacement. The introduction of analog insulin was an important advance because with regular insulin people need a snack to cover the tail of their insulin. And then just over ten years ago the introduction of the first pump with a bolus calculator which was the Delta Cosmo and as you know the reason we are here today is that has become the standard in terms of the way insulin is dosed using pumps. And the formulas that are being built into those pumps are the formulas that are used in injection therapy as you well know.

So what I have up here is the standard sort of dosing formula that is used as you know to calculate insulin dose at mealtime. A person based on their carb ratio and their carbohydrate intake they can multiply that out and come up with an insulin dose.

What I should tell you while this is clinically validated, we know that it is helpful and it works and it is the underpinning of intensive therapy and improvement in A1C that we've seen over the past two decades. It has never actually been scientifically validated as working. And really the question is to what degree does this work in practice and there is our answer there yes, it works but not really as well as supposed.

So first of in this talk I really want to kind of go through some of the limitations and assumptions that underlie the kind of approach to insulin therapy. And really the one issue that I think is implicit in this is really the assumption that accuracy in carb counting is a realistic goal for most patients. And what for me was a real eye opener around this is a couple of years ago as part of a quality improvement project in the pump program at the Joslin in addition to multiple surveys we assessed patients carb counting skills with a range of different food models. I just have the data here. For patient's estimation of the amount of carbohydrates in a large apple, 30 grams of carbohydrates and as you can see they are very wide spread in terms of patient's estimation. I mean wildly inaccurate and it is independent of A1C. And we saw this with all the food types and what I should also mention is it is not as if there is a bias in patients consistently under or over estimating.

But I think what it really sort of points onto is that over time people learn experientially that they need two or three units for an apple and they may not know how much carbohydrates there are in the apple but they know how much insulin they need so the point I am making is I think carbohydrate counting is an important foundation but in day-to-day reality of dosing I think this data should make one pause about putting to much implicit faith in it.

The other assumptions that go into this calculation I mean the one question is with use of the insulin to carb ratio really assumes that dietary carbohydrates are the only macronutrient that affects insulin requirements. And as I am going to show you there is some data showing that that fat certainly is a big modulator. And then the use of the -- this approach assumes that getting the insulin dose is really all that matters. And really what CGM has open my eyes up to is the fact that to achieve optimal postprandial control one really needs to not only get the insulin dose appropriate for the carb load but also needs to match insulin action

with carbohydrate absorption. This is shown in this as most of you will recognize as an early mini-med CGMS download to this. This is a patient having cheerios for breakfast which has a high glycemic index so that means that 83% of the carbohydrates of the glucose in the Cheerios is going to be absorbed in the first two hours postprandially. On the top there you can see the insulin form and you can see the central challenge here is the fact that the insulin PD is much slower than the carbohydrate absorption so when one has an early postprandial spike and then later on postprandially the tail insulin kicks in and this person goes hypoglycemic. And the solution here in this particular situation is a change in food choice. Oatmeal which has a lower glycemic index and is a better match with the PD of insulin. You can see a much flatter curve there.

And really what it points to is that to optimize postprandial glucose control it is not just simply a matter of adjusting insulin doses. Sometimes patients need to change their food choices. And I think this in my mind sort of highlights the limitations of focusing on accuracy of bolus calculator settings as the key therapeutic end point when it comes to intensive diabetes management.

Another tracing this is a patient of mine who has steak and fries in the evening and you can see the glucose is going way high overnight. And it has been known for decades now that free fatty acids induce insulin resistance. As you know most of the research has related to looking whether this could be a mediator for insulin resistance in people with central obesity since they have high free fatty acid levels. It hadn't until recently really been addressed about whether dietary fat could modulate insulin requirements in people with Type II diabetes. So whether this FFA induced insulin resistance had therapeutic implications in terms of how we dose insulin in the management of Type I diabetes which was sort of the impetus of this study

which I did with Garry Steil so this is a study in which we brought in patients with Type I diabetes into the CRC put them on a closed loop system and then completely controlled their macronutrient intake. So they came in at noon. At 6:00 p.m. we started them on the closed-loop system and they were randomized either to a high fat or a low fat dinner. The two dinner meals had identical carbohydrate and protein but one was ten grams of fat, the other was 60 grams of fat. Closed-loop control continued overnight, through the breakfast and then the same scenario through the afternoon. And then they were randomized to the opposite meal and closed-loop control continued so we had two 18 hour periods of closed-loop control, one following a high fat meal, the other following a low fat meal. And this is the data from the glucose. So what is shown in the top panel is the glucose on the bottom panel insulin delivery by the closed-loop system. The green there you can see is high-fat dinner. What you can see there is the spot in the identical carbohydrate load down to the gram; patients were consistently higher following the high-fat dinner. And this is despite the fact that the control as you can see shown in the bottom panel was giving people more insulin.

So what this really kind of speaks to is the fact that purely focusing on carbohydrate intake is a limitation when it comes to current dosing formulas. What I should mention here is there is a lot of individual variability in terms of how much additional insulin people needed to cover the high-fat meal. You saw some individual needing almost double the amount.

So I think what this really highlights is that when in practice when it comes to achieving optimal control for patients with diabetes they really need to adjust their insulin dose based on either factors independent of whatever dose comes from a dosing calculation. So if a person is going to be active in the afternoon obviously they'll need less insulin. If it is a meal

that is higher in fat even with identical carbohydrate load, they are likely to need more insulin in that scenario.

So in answer to question one what I would pose is that all bolus recommendations whether they are generated by a bolus calculator or derived from a paper based algorithm are inherently inaccurate since they don't really incorporate these adjustments that are needed for other factors. And that in practice the way these bolus calculations are used is really as a starting point for patients when it comes to deciding on dosing and that based on people's experience in time most patients end up adjusting and optimizing their doses.

So in multiple different use case for the bolus calculator when people are newly diagnosed they are just getting a handle on how much insulin they need to take at mealtime. Obviously having a strict formula to follow is extremely helpful. Patients who are going through intensification of their Type I diabetes, somewhere later on in the course of their life's journey with diabetes but who aren't yet confident in self-management bolus calculator has enormous benefit and value. In time as people's self-mastery of their diabetes improves as they get a greater appreciation of all the caveats and the factors that actually affect their dosing requirements, the dependence and the use of the bolus calculator is going to wane.

And in my experience people with Type 1 diabetes who've had the condition for a long time what I would describe here as the maintenance phase many of them with Type I diabetes aren't using a bolus calculator at all because they know intuitively how much they need to bolus so they are bolusing experientially.

So I think one has to put this in context in terms of looking at the clinical utility of bolus calculators and where they sort of fit in even when it comes down to consideration of

whether they could be tested in clinical trials.

There are other patients who are independently minded or who pre-contemplated who are disengaged from the self-care who also aren't going to be using the bolus calculator. There are some situations where individuals incident requirements are changing physiologically a lot, childhood, adolescence, pregnancy, where the doses and the incidents of carb ratio and sensitivity factors are going to need to be adjusted quite rapidly over time where having a bolus calculator guide dosing decisions is extremely helpful. And that goes alone for use of a bolus calculator for example in Type II diabetes when one is titrating basal insulin levels or certainly in hospital based protocols there is an important role there.

And then another area clearly where bolus calculators are an enormous benefit in patients with limited numeracy or patients with impaired commission where they need something definite or specific to guide them in their decision making and likewise in patients where there is low confidence in their self-management decision making.

So question two which we were asked to address. What information do patients and providers need about how a particular calculator works so that they may appropriately use the calculator for their diabetes management? And what I've shown there is familiar to all of you, sort of the standard formula that used in these bolus calculators to come up with the recommended dose. And what I am going to be discussing here is some literature on how the differences in target doses in different bolus calculators affects the correction dose and then some considerations around a fairly contentious issue is the whole insulin on board and how to calculate that out.

So this is the paper in which they examined the effect of different target glucose goals as incorporated into the different bolus calculators on the correction dose which the

device generated. So looking at the different devices, the Animas and Roche bolus calculators will use the midpoint in the program target into the dose calculation. So if the calculator is programmed with a range of 80 to 140 it is going to calculate the dose down to 110. In contrast the Medtronic's system is going to calculate the dose down to the upper limit of the actual target there. So what they did in this protocol which was a head to head comparison of these three different pumps is they under bolus for meal and then two hours later corrected based on the dose calculator incorporated in the pumps. So with the MiniMed, the Medtronic system, the two hour postprandial glucose was 260, the dose calculator suggested 1.04 units. At six hour postprandial it was 155. For the Animas and Roche systems you can see there 226 and 231, post meal dose recommendation slightly higher shooting for a midpoint target, a lower postprandial glucose but there is more hypoglycemia with that approach.

Insulin on board as you know is an important feature in the bolus calculators in that it helps the patient to kind of compensate for active insulin on board and is important particularly in pump users since it is so easy to take bolus as an increase in risk for dose stacking, it helps minimize risk for hypoglycemia from that dose stacking.

So what is shown here is what is incorporated into the software of the pumps which is essentially a curve describing residual insulin after a bolus. So if a person takes a bolus of 120 minutes, 55% of the insulin is on board that is going to get subtracted out from the subsequent bolus, likewise if they take a bolus later on.

So the real contentious question around which there really isn't a clear answer is like how long do you actually set that duration of action curve. And the literature unfortunately doesn't provide too much clear guidance. So what I have shown here is PK and PD data from insulin and as a highlight on the top there in the top slide I mean one of the issues with PK data

which is often followed by clinician is what is in the package insert, so obviously it is very misleading in terms of getting a good sense of what the true action profile of the insulin is which is shown in the PD profile at the bottom. But you can see shown here and these are individual curves form different patients marked individual variability in the PD and the duration of action. Other factors that go into this as you well know is with increasing insulin dose is increasing duration of action, temperature is going to increase and affect absorption, exercise is another factor, where the infusion catheter is placed, how much subcutaneous fat is another variable. So it is not at all simple.

Another area where there are differences in the pump into the configuration of the instant action curve in the software relates to the shape of the curve where there is linear or curvilinear. In practice because there are so many other variables I don't think this really matters but it is more a matter related to competitive marketing between different pump companies in terms of what curve they actually include in their pumps. So I think the practical issue when it comes to setting duration or action really comes down to the clinical end point you are looking for. If the priority is on avoiding hypoglycemia a patient with history of severe hypos or hypo unawareness and then the imperative there is to reduce dose stacking one sets the duration longer because that is going to reduce the risk for dose stacking and hypoglycemia. The downside obviously is that if the duration is set too long the pump is going to over compensate for insulin on board and is going to be under dosing and the patient is going to fail to reach their glycemic target.

Another factor and I won't go into this in any detail but this is also somewhat sort of contentious is when doing the IOB calculation and calculating the correction dose should one subtract out the IOB from the previous correction bolus only or should one subtract it out

from the previous correction bolus as well as the carbohydrate bolus. And without going into the technical details it really depends on what type of meal or carbohydrate load a person has had. Approach one assumes that there is carbohydrate on board at the time that the correction dose is taken, so there is a low glycemic index meal. In that sort of situation if you have carbohydrate on board you don't want to subtract out the previous meal bolus you've taken.

Approach two assumes that there is no carbohydrate on board at the time the correction dose is taken so that is more appropriate for a scenario where a patient is following a high glycemic index meal. Bolus calculator is not going to know what type of meal a person is eating. In practice what it amounts to is that with scenario two you've got to have more aggressive reduction in the correction dose, this is going to provide more protection against risk for hypoglycemia.

So my answer to question two is firstly while patients need to know the key elements in dose calculations it is not realistic to expect most patients or clinicians to understand the complexities or nuances of IOB calculations. In practice I think it is obviously important to know whether the particular IOB setting or bias are too aggressive or cautious insulin delivery in terms of protection against hypoglycemia.

Thirdly and I think this is an important point in the context of the way the Agency may look at the regulatory pathway for bolus calculators. I would argue that it is impossible to perform scientifically valid studies to evaluate bolus calculators that would be generalizable to real world use.

So a couple of challenges to experimental design which I've outlined out there; firstly that it would be very difficult to have an appropriate attention control group where

patients were just as engaged but not using the bolus calculator. Secondly it is difficult to isolate the benefit of bolus calculator from other variables such as carb counting skills that are going to be determinants in use and success of the technology. I think a bigger issue really is when it comes to study design is how do you actually appropriately characterize the study population because as I was mentioning earlier the likely benefit from or the need for the bolus calculator is going to really depend on how much self-mastery a patient has around their own diabetes self-management. And then as I just mentioned there is inherent bias in the algorithms in terms of the way they would perform or based on the types of food choices people have.

So questions three and four in breaking down these questions I mean one question is how can the FDA foster both innovation and safety of bolus calculators? And then the second question is how does the intended use of bolus calculators by health care practitioners and patients differ? And I am going to answer that first.

And I think the important issue here to really consider is the fact that healthcare practitioners and patients are using bolus calculators in a different environment. And that the challenges and priorities of diabetes management in the medical facility, in a hospital are very different to what patients face in their day-to-day lives using a bolus calculator at home or out-patient setting. In the out-patient setting what I would argue is that the precedent when it comes to dosing is really on inflexibility in dosing. So patients need to learn that while there is maybe a prescribed dose that is kind of a base line that would be best to follow, that they obviously need to deviate from that in the context of say activity or alcohol or as I mentioned earlier if it is a high fat meal whereas the difference in the hospital setting is that the imperative there in a hospital oversight is that patients follow the prescribed medications that they are

given.

The other factor that I would argue and this also sort of relates to trials in the ICU setting there are fewer confounding factors affecting glucose control in terms of food intake, patients are usually in hyper alimentation, exercise is not a factor. You are dealing with foster action of insulin. And so the tight glycemic control is really easier to achieve in the hospital setting without deviation from a prescribed protocol. And so what this leads me to is that I think the scientific validity of dosing algorithms using the ICU can be evaluated much more readily that those of bolus calculators used by patients in the home environment. And obviously with these considerations in mind I think there really needs to be a difference in regulatory approach when you look at these two different environments.

