Q180770 Tidepool-Loop FDA Pre-submission Meeting Notes

Meeting Time and Location:

- May 4, 2018, 11am - 3:15pm EDT
- FDA White Oak Campus, Silver Spring, MD

FDA attendees - Center for In Vitro Diagnostics and Radiological Health:

- Courtney Lias (DCTD Division Director)
- Stayce Beck (Director, Personalized Medicine)
- Alain Silk (Acting Branch Chief, Diabetes)
- Jisun Yi (Medical Officer)
- Yiduo Wu (Artificial Pancreas Team Lead, by phone)
- John Murray (Digital Health, on behalf of Bakul Patel)
- Naomi Schwartz (Software Reviewer)

Tidepool Attendees:

- Howard Look, CEO
- Brandon Arbiter, VP, Product and Business Development

Other Attendees:

- David Panzirer, Helmsley Charitable Trust
- Sean Sullivan, Helmsley Charitable Trust (by phone)
- Pete Schwamb, Loop and RileyLink developer (by phone)

Agenda/Discussion Documents

- This attached document was submitted to CDRH document control prior to the in-person meeting: Tidepool Informational Pre-submission Request
- This attached document was distributed via email prior to the in-person meeting and via printout at the meeting: Tidepool-Loop FDA Pre-sub Agenda/Discussion doc

Background & History

Discussed Loop and OpenAPS

- Reviewed brief history of these open source projects, shared lineage of Medtronic pump control code, noted that projects are different but share an online community via Facebook

Live Demonstration of Loop

- active insulin, temp basal
- use with exercise
- use of 30 minute max temp basal commands
- pump still has basal rate program
- use of different insulin action models

- FDA: how bad is it if you pick the wrong insulin model?
    - fine tuning, not a drastic difference
    - most people have longer durations than 3 hours (but most people have it set to 3 hours)
    - most people not looping have the wrong DIA (duration of insulin action)

- FDA: What happens with super fast acting insulin?
    - Brandon: I use Afrezza with Loop, drip out Novolog. Loop assumes insulin on board for longer, but ultimately self corrects based on glucose fluctuation.
    - Courtney: These are things we like to understand. How would an inexperienced user know to drip out Humalog? We would tell users to not use certain insulins?
    - What types of human factors would there be? May be able to mitigate issues with labeling.
- Brandon: Materially similar to a bolus calculator on a normal insulin pump that doesn't know about external insulin dosed when calculated Insulin On Board.
    - Brandon to Pete: Is there any way to to tell Loop that I got more insulin (than dripping)? Input into HealthKit?
    - Pete: Not currently. Not supported. Perhaps a future release.

- What are the parameters required to set up Loop?
    - target range - no current limits on range
    - can have different ranges per day
    - Basal rates: Currently set manually. Soon, Loop will pull basal settings from pump (so can only do it in one place).
    - Max basal on app and in pump - cannot override pump max setting
    - No current way to read max bolus or max basal from pump

- Calibration requirement?
    - Loop continues working as long as Dexcom generates data. Does not stop working due to lack of Dexcom calibration.

- Bolus
    - Loop allows adjustment in time of eating, can add carb info after the fact (e.g., for missed meal bolus) or adjust time, e.g., if food arrives late
    - use of carb absorption time
    - use of emoticons to indicate compound meals, food types
        - there is one carb absorption setting for each food icon
        - candy is fast acting
        - emoticons groups into different speeds for fast, medium, slow

- Dynamic Carb Absorption Model
    - deviations from prediction are an unexplained effect, assume deviations are due to carb absorption differences, allows us to dynamically account for carb absorption
    - if you said you had a big, 6 hour meal, but it actually absorbs fast, Loop will expire the not-yet-absorbed carbs faster
    - if you have delayed absorption, e.g. delayed stomach emptying, Loop can low temp basal or shut down insulin delivery
    - Are there failsafes? Does the average user need to understand how carb absorption works?
        - Most users don't look at or drill down into carb absorption screen. It's really a diagnostic screen for those who want to understand more.
        - Across the board, most users just let Loop do its thing. It requires very little intervention or tweaking.

