Q180770 Tidepool-Loop FDA Pre-submission Meeting Minutes

Meeting Time and Location:

- August 27, 2018, 12:00pm - 12:45pm EDT
- FDA White Oak Campus, Building 66, Silver Spring, MD

FDA attendees - Center for In Vitro Diagnostics and Radiological Health (in person):

- Courtney Lias (DCTD Division Director)
- Alain Silk (Acting Branch Chief, Diabetes)
- Jisun Yi (Medical Officer)
- Naomi Schwartz (Software Reviewer)
- John Murray (Digital Health, PreCert Program)
- Francisco Vicenty (Digital Health, PreCert Program)
- Martin Ho (Digital Health, PreCert Program)

Tidepool Attendees:

- Howard Look, CEO (in person)
- Brandon Arbiter, VP, Product and Business Development (in person)
- Pete Schwamb, Loop developer (by phone)

Other Attendees (by phone):

- Roy Beck - Jaeb Center for Health Research
- John Lum - Jaeb Center for Health Research
- David Panzirer - Helmsley Charitable Trust
- Sean Sullivan - Helmsley Charitable Trust
- Campbell Hutton - JDRF
- Dan Finan - JDRF

Additional reference:

- Loop Observational Study Protocol v6 (sent to FDA July 31, 2018)
- FDA feedback on Loop Observational Study Protocol (received Aug. 23, 2018), Q180770/S001

Meeting Minutes:

[Introductions. See above.]

Howard:
For benefit of people on phone - have both CDRH DCTD/OIR-IVD and PreCert people in the room.
As discussed in our first Loop pre-sub meeting, goal is avoid duplicate efforts to two FDA teams/programs.

Tidepool is appreciative of the cooperation and information sharing that has happened thus far. Appreciative of everyone being here.

Today's goal: Review FDA feedback and comments on Loop observational study protocol.

Courtney:
Were there any surprises?

Howard: No, none.
Roy: No surprises. Still brainstorming how to get more demographics.

Howard:
Feedback from FDA falls into two categories:
1) questions/comments on the observational study protocol
2) questions/comments on Loop itself
Will try to distinguish questions, but they commingle.

Feedback regarding Sponsor Question 1

Howard:
Regarding challenge of capturing a patient population [in the observational study] that's representative of the intended user population [once Tidepool Loop is released].
This generated a lot of conversation.
Clearly age is not the right way to think about it. My 5 year old nephew is much better on an iPhone than my 74 year old mom.
We don't want to give someone an iPhone test. That doesn't seem right.
We are open to other ideas on how to measure readiness, of both tech and diabetes knowledge.

Courtney:
When enrolling people, get info so you know who you've got [from a demographic standpoint].
Not aware of specific tools being used to measure [tech or diabetes] savviness; this is something for you to consider.
Think of other things that can stand in. Demographics that correlate.

This is also related to Prescription use.
Requiring a prescription can help with this because you can describe your user in the labeling and a healthcare provider will be helping identify users. There are some ways where a prescription can help you get in there.

Over the counter use poses challenges.
Someone with T2D might pick it up over the counter and start using it. For example, what other drugs are they on?

Digital health [team]… are there examples of other submissions that tested tech savviness?

Martin: Is there a tutorial in the app?
Howard: As of now, no, but we can consider that.
Martin:
This is common, that there is a tutorial, followed by a quiz. You can distinguish those who do and don't do well on the quiz. Can also have training and videos. Evaluate the effectiveness of the training. Perhaps enroll people in training who don't do well on the quiz.

Courtney:
We want to understand how savvy they are with the settings on the phone, and how that can impact how the app is used.
Have you researched others who have done this? Researchers, people in the tech community trying to assess a feature. Maybe they've published how they did it?

Howard:
We will need to distinguish between base level iPhone savviness and diabetes savviness.
For example, people may need to understand topics like basal rates, insulin sensitivity factors, insulin to carb ratio.

Naomi:
Think about dependable design of systems [to mitigate risk of how people may interpret and modify settings that affect the app/algorithm].

Alain:
In the study, use questionnaires to understand diabetes knowledge, understanding of diabetes treatment, motivations for pursuing treatments. So we know who's in the study.

Courtney:
It's unlikely you'll find a perfect way of doing this, we understand and recognize that.
We may be setting the state of the art.

Brandon:
Is there anything that can be learned from how this was handled with Dexcom G5 Mobile?

Courtney:
There was Human Factors [testing].
They weren't trying to define a specific population. Different use case, receiving data. They weren't dosing insulin.
This situation is to see if the study has a broad population that that is adequately representative of the intended use population.

Over the counter would be challenging. No insulin pumps available over the counter.
Goal is defining the population that's understandable, that can reasonably be expected to understand use of the app.

Brandon:
Can we define the population as people who have used pump and CGM before?

Courtney:
That's been done. Need to understand the success of people when they tried it, for example if they used a pump 10 years ago and hated it. Need to collect granularity [of information] of when and how they used it [the pump or CGM]

We recommend you collect as much information as you can on people using it [current DIY Loop, in the observational study].

Roy: We'll get IRB approval

Feedback regarding Sponsor Question 2

Howard: FDA feedback recommendation is that type of insulin be captured.

Courtney: Prior comment about some using Fiasp prompted that.

Brandon: Also Afrezza.