So I am going to conclude with some comments really about where I think things need to go in terms of this whole space. And looking where we are today with regulated devices and then this completely unregulated ecosystem which has developed around Smart phones where there is enormous innovation in recent years but no oversight and no regulation at all. And what we are seeing and this is an App that I downloaded from the Internet here. It is an App which has everything that the Abbott Insulinx has in it. The only problem is that the default settings are very dangerous. This has never gone through any review process. If a person started using this it wouldn't be a good thing.

Here is another App and this is actually an App which in principle I think could be quite helpful. This is an App which is an application of the treated target algorithm used to optimize Atlantis treatment in patients with Type II diabetes. So from the standpoint of value I mean it's tremendous. The problem is that the glucose data entry is with a simple slider there and as you can well imagine very easy for a patient to enter the wrong number into the system.

A single slider and slip of the finger there and it changes from mg/dL to mmol/L, not a good thing. So these Apps are out there. They are of enormous value. They are being used but they are not going through any process of validation.

And so where I would argue we really need to be tomorrow in terms of balancing innovation and safety and essentially bringing in this whole ecosystem of Apps in from the shadows is into a regulatory environment where Apps that are used for diabetes management like this go through standard software validation processes. One wants to have the assurance that the calculator works accurately, that a person puts in a number, the number that comes out into the dosing recommendation is what you would expect based on the calculation.

I think the other opportunity represented by the platforms that are being developed by Tidepool, by Glooko is really to have veracity with the data inputs so that one has assurance around that.

And so my concluding comments around issues related to regulation of this bolus calculator is that different risk mitigation approaches in regulatory pathways are needed for software that simply operationalizes paper based insulin dosing instructions prescribed by health care professionals in routine diabetes management versus software incorporating more sophisticated insulin dose algorithms which are going to automatically optimize insulin doses without any health care professional involvement or verification.

So case two I would argue is obviously a situation where since the clinician is not in the loop there has to be full clinical trials to establish the systems are safe and effective. Whereas in case one what I would argue what is really needed here is regulatory approaches and oversight to insure that the software company adheres to appropriate quality control with extensive testing, usability studies and follow up oversight of user experience.

Thank you.

[Applause.]

DR. YANCY: Thank you Dr. Wolpert.

Next we have Dr. Jane Seley. Jane is a Diabetes Nurse Practitioner in the Division of Endocrinology Diabetes and Metabolism at the New York Presbyterian Hospital. She has published extensively in nursing and diabetes journals on the topics of diabetes management and education. Today Jane will discuss educating patients on the use of insulin bolus calculators.

Please welcome Jane Seley.

[Applause.]

EDUCATING PATIENTS ON THE USE OF IBCs

DR. SELEY: See I'm making trouble already and I just got here. Oh, look at that then I can see your faces. Thank you.

Okay. So this is my single disclosure for my one board meeting I attended last year but I am doing due diligence.

So I am going to be talking about some of my favorite subjects. Patients who are taking insulin by either the pen or syringe, not the pump patients, because these are patients that are often not brought into technology I have found. And I think that what we are talking about today is a terrific tool for these patients.

So in particular Type II patients who need to intensify their insulin regime to cover their meals. What I often find is that patients get stuck on just a basal insulin for a very long time. And part of that is the difficulty it takes to get that patient to be able to safely take mealtime insulin. And it becomes a whole process over years where we may start them with a

fixed dose with every meal, offering them no flexibility with what they can eat or when they can eat. It is very difficult. And it takes a very long time if ever to get them to the point where they can actually calculate the right amount of insulin.

The second group of patients that is probably my most common referral, I am using the best words I can use for them, is limited self-care in their history. I don't get the referral that way. What do you think I get told about the patient? They are non-compliant. So I seem to specialize in that apparently. I get all those phone calls. But I do find that many of these patients have never been properly taught to do whatever they've been asked to do. And not only that they've never been asked to do it. They've just been told to do it. So that is probably the biggest part of the problem.

So this is a great population to give them an opportunity to learn how to do it safely and correctly.

And the last and the hardest group is patients who actually do have low health literacy and numeracy who have never been considered a candidate for intensive management. And that is sort of my specialty is to find a way that they can do it.

So this is so interesting of all the people who know they have diabetes, so that is a lot of people, three million of them actually don't take any medication at all. So for the health care professionals in the room, what is the treatment at diagnosis according to the guidelines? Diet, exercise and for Type II? Metformin at diagnosis. So almost 15% are not even getting that message. So then we have almost 12 million on oral agents. And we are going to be talking today about the people on the right hand side. So we have almost three million people with diabetes that are taking insulin only. And then we have another 3.1 million that are taking insulin plus orals. So I'm going to make an assumption that the bottom group is probably Type

II but a lot of the people in the first group are also Type II because think about it, if 5% to 7% of all people with diabetes have Type I, probably closer to 5% these days since Type II has exploded, most of the people taking insulin are actually Type II, not Type I, so we need to focus more attention on these patients and how to get them to do it safely.

So this was given to me by my colleague Donna Tomky who is the former president of the American Association of Diabetes Educators in 2011 and we have another former president here, Melinda Peeples, I don't know if you know that. Melinda stand up for a second, come on. She is waving.

She wanted me to tell you that it is not easy to live with diabetes and that we spend a great deal of time as educators talking to our patients about many, many things. And the AADE7 highlights those main topics, healthy eating, being active, glucose monitoring or continuous glucose monitoring, taking medications and then more importantly problem solving, healthy coping and reducing risk. So it is a lot of stuff to talk about. And it is really a process over the entire number of years they live with the disease because there is always something new coming out. So whatever I taught them last year is probably not completely true this year. It is a good thing, they have to come back.

So I did some research on numeracy in the United States to diabetes. There was a recent published article just the other day actually, I just found it I think in October. So the definition of numeracy is the ability to understand and use numbers in daily life. So there are over 110 million adults in the United States that have limited numeracy skills. Two out of three adults can't do basic math. Now think about what we are talking about here. We are talking about all these calculations that Dr. Wolpert showed us. And we have only 1/3 of the population that even has a prayer that they could do any of that.

So people with diabetes have it even harder than most people because they have to use numbers for everything pretty much with diabetes management. They have to know that their blood sugar is good, bad, or indifferent; right. They have to be able to identify oh, it is too high, I need to do something and so on. They need to be able to count their carbohydrates. We've already learned that they are not doing so well at that. Oh by the way I wanted to add when you said that I was part of a study of diabetes educators who were all nurse practitioners who were specializing in diabetes and we were sent an email with pictures of food on the plate, ten pictures of food on the plate and we were asked independently, we didn't know the others were doing it or who they were to say how many grams of carbohydrates we thought were on each plate. And guess what? We could not agree at all. The data was really painful. And in the end the problem with that is we are the ones that are teaching the patients and we don't agree. So that's a toughie.

So this shows a sample of some of the questions that were asked on this diabetes numeracy test that was developed in 2008 and has been used extensively. And I want to point your attention to the bottom part. So this is a question asking patients to use skills about calculating an insulin dose. So they are being told there what the blood sugar is and that for every -- one unit of insulin for every ten grams of the carb and then they are actually given a chart, a very, very simple chart. Look at this chart. If their sugar is over 120 they take two extra units, all three meals are the same. If it is over 150 they take four extra units. If it is over 180 they take six extra units. So they have to calculate the one to ten carb amounts, you know how much insulin for that. And then they have to add this extra amount. So this is a simplified version of what we've been showing you; does everybody agree? This is much easier. They are being given the numbers. And it is a very small range. Only 33% could do that correctly. Does

that surprise you? It actually surprised me. I was sad.

So this is what I do all day. The first thing I want to do if I am going to try to get someone to calculate their insulin dose is I am going to teach them how to count the carbs and make sure, they've probably learned it before, they might have learned it 100 times but I want to be sure that they know what they are doing. So I am going to talk to them about which foods actually have carbohydrate that we count, because we don't count all foods. And they like to count things like cheese which we don't count and then to learn how to either estimate and do carb servings or actually count to the gram. So counting to the gram is harder for a lot of people. I may have to stop at serving sizes. So one carb serving is 15 grams and the patient might be told they can have four carb servings with every meal. So that is a very simplified version. The other way you can do it and with the challenges of numeracy you can tell them they can have 60 grams with the meal and then they have to figure out how to count up to 60 and for some patients that is very tough. And then you have patients mostly with Type I diabetes that they can have as much as they want as long as they take the right amount of insulin if their weight is good and their glycemic control is good.

But I am going to focus on the Type II patients where I am very concerned with their weight, I am concerned with their glycemic control, that is probably why they are seeing me today and I'm going to probably give them a limit on how much carbohydrates they can have, maybe three to four servings or 45 to 60 grams is a place to start and see what happens. So the next step then is calculating the insulin dose. So there are two main ways that we do this and there are controversies over this which I am not going to get into so I am just going to talk about these two ways.

Way number one is the simplest way which a lot of people use when the patient

is insulin naive. So I have no idea what their response to a unit of insulin will be. So we do what is called the insulin to carbohydrate ratio starting with one unit of rapid acting insulin for every 15 grams of carbs they are eating or for each carb serving. So an example of someone eating 58 grams of carbohydrate I would then divide it by 15 and I would come up with 3.86 units. So what do you think the patient is going to do with that information? Do you think they are going to take three units? Do you think they are going to take four units? Or do you think they might consider all the things that Dr. Wolpert said and decide if they should round up or down? There are all different answers to that and what each patient does is very different. I like the idea with a calculator that it is making a standard decision for them because at least that decision is based on science. And the patient might sometimes go to the lower end and sometimes the upper end for no apparent reason.

The other way that some people do it is the 450 rule. You might have formerly heard it called the 500 rule and some people might have other rules I don't even know about. But the rapid acting insulins we tend to use the 450 rule. If the person has been taking insulin we will add up all the insulin they take, their basal insulin, their bolus insulin and their correction insulin , we will divide 450 by that and that will give us their insulin to carb ratio. So in this case it came to 10.23 for this patient. That is a horrible number. I would never want to tell somebody to be calculating 10.23 because if they are doing rounding or if they are doing it in their head they are never going to be able to do that. So already I am going to have to start rounding and I'll probably tell them 10. So I'll say their insulin to carb ratio is 1:10. So then they would divide ten by the 58 and they would get 5.8 is the dose. And again what would they do with that. Would they take five units? Would they take six units? Who knows?

Step three is to teach them to calculate the correction dose. So the insulin

sensitivity factors more commonly called by patients as the correction dose is the amount of insulin needed to lower the blood sugar from being too high to what the target is. We usually start with one unit of rapid acting insulin for every 50 milligrams blood sugar that we went to lower it. So for example if the blood sugar was 207 and the target was 120 then I would have to lower the blood sugar by 87. If my correction factor is 50, I would divide it by 50 and I would get 1.74 units. What we like people to do is, take that number and add it to the insulin to carb number and not round either of them yet. Add them together first so you are only rounding once. But that doesn't always happen in real life.

The second possibility is the 1700 rule. And you'll hear other names for that. You'll hear 1500 is what we used to use with regular insulin, you might hear 1650, you might hear 1800. We have decided to use 1700 in our practice. So you are dividing it by the total daily dose and in this case it would be 44 which comes to an insulin sensitivity factor of 38.64, that is easy math; isn't it? And they would then divide and they'd come up with 2.23 units. So it depends on which way they are going to round.

So now the patient has done two major math skills. They've calculated their insulin to carb dose, they've calculated their correction dose, they added the two together. And then they have to because they are using a pen or they are using a syringe they have to round it. Now it is possible that they could use a half unit pen or syringe. I can't even count on one hand how many of my patients are doing that. They just don't choose to do that. I mean they could do that. But when you get to that point they usually are going to a pump to get fractions of the dose. And then they are hopefully going to consider all these other factors that we talked about.

So this is what is going on in the patient's head hopefully when they are taking a

dose of insulin to cover the meal they are about to eat and the current blood sugar. Hopefully they are thinking about what they ate, the type of food they ate, how much carb, how much fat, how much fiber, over what period of time did they eat that meal? Did they have any alcohol with that meal? On and on and on. Then they are thinking about their activity. What have they been doing lately? Have they been physically active? Are they going to be physically active after they take it? What kind of activity was it? Was it very vigorous? Was it very sluggish? Did they walk slowly, did they walk quickly? And on and on and on. And all this really matters when they take their medication. Did they take it before they started the meal? Are they going to take after they started the meal? Are they going to take it during because they forgot? Are they going to give it to themselves in a good site or a bad site? Are they going to prime the pen when they take the pen? Or are they going to forget the prime and have a big air bubble? What about that? That occupies space. I mean there are a million things that get in the way of it working the way we wish it would.

Then we have problem solving. So is their blood sugar high? Is there blood sugar low? Are they sick with something else? Or they have complications that are in some way impairing them from doing this correctly or making it not work as well. For example renal insufficiency; you would have to be very careful about how much insulin you take.

Then we have healthy coping. Are they under a lot of stress? Did they have a fight with their boss today? Did they leave something at home that they really need at work? Who knows; it all affects your blood sugar.

Depression is probably one of the most important factors in all of this because what happens when you are depressed. Do you feel like doing all of this? I know I wouldn't if I wasn't feeling happy today. So depression is a hard stop for a lot of patients in doing all the

things we'd like them to do.

And last but not least reducing risks. So all of these things are things that patients are thinking about or should be thinking about when they are taking their insulin.