- Can you make changes, administer boluses remotely?
    - Loop does not support control from UIs other than the user's iPhone app or Apple Watch. Parent/guardian cannot remote control, for example.
    - Nightscout does allow for remote control
    - In theory, Loop could use secure apple control notifications.
    - Courtney: Security can be solved. It's the human element that introduces risk. Do people know what is going on remotely. e.g. "Pass the baton."

- Bolus from phone:
    - Optional security via Touch ID, FaceID, or PIN code
- Exercise target range
- Eating soon mode lowers target BG temporarily
- Apple watch Interface
    - bolus from watch
    - Stayce: Does scroll up down do the right thing, not wrap around?
        - Brandon: Correct. It stops at your max bolus amount. Then you have to turn the knob the other direction to go down.

- Prediction Model
    - Four components (aggregate shown on home screen)
        - Carbs
        - Insulin
        - Momentum
        - Retrospective Correction
    - Detail screen to view each component's impact separately in the UI
        - Again, a diagnostic screen. Most people ignore this and only look at it to understand more deeply.
    - FDA: Is glucose momentum the same for everyone?

        - Pete: Calculated the same for everyone. Simple regression, slope from last 15 minutes. Projected over 30 minutes.
        - This screen is useful when people have questions about why/how Loop is predicting.
    - Pete: Retrospective correction: the only algorithm setting
        - This option likely will be removed and just made de facto - we recommend that everyone uses it
        - Looks at predicted glucose over time, similar to dynamic carbs, but looks when there are no carbs. Look at prediction from 30 minutes ago, compare to what actually transpired, assume that the effect will continue over the next 60 minutes. Assumes you forgot about carbs, or forgot to enter exercise.

General Intro Conversation: FDA Asks Tidepool about what it wants to do

Courtney: Fundamentally - what do you want to do? What do you want to deliver?
Howard:

- Fork Loop code, Tidepool will maintain and support the fork, be responsible entity
- Deliver an officially supported app via the iOS App Store.
- May change the name later, for now, will call it “Tidepool-Loop” (to differentiate from "DIY-Loop")
- We presume prescription required. We can talk about that later. [1]
    - Get prescription from doctor. Convey to Tidepool via web site.
    - Courtney: Can also give code to a registered prescriber.

Howard:

- Presume app is PMA - or at least closed loop component - is class III.
- Tidepool would be the registered developer with Apple, and the registered entity with FDA.
- Apple would see Tidepool’s name, support site, etc.
- Tidepool would provide support for Loop app.
    - Later, also want to talk about community side. Passion in community is great. Would like to leverage that.
    - Also understand a company needs to be responsible for CAPAs, etc. And escalate CAPAs, MDRs to right company (e.g., pump, cgm manufacturer).
    - Notable community feedback that customer service for Loop in the Looped Facebook group can exceed the support they receive from Medtronic or Dexcom customer service.
    -

Howard:

- There are companies that do not follow their respective social media communities. We would.
- We'd collaborate with a pump and CGM company.

Courtney: Currently, Loop pump is unsupported Medtronic. How will that play out?
Howard:

- Some other pump company. Could be any pump manufacturer, e.g., Lilly, Sooil, Tandem, Insulet, Roche, Ypsomed. At least one of them would need to delivery a controllable (via BluetoothLE) pump. Tidepool-Loop would officially support that device.
- CGM: Could be Dexcom, Abbott or Senseonics.
- Tidepool-Loop would not required the use of old, unsupported Medtronic pumps.

Stayce: You wouldn't need RileyLink?
Howard: Correct. New pump would have Bluetooth, RileyLink would not be required.

Courtney: Dexcom G6 is iCGM. I don't know if Dexcom is planning to upgrade G5 to iCGM. Are you only interested in iCGM?
Howard: We love notion of iCGM. If Dexcom put G5 into iCGM, that would make it really easy.
Courtney: You should ask Dexcom if they're planning to get G5 as iCGM. It wouldn't be hard for them.

Stayce: Roche isn't selling in the US.
Courtney: Would it be legally marketed pump?
Alain: All off the shelf devices?
Howard: Yes, would support legally marketed, off-the-shelf pumps.