Howard: Feedback also mentioned capturing manual delivery of insulin. Roy, is that part of the protocol?

Roy: It would be retrospective. Indirectly we'll know. We'll know when they're using and when they're not.

Courtney:
Just get an idea of who is using insulin outside of their pump. We don't expect perfect dosing data. We just want them to report whether or not they're using [insulin outside the pump], roughly how often, what type?

Naomi:
We think this is how this [Loop] might be used. These data points will help us understand.

Howard:
The FDA feedback also includes "Additionally, you should consider whether the number of study participants will be enough for your data analyses given the large number of variables that might differ between device configurations for different patients."

When you say device configuration, assuming you mean pump [type/model] and CGM [type/model]?

Naomi: And [Loop] software version.

Courtney: There may be many software versions, you can aggregate them if similar

Naomi: Can also provide clustered data for G5 and G6 data if it is materially similar.

Alain: Software is biggest thing where there's a difference. Need to understand if there are meaningful differences between software/algorithm versions.

Courtney: CGM configuration also important. There's a meaningful difference in accuracy between the Dexcom G5, G6 and Medtronic sensors.

Feedback regarding Sponsor Question 3:

Howard:
FDA written comments include a question about how the Loop algorithm interacts with the Loop bolus calculator. Fortunately, they are part of an integrated system and work well together, in both closed loop and open loop modes.
We will come back with details on how they work and work together, and any necessary risk mitigations.

Howard:
On to device maker updates.

Brandon: Lots of support for concept of "iPump" across pump companies.
Howard: We've given them all our recommendations for iPump special controls

Brandon: Many of the device companies are also interested in making financial commitment to this project.

Howard: We are farthest along with [Device Maker redacted] and [Device Maker redacted]. We expect there to be more.

Courtney: When you're ready to start talking about submissions, or multiple submissions (theirs and yours, or all yours) let us know.

David:

Without a doubt there will be more than one [device maker]. I'm involved in a number of these conversations - there will be more than one.

The iCGM pathway has opened the pathway to iPump and iAlgorithm. Those conversations getting easier.

Howard:
The FDA comments request a written form of the Loop demo. Can we reference [existing DIY] online video tutorials and websites? Or should we create an exhaustive demo with narrative to include with this pre-submission?

Courtney:
You can reference things available. But we want to know what algorithm looks like.

Naomi: Keep it high level. Can just show screens and descriptions.

Courtney:
You can point to a tutorial and say "We're going to do it like this."
There were a couple times [in our last meeting] where you said, "We really don't use this part." If you know you're going to take it out, mention that.

Howard:
The FDA written feedback also says "we would like to discuss your view of the anticipated commercial version of the device, as well as the compatible device components."

My read of this is "Describe how you will interface with your go-to-market pump(s) and CGM(s)."

FDA: Yes. [Lots of heads nodding yes in the room.]

Regarding FDA Feedback Topic 4:
"Regarding clinical oversight of the proposed observational study, we recommend a clearer description in your protocol of the process for adjudicating adverse events, particularly when it may not be safe for a subject to continue in the study. We recommend that an additional contact be obtained for each study participant, as part of the clinical protocol, in case a patient is not able to be reached."

Roy:
We're not doing active monitoring. That is the nature of the study. We won't be doing real time collection or monitoring.

Courtney:
If a patient drops out of your study, are there mechanisms to find out what happened to them and collect adverse events that happened or didn't. Not intervening.

Roy: Yes. That's the important part.

Courtney: [We want to know] did they leave the study because they got bored, or because something happened?

Roy: Yes, we'll know how many start, then have to stop, and why [they had to stop]. That's a key part of this study.

Howard: Regarding "additional contact".
Roy: Yes, we think that's a good idea.
Alain: If someone drops out and you're trying to find out why, this will help.

Regarding FDA written feedback topic 5:
"We should coordinate additional meetings…"

Howard: Let's start scheduling these follow up meetings. That will help us focus on delivering information that will be helpful.

Courtney: If topics make sense together, that's fine. Meetings on the same day; or same meeting. Whatever works for you. They don't need to be separate.

Alain: Keep all of the information on this pre-sub.

Howard: Will PMA on the same Q number?
Courtney: No, that's different. You have to pay for the PMA. (Sorry about that.)

Naomi: Recommend that you read the guidance on 510(k) vs de novo vs PMA submission.
Howard: Excellent. This is an opportunity for further discussion.

Regarding FDA written feedback topic 6:
"... consider increasing the frequency of reporting of device issues and serious adverse events."

Roy: We'd originally said weekly, but we thought it was too much. In needs to be weekly or monthly.

Courtney: There's some info in literature suggesting weekly was better than monthly.

Alain: There's a balance.

Roy: We'll ping them via email. Will ask about DKA or hypo. If no, that's it. If yes, we'll dive deeper.

Courtney: When do you plan to start?
Roy: Hopefully by end of year. John?

Brandon: Best case scenario?
Roy: Reviewed by IRB next month. Best case scenario November.
Finishing preparation of Recruitment material, questionnaire from Korey. Need to build it into website. Pretty confident for before end of year.

[Meeting wrap up]

Courtney: We know none of this will be perfect. We're trying to work with you to make sure we can use as much of this [information from the observational study] as possible.

Howard: I want to thank both the diabetes team and PreCert team for both putting so much attention on this and collaborating.

Naomi: We're very interweaved.