So I am going to give you a couple of things that patients really do. So the first thing that patients really do, many do is choose their own math method. So they don't have a device like we're talking about and they are given this information, they are taught how to do the correction. They are taught how to do the insulin to carb ratio and now they are about to eat a meal. So I want you to be my patient for a moment and I want you to be good sports and participate in the exercise. So think about how you want to calculate; do you want to do it in your head, do you want to write it down on a piece of paper; do you want to use your cell phone, your computer, whatever you want to do. Get it out. I don't see people moving. Come on, you are going to help me with this. Even Dr. Klonoff is going to do this; right, Dr. Klonoff. He is shaking his head, yes. See.

So your insulin to carb ratio is 1:12. Your correction factor is 45. Your blood sugar was 229 about ten minutes ago. And your target is 120. You are about to eat 79 grams of carbohydrate. I want you to tell me how much insulin you would take. 1:12. ICR is insulin to carb ratio. That is my new favorite abbreviation. You are probably use to the I.C. The patients can't figure that one out so well.

So you take your one unit of insulin for every 12 grams of carb. And you are taking one unit of insulin to lower your blood sugar every 45 milligrams per deciliter. I see a lot of clicking. Are you doing it in your head? I just taught you. Okay. Do we have any volunteers? I know Adam knows. I am not going to ask Adam.

UNIDENTIFIED PERSON: Eight and a half.

DR. SELEY: Eight and a half. Well, let's see. 8.98 is the calculation, so you are very close. But if you were using a pen or a syringe how much would you take?

UNIDENTIFIED PERSON: I swagged it, so I --

DR. SELEY: You swagged it. Well it does come to 8.98 which is really, really close to nine so that probably would be a nine one. Good job. Did other people get nine? Good. A couple people. Probably a lot of people didn't do it. So this is what I see mostly in my real life. Sadly this is the magic wand method. That is me. I actually have a magic wand at work which I have to sadly pull out often. So this is what the patient does and then notice I say they check their blood sugar first. And I write optional because they may or may not have checked their blood sugar. If they are not intending to properly do this, then they really don't need to know what their blood sugar is. So they may not always check their blood sugar which is very scary to me but it is apparently not so scary to them. Then they look at the plate and that plate is 60 grams. How do they know that? Because they've seen that plate before. They've had something like that before or it looks like it should be 60 grams based on very little. And then they will tell me, this is one of the most common lines I get, when I eat a chicken burrito I get four units or whatever it is. So it is really funny because recently I met with a patient after her visit with the endocrinologist in my practice. I've known her for years. And I refer her to my practice. But I don't treat her because we've become friends and I don't think it is appropriate to treat her. So we went to the diner; that is where she wanted to go. And she actually did this magic wand method. And it was heartbreaking for me because this is a very intelligent woman that has very good health insurance and all the resources in the world and actually writes books about diabetes.

[Laughter.]

I am hoping she isn't writing what she does in the books. But never mind. So the funny thing is I called her on it and after we talked for a while I said you know what let's do a one hour postprandial and it was perfect.

[Laughter.]

And she had a lot of carbs. But she was right. So you see. It has to happen every once in a while; right.

Okay. This is the Einstein method. Scary, huh? It gets me a little car sick just looking at it. So this was actually given to me and this is really in use by a very dear friend of mine and former past president of AADE, Donna Tomky, she has some sophisticated patients in New Mexico that can do this. I have very few of them in New York. So she has actually -- this is very helpful because she's given them the numbers. Do you see that? So the numbers are already filled in, so the patient just has to go across. What do you think about that? What could happen with that? Because I'm the nervous type. They might not go straight across. They might go from here to here.

So I'm familiar with this kind of training in a much smaller scale. I frequently am asked to see patients in the hospital that are about to go home. They tend to call me five minutes before the patient leaves. They generally have their coat on and they are half way out the door and I'm coming to teach them everything. And so they tell me that they want this patient who is usually elderly, usually lives alone, usually has very poor or no insurance, to go home one shot a day basal insulin and calculate an insulin dose at every meal. So think about that. That means they have to check their blood sugar before the meal, they have to look at that number and based on that number look at a chart and make a determination. So my chart is a very small chart; nothing like this chart. My chart just has some glucose ranges by 50

milligram increments. So it says 0 to 69 and 70 to 100, 100 to 150, 151 to 200 and so on. So it is not a very big chart. And next to it, it has the corresponding number.

And then I play a game with them. Okay. So let's pretend you are at home tomorrow; you are making breakfast and your blood sugar is 292; how much insulin would you take? Maybe about half of them give me the right answer on that. They've got the chart right in front of them; this tiny little chart but big print. It is not about the print. They can see it. Then I ask them so your blood sugar is I give them something fairly normal, how much would you take? And they may or may not get that right. Maybe half of them do. But the answer they almost always get wrong is I say well your blood sugar is 68 how much will you take. They will give me a number. And right there on the chart it says if it is less than 70 that they are supposed to check their blood, every 15 minutes they are supposed to take 15 grams. It tells them the whole thing what to do about it. And nowhere anywhere says that they should be taking insulin. But they are prepared to take insulin for that. They'll usually go to the next level and tell me the amount of insulin for 70 to 100. I am not making this up. This happens all the time. And so what do you think that patient goes home on? I have to send them home on a fixed dose. I can't trust them to calculate. And in the out-patient setting I'm going to send them to a practice that I know has educators who will work them to get them to a level where they can start to do this.

So I think that is one of the most important messages I want to give you is that taking mealtime insulin and taking the right amount of insulin is a process that may take patients weeks to months to even years. From the point when we first meet them and they might just be on basal insulin and we want to initiate the mealtime insulin to get them to be able to do all the things we want them to do is very difficult.

So I look at insulin bolus calculator as an unbelievable tool for me to get patients there sooner and safer. I really do believe that this is a way that patients will be able to get the right information compared to these other methods that they are using and the mistakes that they are making that I don't even know about.

So I am hoping that this video is going to work. It is just a little over a minute. It is actually the free style insulin video for Canada. It is a promotional video but I want you to see it because it shows the couple of steps you need to do to get your dosing recommendations. And remember that I am showing you something promotional and I have no investment in this. But it was just such a nice way to show you how it works. [Video: Now I'm quite good at math. I mean if you give me a piece of paper and a pencil and a couple of minutes I can work out almost any problem. But when I check my blood glucose and for instance I'm a little high and want to know how much rapid acting insulin to take with my normal breakfast dose I don't always have time to do the math confidently. And I don't want to guess. So now I use this little device here, free style insulin. Quick. Easy. Accurate. Does the math and gives me a suggested dose? Plus I can put a picture of my cat on it. Yes you are in my glucose meter (meow). Anyway I talked to my nurse who quickly set up my free style Insulinx meter with my numbers. So now check this out. One I do a test. Looks a little high based on my target level. Two I tap calculator. And then the meal I am about to eat on this nifty little touch screen. Three suggesting dose pops up. My usual dose is four but the meter calculates based on how my nurse set it up and the meal entry I made a suggested dose of 6 units that could help me get where I need to be. And thanks to the free style Insulinx you know how much math I just did? Very little. It doesn't get much

easier than that.]

So that really was three steps. Did you see that. And the first step was doing the glucose. I really like that these devices both the Aviva Expert and the Insulinx that it is all put together so the patient can do it all on the same device. It is really key. And they also don't have to enter the glucose. You know how many times a patient will miscalculate the glucose when they are using another kind of calculator. They might enter the wrong number, they are not doing that. it is already in there. So that is one step that has eliminated a major source of error. So that makes me really happy.

This ACCU-Chek Aviva Expert is giving a warning that the bolus is too high and it is exceeding the maximum that you set. That is another very important safety feature that if the patient actually pressed an extra digit or something like that or some outrageous number it would not let them, it would be a hard stop.

So this is actually screens from the Insulinx. So what happens is the patient will always get an alert when they have increased the dose. So whatever the recommendation is if they decide to override it and do higher it is going to say that the amount you entered is higher which could cause low blood sugar if it is too much. So they want you to realize that maybe did you mean to do this. And if you did, I want you to think about it; is this too much or not. So that is great. I love something like that. And I think those kinds of alerts are really important.

But the second part of the alert that I really love on the right hand side is what I would see if I was downloading the device and looking at the memory and also what the patient has the capacity to see is the user change. So this really helps me because when I look at user changes when I get this device, we don't have it here yet, but I was just recently at the Diabetes Technology Certification course in Copenhagen and I was training people on this device. And

quite a number of people in the audience were already using it. And this feature is helpful for us to then review information and be able to maybe change the insulin to carb ratios as a result of learning that they always need more, they always need more and look it worked. So it is a great opportunity when you see this information.

So this is some treatment advice in addition that you get. And I think that is probably a Pandora's Box that we are opening for opportunity to give patients treatment advice in these devices all in one place. It could even be healthy messages over time that they could sign up for and maybe ask that they want something daily or they want it weekly or however they choose to get it within the device. Combining all of this technology into one thing is always easier for the patient. So this is giving a low hypo warning limit and it is giving you advice on exactly what to do about it. So based on how low it was it said how many grams of carb to eat and it is reminding you to retest. On the right hand side is a description about the insulin on board. So insulin on board if somebody is not using a device like this and they don't have a pump they are probably not doing that at all. They are probably not thinking well let me think when did I take that last shot and how many hours is that last and how much more is still in me. That is not happening. I don't know. Do you think it is happening, Dr. Wolpert? Probably not. Well he has very smart patients in Boston. I don't know it is not so good where I am for some reason. But he sees more Type I so I think that is a different population. With the Type IIs many of them think they have a touch of diabetes, you've heard that before. Yeah. So they don't think they have to do all this sadly. I made Dr. Klonoff laugh. I love that.

So it also gives you a description of it so the patient can understand it in words that they can understand. They still have two units active and it is going to be another over three hours until it is gone. So that might make them consider doing something differently.

So safety features that I think are really important. The way it is today in the case of the Insulinx in other countries they have to enter an access code to get into the settings menu. So this is a funny story and a true story. When I was going to speak in Copenhagen I was going to teach the Insulinx I had to teach it but I didn't have the calculator. So I need to see it. So one was sent to me and apparently came from Canada. So I decided to be practicing and learning how to do this so I could teach it in a few days when I am leaving over the weekend when nobody is around, of course. And I get all the way through all of the set up and then I find out at the end I can't finish because I don't know the code. I didn't know there was a code because we don't have it here. So I start writing to every country I know from the customer support lines, does anyone know the code? And ultimately I wrote to everyone in California and I was waiting to hear back from the people in California to get the code when I was telling this story to a co-worker that works at the hospital next door to me, he was my former student. So he takes it upon himself to help me out. And this is what he does. He Goggles it. And he finds a UK Blog that a patient asks on the Blog, hey, does anyone have the Canada code. And guess what, there it was. So I got the code four hours earlier than I got it from the company because I was in New York, there is a three hour time difference and because my friend Goggled it. So you know patients are going to get these codes. That is the bottom line. This is going to happen. So it is true, I couldn't make this up.

The second problem that we have with the Roche device is it requires a prescription which I like but it is only being distributed by health care providers as far as I understand it at the current time. So that is a tremendous limitation where it involves getting insurance clearance for it and a lot of extra work that frankly I don't have the time to do that. So I think a lot of people are going to say hey, I don't want to be bothered with this.

So I was told that some of the neighboring diabetes centers in Manhattan where I work actually have these devices already. So I thought I'd talk to them and see how it was going. Every single person I called had never seen it because this limitation of access has made it very difficult for people to get it in their hands. They can't get samples. And they can't get one for themselves to learn on. So I think they are working on resolving that but I actually think the restriction is what is making it so hard for them.

If a patient could go to the pharmacy with an Rx or whoever they get their supplies and get the device and then have some choices of how it could be set up depending on their abilities I think that would make more sense. So I thought about this a lot and what I thought might work, just my idea, you don't have to listen, is if a pocket card was packed in the device and the pocket card had all the settings prewritten on it and blank spaces next to it where either the health care professional would fill it in for the patient with them or I could even tell a savvy patient over the phone what numbers to put in or verify it with them. They probably know their numbers if they are savvy. They are doing this all the time, they are doing these calculations. I mean these are not really mystery numbers. These are numbers the patient should be using all the time. Or maybe they could fax me the form when they get it or I could have forms in my office I could fax them it filled out or email it to them so that they could enter it themselves.

The other thing I thought you might be concerned well how do I know they did it right. Well they could take a picture with their cell phone and then text or email it to me. And I could verify the settings by seeing what they did. I mean this is a new world we live in; right.

So there are ways to do this that would really make it easy to get into patient's hands. And we have to figure out how to do that because we have millions of people right now

who are taking no mealtime insulin or flat doses of mealtime insulin or fudging what they should be doing because they don't have things like this that could really help them.

So some other features I am thinking about and loving is firing an alert when they increase the dose is very important , so not just for the maximum dose, but whenever they increase the dose I would like to fire an alert to say, hey, are you sure? And then always, always, always that it goes into the memory so that we can use that as a teaching point when we are working with the patients to look at when they are giving extra and how they made that decision and make sure that those are good decisions.

When the glucose is low and there is some controversy about this but all the educators I work with all agree with me on this that we would rather the calculator not work when they are less than 70. Reverse calculations are very tough for patients and if somebody is sophisticated enough to be doing that they should probably be on a pump. And that you must be able to set that maximum bolus to me has to be a mandatory feature.