Courtney: Let's deliver something that makes the DIY community feel like they don't have to do all this work.
Howard: We feel privileged to be on these systems.
Stayce: Tidepool's software would not be open to third parties to edit?
Brandon: Like Tidepool today: Open source code is available for others to spin up, but no third party can modify the code includes Tidepool's shipped products without our review and passing through our quality system.

Stayce: Ownership? IP (Intellectual Property)? Revenue model?
Howard:

- Still working on revenue model. Could be free. Could be subscription. Could be reimbursed by payer. To be worked out.
- Ownership - Tidepool would own it.
- IP - all Tidepool code is released under a permissive open source license (BSD2). [Loop code is also currently a permissive open source license, MIT]

[Tidepool note: We believe that reimbursement for closed loop system like 670g is currently the same as an open loop pump + CGM. To be investigated.]

David:

- There are a couple payors that are more forward thinking. We will get Tidepool in front of these two payors. They totally get it. We'd say to them what would we do here.

Stayce: Tidepool will have to maintain CAPA. That and other things will cost money.
Howard: Revenue will be important to that. As is ongoing software maintenance and support.
Brandon: Tidepool generates revenue today. Will figure out a business model that works, this needs to be sustainable. Real costs behind producing, shipping, maintaining, improving.

Courtney: Are you thinking of prescription? [See Note 1 re: Prescriptions]
Howard:

- We thought FDA would require prescription.
- We think no matter how you slice it, this is safer and more effective than the usual standard of care.

Courtney:

- The pump and CGM are prescription.
- We want people using these to not hide it from their physicians.

David: Depends on the physicians.
Courtney:

- We're happy to talk about that point [prescriptions].
- At the moment, there are no over the counter insulin dosing calculator. This is a new thing; but we've been operating like that.

David Panzirer: Are you expecting people coming to Tidepool with Roche, Dexcom bundled. Or interchangeable?
Howard: Labeling conversation. Tidepool does not want to label the whole system. We'd make an app and say which devices you can connect to. Your doctor would have to prescribe pump and CGM.

Courtney: If you want a pathway for G5, you'd need Dexcom to come into the conversation.
Howard: They're moving so quickly with G6. I'm not concerned about the G5.
Courtney: Dexcom could do it quickly for G5 if they put on special controls.

Howard: If we can demonstrate clinical trial data; and we were hypothetically ready in September but G6 still not in market (or covered by insurance [added later]), I think that would be compelling to Dexcom to make G5 iCGM. [Not a likely scenario - G6 is shipping now.]

Stayce: How long would it take to build?
Howard: 6-12 months to do software dev for new pump and all other changes for app.

Naomi: Where's PreCert at? I feel it's in progress; how can that help here?
Will return to interaction with pre-certification program later.

Cybersecurity
Howard: Cybersecurity requirements beyond existing guidance docs?
Stayce: You will have a plan for cybersecurity. You have a plan, you enact the plan.

Componentization
Howard:

- From agenda doc: Loop is (and Tidepool-Loop will be) constructed using a clean software abstraction mode that affords component-level manual and automated testing. It is possible to think of the various components of Loop (and Tidepool-Loop) using different risk profiles, e.g.:
    - Device Data interaction via HealthKit: MDDS
    - Cloud Data monitoring: Class-I/Exempt
    - User Interface: Class-II?
    - Control Algorithm: Class-III
      This concept is analogous to the interoperability model proposed by FDA where a system includes separately testable, and potentially interchangeable parts.
- Is there an opportunity to further componentize the review of Tidepool-Loop and only file a PMA for the Control Algorithm?
- Can some functionality for TIdepool-Loop be classified separately and released iteratively without further review, e.g. can ongoing enhancements to the user experience be considered Class-I or Class-II/Exempt?
- Can we consider a componentized review of the software?

Courtney: As we get further along, we can also discuss a componentized submission.
Courtney: When it's part of a closed loop, things that might otherwise be MDDS may not be.

Labeling
Howard:

- iOS and Watch OS app.
- I'd love to understand minimum age.

Courtney:

- What kind of data you're planning to get in clinical study?
- You want a closed loop claim.
- We can discuss age during discussion about clinical study.

Clinical Study
Courtney:

- What are you interested in doing?
- Are you planning to try an approach where you gather existing data? Get new data?
- Proposing something other than a trial?
- I think age is linked into that.

