

Adrian H.: [00:00:04] Hey, this is Adrian Hernandez and welcome to the NIH Collaboratory Grand Rounds Podcast. We're here to give you some extra time with our speaker and ask them the tough and interesting questions you want to hear most. If you haven't already, we hope you'll watch the full Grand Rounds Webinar recording to learn more. All of our Grand Rounds content can be found at rethinkingclinicaltrials.org. Thanks for joining.

Lesley: [00:00:27] Today we're here with Dr. Steven Steinhubl who will be reflecting on a Digital Pragmatic Direct to Participant clinical trial for identifying undiagnosed atrial fibrillation in a large health plan population. Welcome Steven, it's great to have you with us.

Dr. Steinhubl: [00:00:45] Thank you Lesley, it's a pleasure to be here.

Lesley: [00:00:47] Let's begin by having you tell us a little bit about your study.

Dr. Steinhubl: [00:00:50] Well, the study which we called mSToPS, which is mHealth Screening to Prevent Strokes, was initiated by an early conversation over five years ago with Aetna around, okay, how can we do a trial together reaching out to our members across the nation that can help decrease the risk of stroke. So after much discussion and planning we said, "Okay, screening for atrial fibrillation, undiagnosed atrial fibrillation, would potentially be very valuable doing that." Once we decided "Okay, this is the problem that we're going to try to address," and then we, our team, which has behavioral scientists and clinical researchers and big data analytics, worked with the Aetna team to flush out a trial that was designed to be digital by its very nature so that outreach would be digital to Aetna members and that for individuals who consented that they would wear a ECG patch.

Dr. Steinhubl: [00:02:00] After we looked at many different solutions for best monitoring, and we decided to that the iRhythm Zio which provides up to two weeks of continuous ECG monitoring, would be what we used. And then committed to returning those results to the participants. So we really wanted it to be a trial that answered the question about screening for atrial fibrillation, how effective is a strategy of an ECG patch at doing that, but designing it in a digital and patient-centric way that provided results that we were hoping would be pragmatic enough where Aetna or other large health care payers could say, okay, we want to implement this or we want to implement this part of what you learned or refine this part of it, but that they would be truly real-world results.

Lesley: [00:02:53] That's great, and can you summarize what you found?

Dr. Steinhubl: [00:02:57] Well, there were two trials built in. We wanted one to show that we could do a prospective, randomized trial within the health plan. So there was a four month primary end point that looked at consented individuals who agreed to be active monitoring and they were randomized to either immediate monitoring with the ECG patch or delayed by four months. So the primary end

point was looking at the rate of AFib diagnosis in the actively monitored versus, or the immediately monitored versus the delayed, and we found a nine fold increase in the diagnosis of atrial fibrillation in the immediate monitoring cohort.

Dr. Steinhubl: [00:03:40] We then combined that cohort into one, those two groups that immediate and delayed monitoring into one actively monitored cohort and compared their outcomes at one year relative to age, sex, and CHADS VASc score matched observational controls. And then in that group out to a year found a three-fold increase in the rate of diagnosis of atrial fibrillation in actively monitored relative to the observational controls and associated with that an increased use of anticoagulants, but is also an increased utilization of things like cardiology outpatient visits, primary care visits. But interestingly, but just not a prespecified end point, we also saw a significant decrease in hospitalization and ER visits for those who were actively monitored.

Lesley: [00:04:33] Good, good, thanks, thanks. It's always helpful to have that before we dive into some other questions that I have. And one is specifically around the nature of the pragmatic study or that aspect. In the Collaboratory, we often think pragmatic is another way of saying lots of unexpected surprises along the way. So I'd love for you to maybe touch on what you learned and in particular, aspects that you designed to be pragmatic but maybe learned along the way that pragmatic wasn't quite that.

Dr. Steinhubl: [00:05:13] It's a great question and the podcast we don't have enough time to go over everything that didn't turn out or that were surprises. But, I love your definition of pragmatic, and that's very much the case. But I honestly think clinical care is like that in all the variation in it. So I'll start with what we kind of knew would have the most variability, but I was still a little bit surprised by and that was, so there were no physicians involved in the study in the sense of multiple cohorts or health care systems being involved. Everything was direct to the participant. When the participants got their results, especially those who had new diagnoses of atrial fibrillation or any other actionable things, when we discussed those results with the participant, we always asked for their permission to share the results with their practitioner and then get their practitioner's... whether it be, for most people it was a primary care doctor, for a very small number, cardiologists, and then we sent them their results.