So the bottom line I think that many patients would benefit from guidance when they are determining their insulin dose however that guidance might be. I do believe that these bolus calculators are a great way to do it though and especially if they are incorporated in something they are already using. So I like that it is already the glucose meter and that the glucose result is already put into it, they don't have to put it in. So I am the one that develops the insulin order sets at New York Presbyterian, lucky me. I am the owner of them. I don't know what that means. I don't get any rent. It is very unfortunate. But one of the things I was able to do was every single patient that came in or went on glargine guess what dose they were started on? Every single patient in the hospital could be 200 kilograms, could be on steroids, could be all kinds of reasons why they would be very resistant to -- very sensitive -- resistant to

insulin but they were put on ten units. Where did that come from? I have a Zeneca person here. Because the original studies for glargine everyone was started on ten units and then they were titrated from ten and that stuck. So everybody gets placed on ten. It is ridiculous. I have got an average length of stay four days and you start people on ten or 200 kilograms. It is not even going to touch them. So I built a bolus calculator. I'm sorry I didn't go to FDA with it. Am I in trouble?

[Laughter.]

Using medical logic memory what it does is it pulls the weight already into the order set from the medical record. That was a key thing because I was concerned if the house officer had to enter the weight, they'd have to go looking for it, it would take them more time, they would hate that, they'd never want to use it and in addition they might put the wrong number. So I think that that step of that glucose going right in is the same kind of thing. It is very key.

And then in the case of my order set it actually takes into account certain sensitivities. So there are five different levels of intensity of that insulin dose. So they have to choose from the five looking at next to it, it says what each of them are. So for example the high dose order says for somebody who is morbidly obese or on steroids. So it is very clear what we think that patient will be. So that kind of thing I think is terrific.

So bolus calculators based on algorithms that we are already teaching people is a win/win, because everybody will be comfortable with it from the get go. So if we are using the same kind of calculations of the insulin to carb ratio and the correction factors and the insulin on board I would be so comfortable with that, I wouldn't need to know anything more if that is what was being used.

And I asked a lot of my peers including all the board members of the American Association of Diabetes Educators, I actually have to run out of here at 3:00 to go to a board meeting so I polled my entire board and I asked them what they thought was important and they pretty much agreed with everything that I said and especially the last one that they would be able to know the algorithm where it came from and that it was something they were comfortable with.

So that is it.

Thank you.

DR. YANCY: Thank you.

[Applause.]

DR. YANCY: Thank you both very much.

PUBLIC COMMENT SESSION:

DR. YANCY: At this time we are going to open up the floor to Public Comments. We do have quite a few people who have registered or during their registration identified that they wanted to speak at this moment. I have a list of those participants here so I'll do my best at calling out their names.

If you could just come to the front microphone here, identify who you are, where you are speaking from or what organization you are representing and limit your comments to four minutes. I want to ask my colleague, Jim Mullally to handle the timer for me or manually handle the timer for me. And then we will get started.

We have Bennet Dunlap, Ping Fang, Mike Flis, Niels Knutson, Anna McCollister-Slipp, Stephen Shaul, Scott Theil, John Towns, Jennifer Schneider and Mr. Altman. I don't want to mess up the first name. Okay.

Can I have Bennet Dunlap first?

MR. DUNLAP: Thank you. Sorry for taking your microphone there. Thank you Howard and Jane, those were both lovely presentations about the importance of doing this in the real world and I made a lot of comments earlier so I'll be super brief so you can have the microphone back.

I'd just like to say one of the components of all this process that needs to be considered is the blood glucose value that goes in from the finger stick. And as Dr. Klonoff and his peers have written in their journal and other places these things aren't all performing as we would hope they are. So I would encourage that when FDA has their new round of glucometer rules, hopefully soon, that they include labeling in there or that vendors seeking approval under that new guidance specifically ask for a label that says to dose insulin, to calibrate a CGM, to make therapy changes and to feed bolus calculators so that we know that we are using the accurate devices to start.

And that is all I've got. Thanks.

DR. YANCY: Thank you, Bennet.

Ping Fang?

MR. FANG: Thank you for having this forum. This is a wonderful event. As for the comments I was thinking looking beyond the need to do interoperability's can we look into how the different ways at the different places within the whole ecosystems to do interoperability. Identify the standards from the device to between devices, from devices to mobile units, from mobile units to the cloud sources, and to other systems. So I think this may help ease the burdens of doing interoperability's and provide a stage different ways to provide -- making progress depends on the device manufacturer's ability and their schedules.

The second point I was interested is through -- if we can make certain algorithms available both within the device as well as outside the device then we can make more innovation by third parties through software perhaps. But nonetheless if those algorithms are the same as the device used themselves then device manufacturers can be protected for their IP as well.

Thank you.

DR. YANCY: Thank you.

Mike Flis, F-L-I-S.

MR. FLIS: Good afternoon. This is Mike Flis on behalf of Roche Diagnostics.

I'd like to thank FDA for providing the opportunity for public comment and discussion. As mentioned earlier Roche has some experience with developing and commercializing devices with bolus calculators.

And based on our experience we'd like to offer the following comments in the form of answers to the four posed questions.

Question number one: How can patients and providers be confident that the insulin bolus values obtained are accurate and appropriate for their use? Bolus calculators are based on algorithmic models. The algorithm should be set up to insure they are physiologically based to include personalized insulin to carb ratios and insulin action information. Additional health event parameters such as exercise and stress can also impact recommendations made by a calculator. The parameters used in a bolus calculator need to be established by a health care professional to demonstrate safe and effective use. Validation studies must be conducted for any bolus calculator to insure accurate advice is given.

The second question: What information do patients and providers need about a

particular calculator? Bolus calculators may work differently. Both patients and providers need to know and understand what parameters are used in a particular bolus calculator and how they impact the bolus advice calculations to insure safe and effective insulin administration. And the opposite, both patients and health care professionals must know what parameters are not included in a particular bolus advice algorithm so these parameters can be addressed separately prior to determining insulin administration.

The third and fourth questions go to how can FDA foster both innovation and safety of insulin bolus calculators. I'll skip to our answer for number four due to time. By having some level of oversight of bolus calculators the FDA can insure continued innovation and use of safe and effective insulin administration for patients. The safe and effective administration of insulin may be greatly enhanced by the use of a bolus calculator by patients. However this should be under the supervision of a health care provider and adjustments may be completed based on the patient's requirement at the time in a treatment continuum. This may help bring greater patient engagement with their course of therapy and supports their self-management behaviors.

Thank you.

DR. YANCY: Thank you.

Niels Knutson.

MR. KNUTSON: Good afternoon. My name is Niels Knutson. I am the National Manager of Government Relations with JDRF.

I'd like to thank FDA for organizing this meeting today and for inviting community input.

I'm here to speak today and underscore a few points from this morning on

diabetes device interoperability which is important to people like me who have T1D. When I was diagnosed with T1D 17 years ago a blood glucose monitor, two bottles of insulin and a box of syringes were all I had to manage my blood sugar levels.

And since then new technologies have continually made life easier. Today I am fortunate to use an insulin pump, a continuous glucose monitor and blood glucose meter to manage my blood sugar levels. And each are a critical factor in reducing the burden of T1D on my life.

While these devices make it easier to maintain blood glucose control each must operate independently of one another limiting my ability to view or share with my doctor all available data points in one universal location. And access to a complete picture of data including bolus levels, basal rates, blood glucose levels and overall blood glucose trends would mark a significant advancement in T1D management.

Last month I went to the University of Virginia to participate in a clinical trial testing an artificial pancreas system where an insulin pump and CGM communicated through a third device to automatically control blood sugar levels. And using that platform I was struck by how useful it is to see blood sugar levels and insulin infusion rates collected all on one screen.

Looking more broadly any tool that would allow me to download data from my diabetes management devices into one place quite simply would improve my life and make T1D management easier.

In an ideal world I picture diabetes data management software that gives me options on how to view data, where to download it from, how to set alerts that fit with my lifestyle and a platform that keeps pace with the fast development cycle of consumer software so I can be assured that it is safe and current with modern technology.

Looking ahead JDRF is interested in fostering further development of diabetes software while supporting smart regulatory framework. We are particularly concerned with insuring that the T1D community understands the regulatory requirements of the many varieties of diabetes software on the horizon as most potential developers are not traditional medical device manufacturers.

Thanks again for the opportunity to speak today. We appreciate FDA looking to all stakeholders in considering device interoperability and look forward to the ongoing work ahead to advance this important field.

DR. YANCY: Thank you.

Anna McColister-Slipp.

Steven Shaul.

MR. SHAUL: Hello. I'm Steven Shaul. I am a patient advocate. I am 52 years old. Live in Baltimore, Maryland. I've been living with Type I diabetes for 23 years. Like everybody else who was diagnosed around the time that I was diagnosed in 1991 we didn't have a whole lot of devices available to us at that time. But we were thankfully able to use blood glucose meters that operated with just gave us a reading based on one single drop of blood.

Well today with the multiple devices that we have we are still operating under the same premise, single drop of blood to a glucose meter that then informs all the other things that then informs all the other things that we operate with. And whether it is a CGM or an insulin pump or a low glucose suspend system or something else we are still operating under the same premise.

And that is okay except when it is not because we still can't get that drop of blood or that CGM or that insulin pump or that LGS system -- we can't get what it is doing to

work all on the same platform informing the same data sources. Now that holds us up from sharing our data with our families. I'm not talking just CGM data. I'm talking about insulin to carb ratios, correction factors, insulin dosing guidelines; all of that. It keeps me from informing health care professionals on a real time basis either at appointments or if God forbid I wind up in the emergency room unable to speak for myself. It keeps researchers from being able to use my data to inform and support their discoveries. And it keeps the devices that I wear from working more efficiently keeping me from achieving better outcomes with less effort.

I am talking big picture here. Talking about multiple devices. And I realize that things have to go in stages and we can't have everything all at once but what I would ask is that when we consider interoperability that we consider multiple devices as we move along the scale of making things more interconnected.

I mean let's face it we are now talking about cars that can drive themselves, possibly delivering packages via drones but the diabetes devices I'm using are still dependent on year's old technology that is combined within the length, breadth and depth of the device itself for the most part.

If my data is available on one source where I can control who sees it but once I make it available it is easily accessible, that is the jackpot for me. Guess what if that ever happens I'm still going to want an insulin pump. I'm still going to want a CGM.

The talk about the proprietary nature of software or intellectual property rights, I totally understand that and I am respectful of that. But that argument doesn't hold water for me anymore. It is a 20th century complaint for a 21st century world. The software that is designed for my pump is not a separate line item. It is baked into the price of my pump. And really from a patient prospective I think it is more important and it is more helpful obviously to

have things more interconnected and available where everybody can get access to it and particularly me as a patient.

People with diabetes need and are deserving of 21st century technology that will not only help us reach better outcomes but will help those people who help us reach better outcomes.

Thank you.

DR. YANCY: Thank you.

Scott Theil.

MR. THEIL: My name is Scott Theil. I'm the Associate Director at Navigant and I'm here speaking on behalf of Continua where I sit as regulatory working group chair.

On behalf of Continua I'd like to thank FDA for hosting this workshop and providing some opportunities for public comment and discussion. We advocate that FDA take that next step and not only the acceptance of the 11073 standards but also move on to accepting certification against those standards in lieu of data that is being provided in pre-markets filings.

Continua recently entered into a collaboration with the mHealth Summit and HIMSS to create the Personal Health Connected Alliance or PCHA. So the focus for Continua has expanded even beyond where they originally started. But new PCHA is an extension of Continua's vision with a goal to create a market environment for personal connected health by generating greater awareness, availability and access to consumer friendly personal health technologies. This empowers individuals to better manage their health and wellness anywhere, any time.

I think from the session earlier today we all heard that interoperability is an

important thing to have. We've heard it in some of those speakers prior to me. We've seen it in the FDASIA Health IT Safety Report. We've seen it in the EU Green Paper. We've seen it in the Institute of Medicine Paper on Health IT and Patient Safety. I think we all agree interoperability is an important thing and we need to move more quickly to get to that point. We believe an active and purposeful design of devices and systems for interoperability can achieve in part through application of good science and engineering practices which are core components of an effective quality system.

We work collaboratively with IEG in criteria selection for a lot of the standards that we bring into our design guidelines as well as the implementation of the certification testing that goes on with that which is independent.

Continua's work has also inspired IHE to create a certification program similar to what we have. PCHA supports the efforts identified in this meeting and proposed in the FDASIA report around end-to-end device interoperability and certification. It is not just about getting the data back and forth between the various devices or even to the EHR it is all about getting good actionable information in a quick way and an easy way to the end users.

Outside of the U.S. we saw earlier today that there are countries that are mandating Continua design guidelines be accepted and be used. Continua design guidelines are also accepted and published in the ITUT as an International Standard H-810 earlier this year.

Continua and PCHA believe that the foundation of standards based on interoperability for personal medical devices and services has been created to a point it can and should be implemented consistently. To insure correct and consistent implementation of these design guidelines Continua created a strong certification process with a best in industry practice.

As part of our ongoing efforts to update the Continua guidelines as it was mentioned earlier today PCHA is working with IEEE to adopt new published standards for CGM as well as insulin pumps and we look forward to publishing those in our 2015 Continua design guidelines together with the Associated Continua Certification Program.

Again we call for FDA to acknowledge these types of certification programs as well as any particular device mark in this particular case the Continua logo to be accepted as proof of successful completion of interoperability certification.

Thank you.

DR. YANCY: Thank you.

John Towns.

Jennifer Schneider.

MS. SCHNEIDER: Hi I'm here talking on really as a patient advocate. I think that the really exciting thing about this discussion for bolus calculators is how it can lead to more patient engagement; really empower patients to be able to self-manage in a way that they can't without these bolus calculators. And with Smart phones being so prevalent right now and this really rich App ecosystem there is an opportunity to have a vast array of different bolus calculators. So you could really have a lot of engagement with an App that appeals to a teenager is probably different than an App that appeals to an older person or even a child. So I think that we have this opportunity for a great diversity of Apps and perhaps a diversity of algorithms to fit different needs especially with the App ecosystem where you could bring in other information like activities, other Apps that are being developed like Nutshell.