Howard:

- Roy Beck, with David, JDRF, Tidepool, designing a non-interventional study of Loop users. We'd love to use results to support our submission. Is that ok?
- Are there certain things we should make sure that study captures?
- What on top of that do we need to do? Based on 100s or 1000s of users?

Stayce: We love the use of real world data.
Courtney: A council is talking to Roy about design.
Howard: If Roy generated real-world data…
Courtney:

- I think he's going to take people on Loop, ask: how are they're doing?
- What fork are they on? Are the forks different?
- How long have they been on Loop? New Loop users?
- Overarching question of: can that information be used?
- If it's relevant, absolutely, you can use it in your submission. If it's relevant to safety, absolutely can use it.

Howard: As for forks, most people in real world are on the master branch.
Brandon:

- Forks and versions are two distinct concept. Most people are on the master branch, not a customized fork. Unclear to what extent people keep up with the latest version.
- Observational study should capture:
    - [ ] Fork / dev / master, version.
    - [ ] Using full time?
    - [ ] New users on Loop would be helpful
    - [ ] Will CGM data be captured?
    - [ ] Duration of time on Loop

Courtney:

- Certain lengths of time are too long [for survey questions]. If you're asking about hypoglycemia events, it needs to be reported quickly because people may not remember if help was required.

Stayce:

- If Roy is willing to take Tidepool's needs, that could be a tool. I'm not going to say that's all the data.

Howard: There will be opportunity for prospective and retrospective.
Alain: Representativeness of overall population?
Courtney: When you think of kids, what are you hoping for? Some companies are concerned that algorithm may not work in children.
Howard: Anecdotal, but I know there is a doctor who put his 6 month old [with T1D] on Loop.
Courtney:

- Sounds like you want to support kids. Include data for kids in the observational study if you can.
- Some developers are designing not be used for kids.
- FDA is supportive of the systems coming to market for kids and adults.

Stayce: We want a physiological and algorithmic reason [if you are NOT going to label for kids].
BA: What is the threshold of acceptability?
Stayce: Data collection on kids.
David: If we're going to do this we have to do this for kids.
Courtney: When you get to 0.5-2 years old and there's no CGM, you have a problem.
David: Why no approval?
Courtney: Performance, or it's hard to do the studies.
Courtney: Usability for kids is done via human factors with parents.
Stayce:

- Parents
- Adults giving care for other adults / diabetes naive adult such as nurse.
- Kids at whatever age the kid is expected to use it themselves. An 11 year old should do it themselves; a 6 year old maybe not.

Alain: How much in use data can we take advantage since it's already in use?

Human Factors
Courtney:

- I'm open to non traditional human factors.
- And people's ability to follow your instructions to link.
- Depending on how similar your UI is to Loop; can you analyze the online support groups for human factors complaints? If there were a lot of complaints and now there are fewer.

David: I think half the complaints are mostly about communication drop outs [phone to RileyLink, RileyLink to pump, or with Dexcom].
Howard:

- Great suggestion.
- We can analyze stream of comments in Loop group.
- Sort into: a) things that would be an issue with Tidepool-Loop; b) things that would not.

Courtney: Or show what used to be a problem, and what Pete already fixed.

Courtney:

- Show that the comments for the issue have gone away as the issue was resolved.

Brandon:

- Recapping Courtney. Loop being out and iterating for two years may have been a meaningful human factors test and mitigation. We should go back in time, quantify complaints, show what's been addressed. Do retrospective human factors analysis.

Courtney:

- Collect info in clinical trial, too. A lot of human factors usability data can be collected as part of that study.

Naomi:

- This is also less contrived than traditional human factors because people are actually using it.

Howard: Can also do surveys in the Looped Facebook group.

Courtney: Also will get new, naive users in there. It's not ideal to do a passive survey because there's bias of who's willing to do it.

Courtney: Back to clinical. Does Tidepool have a clinical advisory team?
Howard: We'll work on this with Roy Beck, Anne Peters, Bruce Buckingham, Jeremy Pettus. We do not have a clinical advisory team specific for this project [yet].
David: We're putting together a group of doctors.
Courtney: I think it's important Tidepool have Medical advisors.
Howard: We do have that. Saleh Adi, Anne Peters, Irl Hirsch, Bruce Buckingham are Tidepool's Medical Advisors.
Courtney: You need a process that loops medical advisors into some decisions.