So I just think there is a tremendous opportunity here. Obviously the challenge for the Agency is to figure out where that line is that's been really what the talk for today has

been a lot on. And I wonder if that is really the role for some of the physician leaders and academics to help out in figuring out systems to really be the engine behind these Apps and then ways to validate that they are performing as advertised.

But I wanted to really underscore the opportunity here for a lot of diversity and innovation of these Apps that can really help and create engagement where we don't have that right now.

Thank you.

DR. YANCY: Thank you.

And Altman Yerachmiel (ph).

All right. Well at this time we are going to take a 15 minute break. We will reconvene at around 2:25. And at that time would the panel members please come to the front podium and take your seats and we will begin our panel discussion at that time.

Thank you.

BREAK

DR. YANCY: Can I ask all speakers to please come to the front and take your seats.

Thank you again. We are going to get started with our panel discussion. Moderating this panel discussion is Dr. David Klonoff. He is the Medical Director at Diabetes Institute at Mills-Peninsula Health Services at the University of California, San Francisco. He is an endocrinologist and he is always welcome here to moderate this session.

I am going to ask Dr. Klonoff to begin the session.

Before we begin the session I am going to ask each panel member to again introduce themselves and then we will get started.

Thank you.

DR. WOLPERT: Howard Wolpert. I am adult Endocrinologist.

DR. MALLALLY: I am James Mullally, I am a Scientific Reviewer in the Office of In Vitro Diagnostic and Radiological Health.

MR. BROWN: I am Adam Brown. I am a Senior Editor at diaTribe and also a Type I.

DR. SILK: I am Alain Silk. I am a Scientific Reviewer in the Office of In Vitro Diagnostics and Radiological Health.

DR. LIAS: Courtney Lias. I am the Director of the Division of Chemistry and Toxicology Devices here at FDA.

MS. YEUNG: Melanie Yeung from the University Health Network, Vice Chair of the IEEE Insulin Pump Standard.

MR. STEVENS: Hi, I am Alan Stevens. I'm a Reliability Engineer in the CDRH Office of Device Evaluation, General Hospital Devices branch.

MR. SCOTT: Steve Scott. I am from Abbott Diabetes Care. I run the Research and Development Department.

DR. SELEY: Jane Seley, Diabetes Nurse Practitioner at New York Presbyterian Hospital. And I do want to tell you I am running out of here at five to three to get my cab to the airport. So I am sorry.

DISCUSSION

IBC P ANEL DISCUSION

DR. KLONOFF: We've had some really good comment that I've heard today. We've heard medical, we've heard engineering, regulatory. Most have been in one of those

three areas. And what to me makes it so interesting is that insulin which we are talking about insulin dosing calculators, insulin is like no other medication. We know it is the most or second most dangerous medication in the world and yet we let patients go out and determine their own dose. There is really no other medicine like that. And using a bolus calculator can be a tool that can make the insulin dosing work better.

But what I've heard so far and I intend to ask the panel about this is what is the difference between doing basic calculations of the dose which are pretty simple like looking at the insulin to carb ratio and possibly looking at a correction factor and compared with doing more advanced dosing such as what a bolus calculator can provide. This would include factors such as foods that affect the glucose level besides carbohydrates like protein and fat. And Howard is an expert in that. And what happens when you take into account bolus on board? And there are many ways of taking that into account. What happens if you look at carbohydrate on board? There are different ways of looking at that. As Jane pointed out what about stress? What about exercise? What about day-to-day changes in physiology? All those factors are very important but for the most part those are way beyond the ability of a patient to calculate with pencil and paper and that is the reason why bolus calculator software can be very valuable.

I look at the difference between doing standard calculations and using bolus calculator software as the difference between driving a car and driving Indy 500 race car. You need a license to drive a car but you really need a special license to drive an Indy 500 race car. It will get you where you are going faster but it can crash if you don't know what you are doing.

And what I also heard here today was that we talked about what it takes for good outcomes and that is what I am going to be asking the panel about today. What are the factors that are needed for good outcomes using bolus calculators compared to not using bolus

calculators?

I also want to point out one other feature about a similarity between blood glucose monitors which are closely regulated and bolus calculator software which is maybe going to be tightly regulated or maybe not so tightly regulated in the future.

Patients want to know what is their blood glucose and, of course, you could go by your symptoms which would be a simple and probably inaccurate way of figuring out what your blood glucose is or you can use the blood glucose monitor which has to be cleared by FDA. Now when it is time for your insulin dose you can go by what you think it is, with a simple formula like what Jane said which is the magic wand, or you can do a simple calculation. That is the simple way. Or you can use something that is very accurate that requires software and requires FDA clearance at this time.

And when we look at what the FDA requires for blood glucose monitors to demonstrate safety the FDA requires that there be safe analytical accuracy. Right now they are not so big on this but ISO is safe clinical accuracy. So they definitely have to have analytical accuracy and to some extent clinical accuracy. And certainly for surveillance you have to have clinical accuracy. And finally it has to be safe that there is not going to be transmission of a blood borne virus.

And I would submit that comparable types of safety which we have to have in a insulin bolus calculator would include three factors. One is that you have to have validated software and Mike Flis from Roche made that point. And you have to be sure that the calculator does what it is supposed to do. And second you need to know what are the formulas that went into it. I think everybody agrees on that so that both the patient and the health care professional can understand what they are getting into. And third you have to know what is

the qualification of at least one of the writers. I just would never recommend bolus calculator software to a patient unless I knew that there was a health care professional who is a diabetes expert that was involved in writing the software. It could be a physician, it could be a certified diabetes educator, has to be somebody who knows diabetes. If it is just a really smart engineer, for me that wouldn't be enough.

So I've raised some areas where I think that there is comparability to say blood glucose monitors need to be regulated; I think insulin bolus calculators need to be regulated.

But let me look at the flip side. When you take a blood glucose monitor at this time as far as I know the FDA does not require that you do a clinical trial to demonstrate effectiveness. In fact that is the subject of many arguments. Is blood glucose monitoring really clinically useful. And we go over this and we say well it is just so obvious it can't even be tested. And there is no real study on this. Just something we know.

And it may be the same thing as an insulin bolus calculator so important do we need outcomes because it is so obvious that something like that is very helpful. So I'm going to start out the discussion with asking whether we even need to be regulating insulin bolus calculators assuming that they are developed the right way.

So I am going to ask each person to talk about what are the benefits and risks of Insulin bolus calculators and do you think they need to be regulated.

Actually I'm going to start with Jane because she is not going to be here very long. We will start with Jane and move in this direction.

DR. SELEY: I actually do think they need to be regulated to some extent so that I can feel safe recommending them to my patients. I would be really concerned if something was just handed to me; I knew nothing about it. I have a sense of confidence if I know it has

been cleared. And I think that is really important and I think that my peers will all agree with me.

DR. KLONOFF: Does everybody agree with Jane on that?

DR. SELEY: I mean my educated peers.

[Laughter.]

I am sorry.

DR. KLONOFF: Not your panel peers?

DR. SELEY: Not my panel peers.

DR. KOLONOFF: Panel peers. Okay.

DR. SELEY: I should have clarified that.

DR. KLONOFF: Steve what do you --?

DR. SELEY: And probably my endocrinologist peers. I would love to poll them.

DR. KLONOFF: Well, okay.

Steve what do you think?

MR. SCOTT: I think Howard described it well enough in his discussion where he was trying to demonstrate the differential between what were devices that had gone through regulations and those devices that had not.

DR. KLONOFF: Uh-huh. Alan?

MR. STEVENS: So I wrote down the three things that you mentioned. And I think that that follows pretty closely with the way we review bolus calculators. And one of the primary things that we are looking for beyond just the clinical validity, what is the basis of the algorithm; is it in literature, whatever, is how is it implemented in the software. Is the software validated? What is the technology? You know if you are using a touch screen have you -- and

we have actually seen in our reviews mis-calibrated touch screens leading to data entry errors. So our review, the benefit side of this is pretty clear to us if it is a valid algorithm we are focused on making sure that the risks are reasonably low based on the design. So that is pretty much all I have to say about that.

But yeah I think that the oversight is warranted based on some of the errors that we've seen in our review.

DR. KLONOFF: Thank you. I'm going to ask two more people to comment on this one, then we are going to go on to another topic unless somebody wants to say they don't think it should be regulated then I'll hear them. Otherwise I'll assume everybody else after these next two comments feels that way.

Okay. Melanie.

MS. YEUNG: Yes, so I was just going to echo some of the things that Alan said. I think that the usability and the user experience on using the bolus calculator should be a fourth kind of point; the human factors around how they understand the algorithms that go into it, the parameters that they need to input as well. And the output when that information eventually does get transferred to an EMR that that clinical system also represents that information correctly as well.

DR. KOLONOFF: Usability, thank you.

Courtney.

DR. LIAS: Instead of commenting on this since I'm here to actually find out the answers to these questions I actually recommend we hear from Adam and Howard Wolpert on this.

DR. KOLONOFF: Adam and Howard.

MR. BROWN: So in terms of whether they should be regulated I actually think the question is really about Apps and software because if it is on a pump or a meter it is going to be part of a regulated medical device. So I worry a little bit less about that.

Where I think it is hard -- where the FDA I think needs to figure out where to draw the line is on this sort of what Howard showed in his slide and the line between the Apps all the way on the right that are -- there are at least four bolus calculator Apps that I found that are on the APP store right now and the line between that and Apps like Tidepool and Glooko and diabetes people who are making those Apps. It seems -- I mean I haven't downloaded a lot of the Apps that are on the App store for bolus calculating but I think Howard's point about default settings is a good one.

And in terms of human factors I think -- just chatting actually at lunch I learned that it is weird to me that the FDA doesn't actually get the physical devices in front of them to like run through the menus and play with them and see what they feel like. And I think it is actually really hard to go through human factors without having the device in front of you. So I know I've seen -- and maybe you should correct me if I am wrong.

DR. LIAS: Sometimes we have the demos or things like that.

MR. BROWN: Okay.

DR. LIAS: Or sometimes we can go download the App

MR. BROWN: Okay. Well fair enough. But yeah being able to actually play with a device I think is a really important one.

DR. LIAS: I do want to ask a clarification question a really quickly. So Jim's presentation earlier meant to talk about different aspects of FDA regulation. A lot of time I really do believe that most people when they think of FDA they think of FDA is going to require

three clinical studies, phase 1, 2 and 3 development like a drug and a big approval. And that's -- we just wanted to make the point that FDA regulation is a lot of different things. And it doesn't always include those types of things. So I wanted your opinion on which parts of some of the things you heard earlier do you think are important for Apps. So for example I think it is very clear to me from the discussion today you know just like Alan said the benefits of a device like this that works well is very clear.

So the question is how well does it need to work? So does it matter if the device actually doesn't do the calculation correctly? Does it matter if they make a modification and that screws up some logic in the software that actually creates an output that is not what they intended it to be or not what you would expect it to be? How much would patients rely on that? But the answer is they wouldn't rely on it. And does it matter that maybe there is not as much regulation that is needed in terms of software validation, in terms of design control. But if it does matter that the App actually function the way it is supposed to function, that is one of the things that regulation is intended to accomplish.

So I wanted to clarify that because I do think when people think about regulation they think only about pre-market review. And we are also asking about some of those other aspects and how useful they may be.

DR. WOLPERT: I think the FDA has an important role or I think it is -- I mean I think that obviously the balance between innovation and regulation. But I think what you are referring to is more in sort of the post-marketing stage where if there are modifications I think there needs to be some ongoing oversight around that.

DR. KLONOFF: An area of review that has come up for some people who have said that they think the FDA is reviewing, regulating too tightly do people think that the FDA

should be regulating the way it appears that they are regulating now to what appears to us or they should review very lightly or perhaps not regulate at all.

DR. WOLPERT: The point I would raise there which I mentioned in my talk is I think the big distinction here that needs to be drawn when it comes to a bolus calculator algorithms is whether you actually have a system which is automatic and optimize insulin dosage without any clinical verification. So an AP system for example I mean that is clearly a situation where you need some clinical trials to assess safety and effectiveness.

As I mentioned in my talk these other scenarios where essentially all we are talking about is operationalizing something that a paper based algorithm that is part of routine standard care I think enters a completely different realm because that is something that is an algorithm that is already being routinely prescribed. So to me that should be the big distinction here when it comes to reviewing bolus calculators and whether one could just go the pathway of software validation or whether there needs to be some kind of clinical trial involved.

DR. KLONOFF: Jane what do you think about the idea of safety and effectiveness both being tested for?

DR. SELEY: I would really like to see a soft regulation that made sure that the safety things that we said like a maximum bolus that you get an alert when you override the dose recommendation, that it goes into the memory, those kinds of things that the manufacturer has to fulfill a checklist of things we know that could make it safer. But to be doing clinical trials on something that has so many variables we are just never going to have a device. Meanwhile patients are doing the magic wand. So there has to be some blending of that. And I leave it up to FDA. They know what is reasonable and what would impose huge barriers. You know you've worked with this many times before. But just to make sure that we

are doing the best we can to make sure that what I'm telling someone to use I have some sense that I know it has those things makes me feel better.

DR. KLONOFF: Steve you've dealt with these. What do you think? Safety and effectiveness.

MR. SCOTT: Well, I think someone mentioned I think it was yourself David mentioned that you'd like to see a health care professional involved in the design. And so that is the approach we took. You could see the extensive research we did to go into the design calculator. So I think from my point of view it was important that we understand the total software validation to make sure that the system actually does what it is intended to do from an engineering point of view. That is the easy part. The part that took us the time was to come up with a design that could be workable in the hands of the person that sets it up, the health care professional, and then workable in the hands of the user who actually has to use the calculator.

DR. KLONOFF: Adam?

MR. BROWN: Just so I've been thinking about your question. So I think what you are really driving at is what if I went home and wrote a bolus calculator App and put it out on the App store, how dangerous is that? Is that sort of really a key question?

I kind of feel like a bad bolus calculator App is still going to be better than patients doing it on their own. And this is still probably safer.

I know that might draw some -- I know Howard is ready to go but I also feel like there is something to be said for good software that is out there kind of rising to the top. And clinicians and patients -- software that gets released if it gets good reviews from bloggers and things like that it kind of rises to the top and the marketplace often can take care of a lot of

that. So I -- yeah, it is a tough one though.

DR. LIAS: What about the responsibility of somebody just -- when they say -- you develop an App and you put it out there and then somebody send you an email and says hey I'm using your App and I notice this problem. You know is there a responsibility on your end to actually fix it or not? That is made explicit in a regulatory environment. That is not explicit in a non-regulatory environment. So just pointing out some of the differences there.

MR. BROWN: Yeah. I mean that seems pretty reasonable to me. And I guess that would fall more along the lines of what has been done with CGM software recently. Is that -- I don't know the specifics of enforcement discretion. So --

DR. LIAS: Enforcement discretion means FDA doesn't do anything.

MR. BROWN: Okay.

DR. LIAS: Well I mean we could choose to apply enforcement discretion different ways. So we could choose -- most frequently enforcement discretion means we are just not going to regulate.

MR. BROWN: Right.

DR. LIAS: That is because we don't see the need. The medical mobile Apps guidance is a lot of examples of applications where we see these are technically devices but we don't see the need for FDA to step in and do anything because the risk isn't very high --

MR. BROWN: Uh-huh.

DR. LIAS: -- for these types of things. And so there are some examples in that guidance and that guidance also outlines here are some other things that FDA is going to apply a regulatory authority on. And then we have titrations and how we do that. So there is that Class III products which need, you know --

MR. BROWN: Uh-huh.

DR. LIAS: -- go on everything and then there is Class I products which really just need hey, FDA we are going to be selling this. Just tell us that. They need to have design control meaning they have to have good software validation practices in a nutshell. And they have to collect complaints and if something goes wrong they have to fix it. Those are sort of the lower part.

MR. WOLPERT: The point I was going to make, Adam, in response what I sort of envision may well happen here is we are going to be shifting from this realm of sort of consumer Apps once we have validated -- software validated Apps that have been developed through organizations or companies that have data input I think the utility of those Apps is going to be so much greater than any of these Apps that are currently available that what I would envision may well happen in the marketplace is those Apps that have connectivity to those data inputs are much more valuable than a take off.

The other thing I would say is that I think I would also envision that in terms of where digital health is evolving that we are going to be shifting to a lot of provider prescribed Apps in the sense that prescribing an App will be part of the routine care process. In terms of me handing a patient a sheaf of paper or sending them a PDF, I'll be prescribing an App. And I think once that happens we may be moving into an era where a lot of -- away from the sort of the consumer model of Apps into an era where Apps become an integrated part of health care. And I think once we get into that space there is going to be an opportunity for a lot more oversight.

And you know just to give you an example of patient population I have which is fairly sort of sophisticated middle age adults are not downloading that many Apps themselves.

I think where it is really going to take off is once it become integrated in part of the health care system so the Apps are prescribed and the data from them is reviewed as part of the care process. And so I think in a sense that is going to make this sort of consumer realm of Apps less and less relevant as we move forward.

DR. KLONOFF: I have to just put my two cents worth in because I feel really strongly FDA that you can't walk away from regulating Apps if they involve something as important as dosing insulin. And of course there are a variety of Apps that we could be prescribing but there is nothing more dangerous out there that a patient can get their hands on to my knowledge. There could be an App for dosing radiation therapy which is dangerous but a patient would not be in possession of a radiation emitting device so we wouldn't have to worry about that. So that is -- I just feel very strongly.

And I'll just say that in preparing for being a moderator here I talked about this with many health care professionals and many patients in California, everybody said they think that the FDA has to be regulated to protect patients. I am not saying you don't feel that way. I am saying this is what I am hearing and one reason for this if we look at where did the FDA -- why do we have an FDA; that is because earlier in the 20th century there were some snake oil medicines, let the public beware, good products rise to the top, bad products don't. And a lot of bad products that were just junk were rising to the top. And that is what led to the impetus of the FDA that the public felt the public needed protection. And that is what we look to you for. So I hope you don't stop providing protection.

Now I am going to ask another question here. How do patients use bolus calculators? And how do health care professionals use bolus calculators? What is happening with these products? Especially I'd like to hear from the patients and doctors here.

I'll start with Adam, what do you see? And then Howard what do you see?

MR. BROWN: In terms of? Can you hone it down a little bit?

DR. KLONOFF: Yeah. Do you find that people are using these frequently? Do they use them all the time? Or do they use them selectively like when they are hypoglycemic and then not use them at other times?

MR. BROWN: Yes, I think Howard's slide on what the different stages of diabetes, I think that put it perfectly into perspective. So for me I'm very much an experiential boluser because I can just factor in a few more variables than the calculator can but for someone who is newly diagnosed, for someone who is intensifying, all the patients Howard said I think they are tremendously valuable. And what excites me is the ability to make them so much better just by getting a little bit more innovation in them.

DR. KLONOFF: Uh-huh. Howard.

DR. WOLPERT: I just echo what you said. Obviously there is a lot of utility in certain patient populations particularly when they are mastering sort of the basics of diabetes self-management in terms of using the bolus calculator. I think what I always tell patients and I think it is important and sort of to keep in context is that unfortunately sometimes too rigid a focus on using can set people up to fail because with all the vagaries that affect people's glucose I mean unless people kind of realize that despite the best efforts their numbers aren't going to turn out right using the system and that it is not any fault of their own. Unfortunately what happens to some people in a sense is it actually -- they become more disengaged from their care. So I think it is very kind of complex in terms of where the place is -- I mean I think this is the art of medicine in terms of assessing where it best fits in. And just like I illustrated in that slide you kind of mentioned, I think there is sort of a continue here in terms of people's

lives journey with diabetes where different tools and I envision it will be with different Apps that come along are going to have a different place.

DR. LIAS: That is something I am interested in hearing about also is what is the spectrum of patients. You mentioned that some patients may not even know how to judge whether that number is correct coming out of the bolus calculator for them. But then some people do obviously Adam has a lot of experience with his own diabetes and he probably takes that number as a recommendation. How many if you could ball park what proportions of patients do you think rely on that number as this is the dose I should take versus the number of patients that are able to really consider it a recommendation.

DR. WOLPERT: So the way I'd answer that is often I say to my patients I'm just sort of a coach helping them to make more informed decisions around their diabetes self-management. I think that whatever answer I give you about now which would be a total guess is going to be totally different in five years because I think what the potential is in terms of what Howard Look was illustrating there once you have all the data together and people can see their glucose and can see their insulin and they can see the impact of different foods on their glucoses what we have the opportunity to do here is really for people to dig deep into understanding their own physiologic responses. I mean once it is easy for people to assess whether they need five units for that reader or seven units because they are getting data and they are getting data reports that synthesize it together so they can understand their own physiology and responses you are moving in a completely different realm here where people -- I think people's self insights in being able to judge that is going to be all that greater. I think today you are still depending on people being fairly engaged and getting coaching and guidance from their care providers so they can understand all those factors. But the potential there and

we move into this next era with all these Apps and appropriate data reports synthesizing I think it is ready to give most patients with diabetes the insights that they need to make these judgments.

DR. LIAS: I agree that is exciting. But I wonder about today? Kind of is it more frequent that a patient who is starting out that would be sort of in that heavy user category of insulin dosing thing would be able to do that now or do you think most of them can't do that?

DR. WOLPERT: I think it depends on the care process -- you know just to give you an example when people are bringing in their data and so the question is why did you go low after lunch this day versus the other day? Was there exercise? And so there is the teachable moment. And then people gain that particular insight. So I think a lot of it has to do with how much of the guidance and informed data review so that people can kind of learn from their experiences and actually see where the caveats are.

DR. KLONOFF: One of the keys here is since you are giving somebody such a powerful weapon that they can get away -- it can get out of hand is education. Whether it is mandated or just obvious for the physician because it is the analogy I used earlier about the car and the Indy 500 race car, you have to really know what you are doing with this device or you can end up someplace you don't want to be.

DR. LIAS: I think the question I am getting at is more is the learning intermediary question. You know if you have a calculator that recommends a dose but you know enough to judge it, you know there is very little risk there because you can say that is ludicrous, I'm not going to do that. But if you don't have that information and you basically well that is what it said to do I better do that. I don't have a good sense of how -- what the balance is between people who can and can't judge that.

DR. WOLPERT: The way I'd respond there is I think it is better for people to get some guidance than to be left in a situation where as Jane sort of illustrated it that they really are guessing completely. So it is not perfect in terms of where we are starting. But it is better than the alternative.

DR. LIAS: Well, certainly I think that point came through very clearly. I'm getting at more if the calculator malfunctions --

DR. KLONOFF: I'd like to --

DR. LIAS: -- and spits out you know you should give yourself 15 units and they should get five.

DR. WOLPERT: I don't know many patients who would just sort of blindly follow a guidance like that.

DR. KLONOFF: John Walsh --

MR. BROWN: I think patients can identify very egregious erroneous calculations. I would think the vast majority could because if they've been sent home with insulin they've been sent home with instructions. Even if the education was minimal I think people can identify 15 versus five I would think.

DR. KLONOFF: John Walsh wrote in journal Diabetes Science and Technology some data and it showed that when you had to change the dose frequently patients were more conservative than the change that the bolus calculator was recommending and he implied that was that they recognized how to do the safe thing.

I want to see is there a patient in the audience that would like to address this question, namely, do you as a patient have enough information or knowledge to modify the kind of dose that is recommended from the bolus calculator in case it looks surprising. Would

you follow what it says or would you modify it. Anybody want to say?

UNIDENTIFIED PERSON: Since nobody else raised their hand I --

DR. KLONOFF: Thank you.

UNIDENTIFIED PERSON: -- agree with what Adam said. It is really -- we are capable particularly as we become more experienced in seeing if something doesn't look right. But also you know I think it is a matter of we're a team. My health care professional needs to give me those guidelines but also I need to take those guidelines and then be responsive to whatever day to day influences may occur that may make me adjust something. And also what if for instance I am -- I go home with a set of instructions I have one profile for my bolus and one profile for insulin carb whatever. And then three weeks later I start an exercise routine which is going to totally change how I use insulin. Now I have to do something different. How do I deal with that? That is where the continual education kind of comes in. So I think it is a team effort but also I think that as we become more experienced with it certainly patients understand their diabetes more than anybody.

DR. KLONOFF: When you see numbers from the bolus calculator are you confident that those are the correct numbers for you then? Or how do you feel?

UNIDENTIFIED PERSON: I am but like I discussed with a couple of people today I have an endocrinologist who was very adamant that I understood how my insulin pump was calculating boluses before she would agree to let me go on a pump. And so in my case it was very helpful, I'm pretty good at basic math so that wasn't so hard but I think she was very good at making sure that I understood what was going on so that when I saw a number I could identify that it was on.

DR. KLONOFF: Education is very critical. I think you and I agree on that. What

we are going to see I would like the panel to comment as these bolus calculators become increasingly sophisticated and take into account additional factors that are not really part of the basic equation now such as protein and fat intake, day-to-day stress, recent exercise, carbohydrate on board, two types of insulin on board, a beta correction, and recent meal insulin; do the people on the panel feel that the patients will still have enough information to recognize an incorrect value and still safely override it?

Adam would you be confident if you had a super sophisticated bolus calculator that you'd still know enough if it didn't look right to do something different?

MR. BROWN: And you are saying this is just software out there kind of on the App store or something, unregulated? So I am on board with that.

DR. KLONOFF: Either one regulated or unregulated?

MR. BROWN: I think unregulated it gets -- I think the thing about bolus calculation now is it is hard to do the math but it is easy to identify an erroneous dose fairly easy because it is very linear sequential math. Once you start getting into algorithms and analytics I think I'd be a little less confident that I understood the dose and that I knew the logic it was taking. So I know a lot of times I'll plug in things to a bolus calculator, get a value and say hey, I don't understand how it is figuring that out. And then I'll look at the IOB, I'll go back and it makes sense because I've tried different pumps and calculators come out differently. But once you get into algorithms and there is no single line item that can explain we took off this much for this, we added this much for this, I think that is a little harder as a patient.

DR. WOLPERT: Where I think there may be a dividing line is I think the limits in terms of what you can do with syringe or with pen into the most sophisticated bolusing is pretty limited. So any type of more sophisticated algorithms are going to need to be

incorporated into an insulin pump. So I think it is going to take these more complicated boluses out of the unregulated round just because they'll have to be integrated into a pump.

What I would envision and this is something that Garry Steil and I are working on in to the more complex boluses because I don't think it is going to be that simple to just come up with a standard formula. I think what it is actually going to entail is some kind of testing protocol for patients to actually use to actually define what parameters they need to follow for say covering a high fat meal. So I don't think it is going to be as simple as actually just selecting a sort of default settings to actually program that in. So I think with a different -- that will entail a different way of actually setting the boluses. There would have to b a protocol to actually validate that this bolus setting for say high fat works before it actually gets implemented. I think you kind of circumvent some of these concerns.

DR. KLONOFF: I'm going to propose that technology I think is really needed. And I think it will be helpful for the FDA doing their work. One of the reasons why the FDA does fairly easily about bolus calculators with pumps but has not been so readily accepting of free standing bolus calculators whether with a meter or just anything that is not part of the pump is because if there is an incorrect insulin dose with a pump you have a record you can figure what went wrong, you can fix the problem. But when it is with a free standing device you don't have a record. So what we need is an insulin pen that transmits the data and therefore will have the same information about dosing data from the pen that we would have from a pump. And recently last week Cambridge Consultants in England announced they have a pen called a Keyco pen and I wouldn't be surprised if this is going to be the first of many pens that will transmit the dosing. And the way it works is you can hear the number of clicks as you dial the dose and if you click it up one way it hears clicks, if you dial it back down it hears a different kind of click

and it knows how many units you dialed up. And I think if that type of feature becomes readily accepted that you at FDA might be more open to this type of software because at least you will have a remedy of looking at the insulin dose. I don't if anybody from FDA real quick comment on that.