Courtney: Clinical study. Are you envision other sorts of real-world world evidence?
Howard: Roy Beck [Jaeb center observational] study
Courtney: Things to think about:

- Safety information.
- More types of events?
- Alarming number of events?
- Hyperglycemia leading to DKA?
- Hypoglycemia on your system vs standard of care?

Howard: Does Tidepool need to generate baseline data?
Courtney:

- Medtronic had baseline data in their study rather than control.
    - Used duration to get safety information
    - Exposure: Certain number of individuals for a certain period of time.
- Also think about challenges to the system, e.g. exercise.
    - People have been critical of putting kids in a camp where they eat whatever they want. If you get more exposure, the less you need to do it in a contrived way.
    - Balance of making sure there's enough people to qualify as enough exposure.
- Have a variety of people:
    - Age
    - length of diabetes
    - education level
    - Unless you're going to reduce labeling.

Howard: There are hundreds if not thousands on Loop. WIll it be sufficient to gather data on those people, or will we need to do control studies?
Courtney: We won't ask for control studies. We'd like you to get some new users.
Stayce: People won't remember retrospectively their hypo events.
Courtney:

- Ideally they'd be using your app and pump.
- We don't need a control.

- App can ask questions about hypoglycemia.

Courtney: You can start with the existing system, then just show confirmation with your own pump and app. We are willing to let you leverage that data provided your app is similar enough.

Courtney: It's not hard to get an IDE.
Howard:
- I think we can have an app with largely Tidepool-Loop built UI relatively quickly.
- We could run a pump with RileyLink.
- Then do a smoke test to confirm it still works with the new pump.

Stayce: Numbers will be based on the differences between the two system.
Courtney: We'll want ages 2-6, 7-14.
Stayce:
- Jaeb doesn't want responsibility to actively recruit.
- For your system, you're offering to take the responsibility.

Stayce: "Bridging study" is the right terminology.

Howard: Can we run the study where the majority of the software (e.g., algorithm) doesn't change but we still iterate for some components (e.g., for the new pump)?
Naomi: What Howard is asking: If he is looking at his software as the system that he is testing, what parts can change later after the first study?
Courtney:
- If the Jaeb study is applicable, your IDE study can be pretty small.
- If Jaeb is willing, would be good to talk about the design.
- If Jaeb is willing to structure his study so it's most usable for shipping, we're willing to talk.
- If you're talking to payers, and we hear what they need, and we can get what we need. We don't want to ask you for things that they wouldn't ask for.

Courtney: We might say, "That's fine with us, you can do it that way instead."
[Tidepool notes: We'd be very open to having the FDA there with us for discussions with payors.]

Howard: We touched on challenges [to closed loop algorithm use]. For example, Tandem did a ski study. If we show diversity in age, use, use cases, we don't need to construct a ski or camp study?
Courtney: Medtronic did 100 patients for 3 months. If you have kids going to camp, school, vacation through their regular life, that's fine.
Sean: Jaeb's upcoming study would be using [older] Medtronic pumps [with Loop]; bridge study would be new pump. Is there any concern there, or are they interchangeable?
Courtney: We expect the pumps are similar. That's what the bridge study would test.
Stayce: That's what you need to explain to us.

Courtney:

- To claim iCGM is specifications for the algorithm. We are going to need - you'll have to tell us why your algorithm for glucose inputs are consistent with glucose outputs in iCGM. That will take a little thought. I'm sure you can do it, but think about it now.
- G5 performs similarly to G6.

Alain: Same idea as use with [older] Medtronic pump vs next pump. You need to claim what your pump needs in order to perform.
Courtney:

- With iCGM [de novo special controls], allows for small percentage of out of confidence range readings [ref 2]. You should think about that, what your device needs. Need to show how your device accommodates those readings.

FDA PMA Submission Requirements and Process;
Impact of Tidepool Participation in FDA PreCertification Pilot Program

Howard:

- We're part of the Pre-Cert program. We've shared our quality system with FDA, both CDRH-OIR and Digital Health Pre-Cert team. How should we think about what we should put into a submission for Tidepool-Loop?

Courtney:

- We can talk about the PMA scenario.
- In a PMA, typically would have Quality System information. Validation/verification info in software documentation would be reviewed in PMA. Also get an onsite inspection.
- We'd encourage approval of processes where possible, like updates. We don't need an update any time Apple releases an update.
- My understanding that PreCert will cover most of that. You'd be inspected; demonstrated processes in place; something would be reviewed. I'd not be surprised if there's no V&V info at all due to PreCert.
- What we need is more related to functional studies. Demonstrate people can connect to them to make a connected system. That's inherently part of the other studies.

Stayce: Need to include critical functional elements, like 30 minutes of temp basal.
Howard: PreCert is still playing out. Can we start showing you quality system now; get all of that out of the way.
Courtney: John, where's the point at which PreCert will do that? If not soon, we can do that soon.
John:

- Part of PreCert is closer collaboration. We're doing that today. Another company is working with ODE. The working model is not due to stand up until December. Then there will be one year of testing. Shift the center. Instead of collect all 12 elements, we can move some to the [pre-cert] excellence appraisal. We'd already have assurance they're going to do V&V.

- Tell us intended use, clinical data, validation (show that users can use it). We can establish different models and better ways to interact.

Naomi: I'm aware of that discussion as a reviewer [of the pre-cert program].
Courtney:

- So what does that mean for Tidepool?
- There's another process (you may not want to do it) that's always available: There's a modular PMA. You send certain things in early. Clinical data is the last module. That's an existing process.
- If you want to develop another way to look at things ahead of time, we're willing to do so.
- What data do you plan to generate, what's the timeline?
- Then FDA can consider whether PreCert will work.
- I don't think it's a good time to do it now.
- We need to understand what pump you're going to use.
- We need to understand whether PreCert will handle EMC, Wireless.
- We need to know some parts of your systems, your partners.
- There are multiple ways this can be done and we're used to working with people ahead of time.

Howard: Based on that, I think we should start thinking about starting to submit components. A few months down the road we'll have a better sense of pump partners. There are things we can do as that plays out. Big chunks of our quality system exist. I'd be happy to show you those things (build, test software, track bugs, etc). So we can focus on the clinical study stuff. I think we can move faster than PreCert.
Courtney (to John): Are there elements of PreCert that can be leveraged?
John: I think there's a lot of alignment, so should be leverageable.
Naomi: Has it been digested?
John: No, that would need to be done.
Courtney: Tidepool and my team at CDRH will work together, and CDRH will keep PreCert up to date.
Howard: We'd love to not duplicate efforts. But we will if it's helpful to the cause.
Howard: Should we re-share what we've already shared with the PreCert team?
Courtney:

- Here's what we've done wrong in the past. We've looked at software and then there are changes. Then so many things change that we have to start over.
- Step one is knocking out the timeline. There will be a point that we'll tell you to stop [changing software] before a problem happens.
- The other thing that companies do wrong is when companies iterate after the submission and it slows things down. Maybe you want to update the UI, but that may negate your clinical study data that you've already collected.

Howard: Good segue to iterative software development.
Courtney:

- We're not saying software shouldn't change.
- Bug fixes, etc., just talk to us first.

- Accommodating OS updates are expected.
- Different category than I found a bug in how Loop delivers insulin and we need to fix it. How you fix it and when you fix it is better to make us aware and find out if we agree.
- There's a point at which you haven't reached it, communicating about those things is important. But some of your updates won't fall into this category.

Howard:

- There's not a clear demarcation line.
- Substantive algorithm change, we should talk through.
- Adding a secondary display of data is different.
- If we change the pump settings UI, would we need to talk with you?

Stayce:

- That might be a nice to have and we recommend you not do that.
- Does that merit another human factors study?
- Sometimes it's better to get it approved, then make the changes.

Courtney:

- But there are areas we can talk about ahead of time. Even algorithm change.
- Usually we'd say no, but, we encourage people to identify parts of algorithms they can tweak. Within certain bounds.
- Talk about the types of changes and the acceptable bounds of little changes.
- Need to consider user safety and new risk introduction
- Have an approach to address these things for any given type of change. You have a process.