Alan. What do you think? Would that make you more inclined to accept bolus calculators if this kind of pen information was available and you knew exactly how much insulin a person was using?

MR. STEVENS: Well I mean I think that obviously I review whatever is submitted and if that was submitted we would review and look at the risks associated with integrating the wireless technology, where the communication between the pen and the application -- the software application I don't have an inherent problem with that approach. And I think that that raises another issue with the current stand alone calculators versus the pumps which is -- they are not -- the calculator itself is not automating the tracking of insulin on board, whereas the ones that are imbedded in the pumps are. So I mean that would address certain issues.

MR. BROWN: Just to hop on that. One thing I think is really important is that most people aren't -- most people are just out there in the real world right now not using a pump, they are not keeping track of insulin on board. So again even a meter with a bolus calculator where a patient doesn't enter every single dose is still going to be better than a patient out there on their own without a bolus calculator.

DR. KLONOFF: Okay. What concerns do people on the panel have about potential adverse effects if the bolus calculator recommends the wrong dose of insulin? How much concern do you have? We've talked about maybe there is an erroneous dose? How bad is it? How bad could it be? Or how worried are you?

DR. WOLPERT: In response to that question that Courtney raised I think most patients, they know how much insulin they usually need for different meals of the day. I mean if the bolus calculator is going to give them an erroneous recommendation I think people know from their experience that that is an outlier and that it is an error. So I think in practice I think this is probably more of a theoretical concern frankly.

DR. LIAS: Are you at all concerned about incremental small problems. We have some examples in the slides of calculation errors because of carb counting and other types of errors that create two or three unit differences in the doses. Over time are you concerned about knowing that obviously bolus calculator is not the only potential contributor to that type of thing? We do recognize that but since we are talking about bolus calculators today if there was a consistent problem in the type of number they are getting are you concerned about that?

DR. WOLPERT: Well I mean carb counting errors are inherent in the way everyone sort of manages their diabetes. I think any type of systematic error is going to show up in the blood glucoses and that is going to be the tip off to reassessing the dose and which is what the case is in routine practice now. But I think for most patients particularly with the types of data analytical tools that are becoming available and connectivity that will be identified automatically if there are repeated errors that lead let's say to hypoglycemia. So I think a lot of these risks that are inherent in diabetes management today are going to be mitigated by having those other tools available.

MR. STEVENS: I just want to comment on that too because from my perspective what I see is a lot of very well educated people on the panel and in the audience so the ability to identify errors from a computer system I don't really have any data to support that that is really widespread throughout the population. And I mean I just in my experience over the last

ten years reviewing insulin pumps a lot of times we don't really know where the problems are coming from when we see adverse events whether it is the pump or the insulin or the patient, the recommendation. I mean there is a lot of unknown from my perspective and whether or not the patients themselves understand the perspective I have is that people believe what computer systems tell them, we've kind of become conditioned to that unless the error is really obvious. And that is one of the examples I've heard five to 15 when you generally expect five after a meal well of course 15 is going to be obvious.

DR. WOLPERT: What I'd say in regard to that is I think what we are facing at the moment and I think what you are relating is kind of based on the fact that today when you look at the data analytics we have them are put in just as was highlighted by Joe and Howard this morning. We don't have data reports that synthesize the data that highlight these patterns. What I do think the potential is and it is going to happen I mean because this is work already in progress is that once you have the data sources together you'll be able to sort of automatically actually identify whether there is a consistent pattern there. So it is not going to be user dependent on the patient or even the clinician for that matter and that will sort of highlight if there is say a systematic dosing error in the example you relate. So I really kind of do see the potential here once all those data sources can be integrated and one can have not even sophisticated in our analytics but I think it is just pulling together data reports which actually highlight what we know, common clinical problems and seeing if they are in data set. Because if you look at the problem today even with a system like CareLink it pulls all the data together, 30 different reports designed by engineers that are probably of very little value. The problem with a system like that is it is not actually designed to actually pull out clinically important scenarios that commonly occur and that a clinician needs to look for. And even for an expert

clinician it takes time to go through that. If you move into the realm though which I think is going to be possible based on where things are going where one does have software which is born by clinical insight available I think a lot of these potential issues are going to be mitigated.

DR. KLONOFF: What type of information, Howard and Adam and anybody else would you like to know about when you look at bolus calculator like would you read the formula yourself before you prescribe it? Or would you read it only if there is a problem? How much in depth do you want to delve before you are satisfied that this is a good bolus calculator.

MR. BROWN: I will answer that but just to touch on your question. A couple of points I think Jane really put into perspective that bolus calculators are even more valuable for people who have number problems and number illiteracy because they simplify the math. And they are probably safer, a lot safer, than the people doing it on themselves which is just kind of winging it. Go ahead.

MR. STEVENS: I am not arguing that at all.

MR. BROWN: Oh, okay. Sorry. And I think this concept of just shared responsibility the onus should not fall on any one party for full 100% safe operation. So if FDA approves a calculator and people don't use it correctly that is not all FDA's fault; right. I mean patients have responsibility for dosing insulin; right. I mean diabetes is a self-managed disease and we will get it wrong. And that is not the FDA's fault if products get approved and that happens.

DR. LIAS: I think we are just trying to find out how these work.

MR. BROWN: Okay.

DR. LIAS: So to assess what -- we know what the obvious benefits are.

MR. BROWN: Sure.

DR. LIAS: The benefits are obvious with these types of device. But actually to enable us to titrate the right level of oversight --

MR. BROWN: Yeah.

DR. LIAS: --we have to understand how much people rely on that answer.

MR BROWN: Uh-huh.

DR. LIAS: And whether or not for example a newly diagnosed patient would know that they shouldn't necessarily follow what is coming out of the calculator. More question just trying to give us information on how these are used. But definitely like Alan said I am not questioning the benefit. That is an obvious --

MR. BROWN: Okay. Fair enough.

DR. LIAS: -- attribute of these products.

DR. KLONOFF: Steve when you worked on the calculators did you find that patients were highly reliant or were they just ignoring the numbers?

MR. SCOTT: We have had the opportunity to see some data so as I said to you that we are finding a high proportion of meters that -- we are designed to try to get those meters into the hands of insulin users so we are finding a high proportion are having the insulin calculators switched on. We are also finding which is interesting in terms of the way we designed it as a high proportion of those calculators are actually set up in the advanced mode rather than the simple which is essentially a fixed dose mode. And so the feedback we've got from patients that are using it is that they like the insulin calculators. You can see that we had done that study where 87% of people felt it was a better way. We are still getting that feedback from patients that they like the comfort of the calculator doing what otherwise they'd have to do in their head. One thing I didn't -- I keep hearing the word algorithm and I also think

algorithm is a scary word. It is actually -- the calculator isn't really an algorithm. The calculator is taking an established rule that is given to a patient and is actually doing the math calculation for those established rules.

DR. LIAS: Your calculator does that.

MR. SCOTT: There is -- yeah, there is a little bit that any that has an insulin on board has a little bit because with the insulin on board you can choose a carb linear model and linear model other than the -- I think I heard Howard say other than the insulin duration I don't think there was actually much differential between those models so I think somebody chooses an established model and then you are down to dialing in the correct duration for that model. But I think even in some of the pump models I think they are much more simplified mathematical approach than they really are an algorithmic approach.

DR. KLONOFF: Okay. That is a good point. I want to say Adam I agree with you about people with poor numeracy. There are a lot of them out there as we saw in the assessment paper that was in the Journal of Diabetes Science and Technology. And these people would really benefit from bolus calculator software.

Does anybody want to talk about what type of information you would like to see if you are going to prescribe a bolus calculator? How much do you want to know about it?

DR. WOLPERT: I think at a basic level I mean one important difference between the devices which are sort of hard. In one study I saw the effect that they use different sort of calculations for actually assessing what target to go to. So that is an important consideration I think or difference I think between the devices. There seems to be standardization around most of the pumps whether they consider both food or correction bolus in the IOB calculation versus correction. I mean I think in practice just knowing straight IOB of total insulin is valuable. But

like I related there are so many variables that impact when two duration action of insulin that it is really a matter of how much security you want for protection against hypoglycemia in terms of the way that gets set.

DR. KLONOFF: You know for doctors who are real fine tune people there are a few minor differences in insulin on board that probably don't make a big difference on the whole. But one interesting point is insulin on board is a concept that is intended to slow down if you don't push to much insulin or you will get stacking. But it is possible to actually require negative insulin dosing because you could have so much insulin on board that when it is time for a dose you don't need any, you have more than that much insulin in your body compared to what you are about to give yourself. So what you really need at that moment is negative insulin and there is -- not only you can't deliver a dose of negative insulin but it doesn't even show up on any of these calculators. And many of the monitors do have a different way of expressing insulin on board. But none of us seem to really feel it is that important, these differences. Would you say that is true Howard that clinicians don't seem to care that much?

DR. WOLPERT: I absolutely agree.

DR. KLONOFF: All right. Howard knows more than anybody and he agrees with that. Okay.

We are concerned now that there could be some design flaws in these bolus calculators which is why the FDA is interested in being involved with regulation. I'd like to ask anecdotally what types of other design flaws you have seen and I mentioned negative insulin on board doesn't exist. Are there any other design flaws that people on the panel are aware of that you've seen on any bolus calculators?

Okay. Yeah.

MR. STEVENS: I can mention from our review process things that we've picked up on --

DR. KLONOFF: Yes.

MR. STEVENS: -- pump systems with calculators on them related to technology. So I mean obviously software is always an issue that we are concerned about in human factors. And then just implementation like I mentioned earlier touch screen calibration issues between hardware and software; we've seen where you actually if you push like a one for example a two might have shown up on the screen based on the way the device was designed. And then more and more as these systems are becoming network cyber security has become a concern that we are looking at. So these are areas that we take a close look at. And that is really what our review is about and we pick -- most of the time the systems work the way that they are designed. But we do catch issues too.

And then on the recall side software is always one of the top issues that we have issues with in general.

DR. KLONOFF: That is what I am getting at; what types of software problems maybe have you seen?

MR. STEVENS: Well you can have -- we've seen decimal place issue. We've seen issues with -- and I am not talking about just bolus calculators themselves but software in general for pump systems or delivery systems. Just anomalies in the software that cause incorrect values. We've actually seen algorithm errors, not in insulin calculators but in some of the wave base dosing calculators we've seen where in certain circumstances you were actually getting wrong outputs based on the design of the algorithm, how it is implemented in the software. That is all I can think of off the top of my head.

DR. KLONOFF: You mentioned some of these might be significant, some might be minor. A few weeks ago it turned out that Apple software which will incorporate glucose values had to be sort of internally recalled because they were presenting in Europe milligrams per deciliter instead of millimoles per liter so they just disabled that so now you can't put any kind of unit. Courtney.

MS. LIAS: That was the subject of a big recall of glucose meters several years ago where people were dropping their meter and the units were flipping for between millimoles and milligrams per deciliter and people were interpreting 7.1 millimoles as 71 or --

DR. KLONOFF: Yeah. So that would be bad.

So we've talked about a few things that we know that can go wrong with the bolus calculators. Does anybody have any suggestions about what can be done to improve bolus calculators? We've heard quite a few in the presentations both from Howard and Jane and Adam. Anybody have any other comments or would like to say what you thought was the most important parts of your presentation for improvements that are needed?

MR. BROWN: I could go. So like I said I would love to see CGM trend information built in in some way even as just a setting where you can set depending on the arrows that appear what percentage increase in your bolus dose you would like or what percentage decrease. I think that would be valuable. I know that insulin dosing claim for CGM is something the FDA is thinking hard about. I can say that I know a lot of patients who dose off their CGM in the real world. So whether it is approved for that or not that is how it is being used. So I -- no, no --I know --

DR. LIAS: I would like to reiterate what Alan said. We can only approve what is sent to us.

MR. BROWN: Fair enough. Fair enough.

[Laughter.]

But I do look forward to CGM info in bolus calculators.

DR. KLONOFF: In September in Journal of Diabetes Science and Technology we published this review article by Signe Schmidt from Denmark titled "bolus calculators". I am going to read the last sentence to you from her article. This is the conclusion. Adam listen to this. "Perhaps the future holds more attractive combinations of diabetes technologies. One obvious possibility would be sensor augmented bolus calculator." So you and she are on the same wavelength there.

DR. WOLPER: I would offer some question here actually because while a lot of people are using CGM blindly and it works fine. I would -- around having sort of standardized adjustment in doses based on rate of change because I think it is so individual that it varies so much from one individual to another. It also varies depending on sort of scenarios in terms of why glucose is going up but a person may have a transient bump in their glucose after they treated low versus actually having an increase let's say in this situation where they've had a high GI cobbler. I think there are so many complexities around rate of change and when it comes down to actually dosing of rate of change I think it is very difficult to kind of codify and I would be adverse to anything standardized around that at this stage.

MR. BROWN: Yeah. I guess what I mean Howard was kind of like how there is a line item for inputting carbs, there is a line item for an increase or decrease you'd want based on the trend arrow but of course you could -- I think you should definitely be able to set that individually.

DR. KLONOFF: So we are here at the invitation of FDA to give them our advice.

So what does anybody -- I am going to put this out to the audience now as well as to the panel. The question is how can the FDA innovate and protect safety at the same time for insulin dose calculators either used by patients or prescribed by health care professionals?