Brandon: Bounds on future changes to components to the app?
Courtney:

- Not after approval. Just before approval.
- To move fast, need to say 'let's just go with this.'
- There's a reviewer here who's trying to understand what's going on. If we're two months out, let's just get through these two months.

Howard: Is there some regular cadence we meet and talk with FDA about what changes we're thinking about?
Courtney: Do it internally. Think about how you'd bucket it. Tell us the buckets and hopefully we say 80% we don't need to see before you implement.
Alain: And how you determined what category things went in.
Howard: I've read every line of code in Loop. It's very clean. A good model-view-controller abstraction.
Naomi: Also should submit an architecture design map for FDA to review. If you can show that, we can use it to say whether we need to review something. Demonstrate level of risk and mitigations.

Howard: Implications on PreCert is we keep chugging away. Anything that can be leveraged, great.

Courtney: Will keep PreCert in the loop and talk about what can be leveraged.

MDR / CAPA

Howard:

- This leads into responsibility with MDRs, CAPAs and other manufacturers.
- We feel strongly that every component of the system should be logging as much as possible.
- We [Tidepool] certainly will do that.
- Every command sent/received to/from pump/iCGM will be logged.
- Detailed logging and auditability is key to traceability, quality, root cause analysis.
- If we presume we are doing that, should we move into MDRs, CAPAs, other manufactures?

Courtney:

- You get a complaint, you'll have a process on whether it's reportable.
- We know we'll get reports for things that may not be Loop. Remains to be seen how many there are.
- If you determine it's Dexcom, they sent you the wrong thing, the plan you send to FDA does need to include your plan to send the report to Dexcom with enough information for them to file their own MDR. Then it's squarely on them to file theirs.
- This may not resolve all finger pointing or squabbles. But logging makes it much easier to see what went wrong.
- Human element becomes the problem, when we're not sure what caused it. Someone got hurt and there's no clear reason why.
- You are the AID controller. You are the one dosing insulin. They are considering themselves using your device.
- Example: "My husband is on Loop. Came home, he's unresponsive. He went to the hospital, had a stroke."
- That's the extent of info. Don't know if there was an occlusion or if CGM was wrong. These things happen. If they happen often, you should catch it. If results trend up, is there a reason based on my device design.
- This is benefit of iCGM. CGM company is taking responsibility for other device using the CGM result. That's why we put this on the CGM manufacturer.

Howard:

- Let's talk about the pump.
- We expect secure Bluetooth LE protocol. Allows us to talk/control the pump as digital syringe.
- Some asked "What if they have PLGS?" We think simplest is to have either the pump or the external controller in charge [via setting in the pump]. Either it's a 'digital syringe' or it the pump is in charge. Avoid competing controller. If the pump loses communication with external controller it can revert to open loop control.
- Today, pump [without CGM] is Class II.

Courtney:

- Insulin pumps that don't connect to CGM is class 2.

- Intended use of CGM would be a primer.
- When that pump manufacturer makes a modification, use analysis in the other system.
- Pumps that claim they are intended for people 18 and older are not responsible for safety in children.
- If we went down that path [controllable pump], the pump would know they are intended for someone else to control.

Howard: If I'm one of these pump companies with a Class-II pump, then add communication/control protocol?
BA: What would pump company have to do?
Courtney: Pump company would come to us and ask is there a Class II way to do this.

Howard: We publish openly all documents. Is that ok?
Courtney: Yes.

Naomi: All docs available. Are manufacturers ok with this?
Howard: Some device companies may ask us to keep device protocol spec document private. That's the one thing we've kept secret upon request. But all source code is open.

Insulin
Some Loopers use Fiasp.
Jaeb should ask what insulin people are using.
Courtney: If in the future, Fiasp was approved for pumps, it would be helpful for you to have that information already from Jaeb observational study.

Mobile Operating System Issues
Howard: People have asked if phone call interruptions are an issue.
Naomi: There are a set of canned mobile device use cases. Have you thought these things?
[ ] Get FDA Document: canned mobile device use cases from Naomi
For example, make sure there are alerts when battery is low
Stayce:

- You'd have to focus on pump.
- If phone call when bolus or basal execution.
- Data from some study showing loss of connectivity. The way it's design to default to basal rates might mitigate.