MR. LOOK: Hi, Howard Look from Tidepool. So really important discussion. Thank you. And thank you for asking that question David.

So I think it is important to make a distinction between the type of bolus calculator that is really just doing math. We saw the algorithm that gets done. And we also acknowledge that people sometimes try to do that math themselves and often are not very good at doing that math. Those kinds of bolus calculators are based on very well understood algorithms. And it would be very simple to say look if you are building a new bolus calculator just show that the dose you are going to recommend is within the bounds of these six other algorithms. And that is actually a very simple bit of software and in the era of big data we can put 10,000 test runs against that simple bit of software. And say just run your algorithm through that and that is good.

To me that is a very different kind of bolus calculator and the kind of bolus calculator that might for example automatically take your FitBit data or automatically take your CGM trend data and make a recommendation or might do something that is totally different than the kinds of bolus calculators we see. So to me there isn't one kind of risk around these bolus calculators and I would encourage us to think of them differently.

There are going to be innovative new ones and certainly they should go through some kind of regulatory review or industry review to make sure that they are not doing something totally crazy. But a new kind of calculator that is just doing the math for me, that is no different than what my daughter does today which is she picks up the calculator on her I-

Phone and she does the math. And I would much rather she use an App out of the App store to do that math because she is likely to do a mistake. And I would even much rather her just using an App that hasn't been regulated because I still think the risk of that is very low.

Thank you.

DR. KLONOFF: Thank you. Garry.

MR. STEIL: All right, David. Garry Steil from Boston Children's Hospital. I'm going to come back to that children's part of Boston Children's in just a second.

But starting with what David really asked why --- think the FDA might be doing. What I am really hearing here a lot is sort of a binary either don't regulate or regulate. But sort of behind that I'm hearing a little bit from David that should there be a written description that should be developed for the doctor to look at. And I guess the question for the FDA, is there some utility in taking a middle stand here and saying that we are going to insure that the bolus estimator does what is described in the written documentation but not look at saying does the bolus estimate of four units; is that too much or too little. Something that just says is the device doing what it is described to do? That is the question. Is there a middle ground here in the regulation, just make sure that the device does what the software says, the software does what the specification sheet says it does.

And then going back to my earlier comment on Boston Children's Hospital the thing I haven't really heard anywhere at the meeting today is anything to do with bolus Calculator difference that might go for a seven year old versus a 17 year old. Seven and under you can't really insure that kids are going to eat what they say they are going to eat so almost everybody boluses after they eat. And likewise if I push it down a little bit further if I look at a one month old baby or two month old baby nobody or up to one year probably somewhere

along those lines nobody would actually bolus until after they eat. They would actually wait until the glucose goes up because it is just you know once you bolus you are done. If you are wearing what the child just ate on your tie you are kind of in trouble. So that -- it kind of comes back -- I know the FDA has talked about this before looking to sort of get more validation as we move into the pediatric population. But I think there are big differences between how you might go about estimating a bolus for as you move from seven month old to seven year old to 17 year old and I think I heard a lot about the 17 year old here today. But I didn't hear anything about the seven month old and the seven year old.

DR. KLONOFF: Pat.

DR. BEASTON: Patricia Beaston, FDA. So I want to also argue that we haven't heard about the 77 year old. You know not everybody is well educated Type I diabetic like Adam. Not everybody sees patients at the Joslin. There are a lot of primary care physicians out there that don't have nurse practitioners and diabetes educators. They are trying to manage Type II diabetics, there is a lot of Apps out there so can you speak to what the additional requirements or transparent consideration should be for evaluating these Apps so they can not only be used safely by well educated people in very high functioning situations but also are useful tools to primary care physicians and their patients.

DR. KLONOFF: I just want to comment I agree that there are a lot of doctors that know less about diabetes than the people on our panel. To me the solution there also has to include education. If these health care professionals don't know much about diabetes they are probably not providing education and therefore these patients to me are not qualified to use those Apps. They should be for everybody.

MR. AL-FARUQUE: Hi Ferdous Al-Faruque with The Gray Sheet. The FDA has said

in its previous guidance that it will use a risk based approach to mobile applications. So I am guessing the FDA is looking at bolus calculators as a high risk App and that is why it is questioning whether it should be regulating these Apps.

And secondly to the rest of the panel members what are your thoughts on that? How high of a risk do these Apps hold and does it warrant the FDA regulating the Apps?

DR. LIAS: So I do want to clarify that we are not here today to say that insulin bolus calculators are high risk. What we are here today is to hear from the community, stakeholders, industry, patients, health care providers how they use this App so we can understand their risks and benefits. The risk based regulation is how we do all medical devices. And part of doing that is determining what are the risks and how can they potentially be mitigated. So that is why the discussion today is so helpful to us.

MR. AL-FARAQUE: Would the other panel members chime in and tell me how high a risk you think these Apps hold?

MR. BROWN: I can address that. I would piggy-back off what Howard said you know when we are talking about a simple paper based calculation; I think that is better than patients doing it on their own whether it is regulated or not.

DR. WOLPERT: I showed in my talks and screen shots of current Apps which have great utility but there was one App, just a single flick there and it goes from SI to milligrams per deciliter. A slide into glucose data I mean that could lead to some real data entry errors so I think there really is -- while I think these are tools or bolus calculations that are used in standard care they are a great utility. As I said in my talk I think a place for the FDA is to insure that Apps with that utility are available but that they have appropriate software validation, human factors evaluation and such.

DR. KLONOFF: These are high risk devices just like driving Indy 500 race car is a high risk device. Just like Dr. Patricia Beaston said they are not for everybody.

We are going to take comments from the people who are standing now. There are three people and those will be the final three comments.

MR. FANG: I think FDA has a tough job --

DR. KLONOFF: Identify yourself again please?

MR. FANG: Oh, I'm sorry. I'm Ping Fang with the Nightscout.

DR. KLONOFF: With who?

MR FANG: Nightscout.

DR. KLONOFF: Nightscout yes.

MR. FANG: And given the challenge of this problem I offer a slightly different perspective and that perspective is perhaps we ought to look at the feedback loop and that is given all these practices, all these correct bolus calculators, wrong bolus calculators; if we can look at the data through CGM, the data tells us whether they are on the right track or on the wrong track. Perhaps that additional information combined with education can give us a little more accuracy or at least guide the user into -

DR. KLONOFF: CGM. Thank you.

DR. LIAS: I would like to thank you and Howard for actually tying the two halves of this meeting together.

MR. ESTES: Hi I am mark Estes from Asante. Great meeting so appreciate the chance to give some input. So how do you innovate and be safe? I think you are almost on the right track today. We recently lived through the experience of getting a device with bolus calculator approved by the FDA and you did kind of the right thing. You asked us really basic

simple questions like how does it work, what is your math, what is it based on, what are the limits on the parameters? And when we weren't clear you asked extra questions. And we got to a place where you didn't force us to jump through flaming hoops. And I think we answered reasonable questions. And those are the kinds of questions you should be asking anybody who makes an App; right. Because it is not the App that is a powerful thing, it is insulin is a crazy powerful drug. And if you are giving advice be it on an App or a pump or wherever it ought to be well founded; right. So I think the path you are on in terms of for our case was a 510K and it was reasonably regulated; it is not far off.

And I say my fear would be if you make it harder you'll crush innovation. If you make it easier you might let something bad through. I think you are not far off. So good job.

Thanks.

DR. KLONOFF: Thank you.

[Applause.]

MR. GHESQUIERE: I agree actually have a very similar comment which is that --

DR. KLONOFF: Again identify yourself, please.

MR. GHESQUIERE: Excuse me. My name is Alex Ghesquiere. I work for TelCare currently. And the comment is that the danger is actually the drug insulin; right. And the gate to insulin is the prescription to insulin. That is where you control access to this dangerous drug. I feel like once the prescription is made then controlling access to these tools that help you dose insulin correctly, you are controlling access at the wrong point.

I think we've seen a lot of data here today that these tools that can help you dose correctly are very valuable tools. I think that we should suggest a limit the controls to showing that the tools work correctly which is to say software validation, verification and not

overly restricted with access through prescription or other restrictions. I think that empirically it seems to me that there is access to dose calculators in Europe but there is not very much access in the United States; so right away I can see that there are obstacles to overcome with the situation today. I think we should be discussing how to remove those obstacles so that there is generally more access to these very valuable implements.

DR. KLONOFF: Okay. Thank you.

Does anybody on the panel have any additional comments? I am going to summarize what I heard. Okay.

So first I think there was pretty unanimous sentiment that we want to see regulation of this type of software. Going into the meeting I didn't know what we were going to see. I thought maybe there would be some people who were saying just stop regulating it let the marketplace be the sole deciding factor. We hear that these products are potentially dangerous for different reasons and there should be regulation.

So why don't these products work as well as they could? Well, they do work pretty well but there are several factors that are needed for an insulin bolus calculator to work. First you have to have proper settings which means the health care professional needs to be educated to put in the right doses because as we heard if you don't have the right basal dose and you don't take insulin on board into account you might be too aggressive or not aggressive enough. You need patient education for these to work because this is a potentially dangerous tool. We heard you need good compliance; that is true for all software. And you need good software.

So what does the FDA look for in good software? I heard five different features should be present in insulin bolus calculating software.

First you want to have validated doses so that when you see a dose on the screen that is what is intended. And that can be tested and the FDA can look at that.

You want to see a system for hypoglycemia avoidance and that goes along with validated doses. You have to be most careful about avoiding hypoglycemia.

Third you want to see the formula so that clinicians like Howard who understand these things can look at it and understand what the product contains.

Fourth something I want to see and nobody contradicted this is that there is some health care professionals involved in writing the software. This cannot be done by engineers alone.

And finally we want to see good human factors and usability studies to make this worthwhile.

And after having said all that just to conclude in one simple sentence insulin bolus calculators require regulation.

Now I am going to turn this over to Courtney for summary.

Thank you everybody on the panel for your participation.

[Applause.]

WRAP-UP AND SUMMARY

DR. LIAS: Thank you David. And I want to thank everyone who participated in this meeting today. Everyone who participated in giving presentations and giving input both on the panels and in the audience, people who are participating by joining us live here at FDA and people who are on the Webcast listening in to this discussion.

I know I personally leaned a lot that will help us try and strike the right balance because that is really our goal in these areas.

So I do want to summarize a few things that I heard today as well.

On the interoperability discussion I was really happy with the way that that discussion went in terms of starting off a discussion that we believe is critical here at FDA. What I also heard is great enthusiasm for increase interoperability between diabetes devices from patients, from regulators and from some members of industry. I think we didn't hear from some other members of industry and so that is obviously an area where we need to do a little bit more discussion to find out how can we improve the practical application of interoperability for diabetes devices because that is really where we want to go.

So at FDA we intend to continue the discussion around diabetes devices and around interoperability to get to the point where we can actually practically apply this. The data standards are going to help immensely. They are going to help the device manufacturers implement protocols within their devices for the data that actually help them get farther toward interoperability. There are other practical applications to making devices truly interoperable and we are committed to trying to help ferret out what those things are, promote other availability where we can and to get these products advanced as quickly as possible.

So the conversation today starts of off on that path and we do commit to having more discussion about that in the future.

The second half of our day was talking about insulin bolus calculators. We really wanted to learn like I said before from patients and health care providers and other stakeholders such as industry about these products, how they are used, people's experiences with them, their opinions about them. And I have certainly learned a lot.

One thing that was always clear to us and I do want to emphasize I think

everyone at FDA recognizes the benefits of insulin bolus calculators, some of them are obvious. Obviously it is easier if you are not good at these complicated math scenarios to have a calculator that can help you with a simple interface put these things in and get out a good answer that can help you with your diabetes care. And also to help you implement more sort of complicated diabetes regimens. So the benefits of bolus calculators is a clear one.

There was clear demonstration of how complicated insulin bolus calculation is as well. And also some distinctions were made about the difference between implementing a paper based calculation in software versus actually implementing novel types of algorithms to dose insulin. Both may be useful but they have different issues and maybe they need different regulatory considerations.

I heard that setups or participation by the health care provider is often desired and that has to be balanced with access. So Jane brought up the issue of how do you get access to these products while still working with your health care provider to make sure that your care and communication is maintained. So that is obviously something that we as a community to talk about as well.

What is not on the table is some sort of regulatory paradigm that would limit access to insulin bolus calculators. So I do want to emphasize that. That is not the point of today's meeting. The point of today's meeting is really to try to figure out what is the right regulator touch.

I heard a few questions about high-risk devices. I don't think anybody has put on the table that these devices are Class III products. So I do want to make that very, very clear.

And then finally this conversation as in a lot of other similar conversations about diabetes, this disease it is very clear that the patient is the key. You know patients working with

their health care providers, working with their family members, working with other people around them; they have to make a lot of these decisions themselves. And the tools that we can help put forward may help them do that.

At the end of the day a lot of these challenges are on the patient. So giving them tools that are safe and effective to help them do that I think is everyone's goal.

And so I hope that some of the discussion we've had today will lead to that in the area of some bolus calculators and device interoperability.

We want you to know that FDA hears about the interest in diversity and choice among patients to get a product that really meets their individual needs; that one person's diabetes is not like another person's diabetes and that they may have different needs for products and tools to help them to create good care.

So conversations like today I hope will move us forward even just a little bit and I personally really look forward to our next conversations in these areas.

So with that I am going to close the meeting and we look forward to talking with you about this again.

Thank you very much. Bye-bye.

[Applause.]

(WHEREUPON, the public meeting concluded.)

CERTIFICATE OF NOTARY PUBLIC

I, MICHAEL FARKAS, the officer before whom the foregoing deposition was taken, do hereby certify that the witness whose testimony appears in the foregoing deposition was duly sworn by me; that the testimony of said witness was recorded by me and thereafter