EMC Testing
Naomi: Need to conduct EMC testing with phone, sensor, pump.
Courtney: If a pump company whose iCGM is controlled by a phone. Plan for communication may include that.
David: Bigfoot and Lilly are probably going through this now.
Courtney: Example: My phone interferes with my baby monitor.
Naomi: Tidepool needs to ensure that pump company has done this testing. There's a huge body of knowledge. Recovery needs to be safe.

Howard: Need to make sure communication protocol is robust to interference.
Courtney: You can send this off to be done.

General Discussion
Courtney:

- Yiduo and Adam Berger working with CDRH and PreCert
- We do a lot of software reviews.
- Connected pump and devices have unique issues because they provide critical functionality.
- This is not an opinion shared throughout the dept: Premarket reviews are not particularly useful. 60% of recalls would not be found in premarket review. We don't see a recall as a problem; they're correcting things that should be corrected. You're not going to describe bug you don't know about. We're not going to discover it. Post market scenario is where a good quality system is valuable.
- Where we get antsy is when design changes. Fundamental design of interface and algorithms we have more changes. Maybe that's two broad categories.

Howard: I think we should categorize things and say "These are the things we can iterate on quickly. These are the things that we should talk about."

Courtney:

1) nailing down time frames are important. They're not nailed down, but they set a framework.
2) What you're planning for with clinical trials.

Stayce: Talk to Roy about whether you want to use his study.

Howard: In summary, could be:

1. non-IDE observational study
2. (Optional) study with RileyLink, IDE in between
3. Bridge IDE with go-to-market pump and CGM study

Brandon: Why IDE in between?
Stayce: Largely to cover level of education gap not covered by a observational study.
Courtney: 7th grade reading level.

Courtney:

[ ] When is the appropriate time to discuss this clinical study?
[ ] If you have a pump partner, we can talk to them (with or without Tidepool)

Courtney: After clinical meeting, figure out feasible time frame. If you have 1.5 years before pump is ready, that's your time to play with. If you have a pump available in 6 months, how do we make this happen in 6 months?

Naomi: We do see of MDRs for loss of comms. Would be useful to look at logs. Document your mitigations for those issues.

Alain: Identifying the pump seems like a bottle neck. If you're talking to people and you think there are things that are stopping them that are relevant to FDA, we'd like to know.

Courtney: If the pump company want to send us something, send a PreSub to me with "Sensor augmented pump intended for use in automated insulin dosing system" so it gets to CDRH-OIR.

Courtney: We say automated insulin dosing instead of automated insulin delivery because the latter is used to describe normal pumps.

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[1] Prescription Topic
Follow up email 2018-05-08 between Howard and Courtney:

Howard:

> In working on editing the minutes/notes from the meeting, we realize that we didn't come back to the prescription topic. It would be great, if possible, to get your thoughts so that we can include them in the meeting minutes. I think the prescription-related questions are:
> - Is there a scenario where the Tidepool-Loop app could be made available without a prescription? Under what conditions would this be allowed (usability, labeling, etc.)?
> - If a prescription is required, is it only for the automated closed loop control functionality, or for the whole app to work? Can the rest of the app be thought of similar to a bolus calculator app (downloadable and usable without a prescription)?
>
> Also, I'm having a hard time finding the appropriate regulations or guidance documents to read up on this topic. I do see some examples of Class-III devices that are available OTC. Do you have any recommended reading?

Courtney:

> This is a good question but not a simple one. It will certainly require a bit of internal discussion outside of our immediate group as well. For example, currently there are no legally marketed bolus calculators or pumps that are available OTC, so there would not be a regulatory precedent there.
> I will see if there is relevant reading, but there may not be a lot. We can talk you through the types of questions that would be considered at our next discussion perhaps. In the meantime, we will try to think here about the main underlying risks that may need to be addressed (if any).
>
> Sorry if that isn't completely helpful, but if nothing else this is a good reminder that this needs to be thought out soon.

[2] Integrated continuous glucose monitoring system (iCGM) de novo special controls detail: https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170088.pdf