Dr. Steinhubl: [00:06:14] When you look at... There was incredible variability then among the different practitioners, which we didn't account for, and there are things I would do differently to maybe help guide the, maybe provide a little bit more clinical decision support. But what was most surprising to me is that the percentage of individuals who were started on anticoagulation with the diagnosis of atrial fibrillation in the actively monitored cohort was a little bit less than 50%, which was not nearly as surprising to me as the fact that in the observational control cohort, so pure clinical diagnosis of atrial fibrillation, it was also about 50%. And I have, and the average in mSToPS was about 74. Our median CHADs VASCs score was 3, so it's a group that should have had a higher rate of anticoagulation

than 50%, but that was real-world. It was surprising and maybe disappointing overall, but that's just the reality of what real-world practice is. I think if we were to do it over again, there are a lot of things I would try to do to try to change that to provide maybe an easier decision tree for the providers looking at results.

Dr. Steinhubl: [00:07:33] The other big lesson, and this shouldn't have been as big a surprise to me. Apparently I thought it was a surprise when we were designing the trial and didn't think of it is, I very unrealistically assumed that once individuals consented and then remember, some of them were delayed to get the patch for four months, and as an older population some were snowbirds who were living in different locations, but it ended up about 1/3 of people in the actively monitored cohort were sent a patch and never wore it. To me that was really a failure in design.

Dr. Steinhubl: [00:08:10] Maybe it is pragmatic. So if Aetna was going to send out a screening and the people said, "Sure, I'll wear it," and then they ended up not wearing it, that's good to know. But that is something that I know that I should have and we can do better by just reminding people and reaching out to people and being more proactive when we know that the patch was being sent out to remind people to wear it and the importance of wearing it. I think that we would have had a much higher rate of individuals successfully wearing their patch.

Lesley: [00:08:42] Yeah, yeah. No, those are good strong lessons, I think, to highlight there. The level of participant engagement or the focus on participant engagement is also noteworthy in this study. I wonder if you could talk a little bit more about how you approach that, how you identified participants for engagement, kinds of activities.

Dr. Steinhubl: [00:09:07] Yeah, and there are, if I breakdown engagement in three different areas, I feel really good about two of them, or I feel okay about two of them, and I feel less okay about the third one. I'll start from the very beginning. So one of the things I would put in the category of a surprise, what I found to be very valuable to us is working with the Aetna team who really have many full-time employees whose job is to know their members, to reach out the their members in a very customer-centric way which is, I think, different than what we do in health care. So, they were very helpful to us in helping, you know, as we discussed the message and the outreach. Because really the beginning of the engagement was trying to tell people a story about the study and doing it digitally, which has some really good and some challenges to it, but you know that when somebody signed up, they were going to actually read it and understand it.

Dr. Steinhubl: [00:10:11] So inviting them to be part of the study, but without, for lack of a better word, freaking them out that, "Oh my god, my insurance company is writing me and telling me at risk for AFib, what should I do?" So, refining that messaging by working with people who have a lot of experience and a lot of history of communications to health care, or communications, health care

related communications was very helpful to us. So in our engagement strategy, we tried multiple different kind of personas, individuals who were altruistic, individuals, and these are kind of fictional individuals where we tested altruistic messaging, tech messaging, "Gee, do you want to? Are you excited about the new tech?" Another messaging was "Learn more about yourself by wearing an ECG patch, or using the gadgets."

Dr. Steinhubl: [00:11:04] So we were able to refine those messaging and with the eventual goal of trying, we weren't able to do it in this study, but as we go forward from lessons learned, is better individualized because in a perfect world, you'd want to reach out with an altruistic people to people who would join altruistically and you'd want to reach out with a "learn more about yourself message" to the individuals who would be interested in learning more about themselves. We have to figure out ways to prospectively identify that.

Dr. Steinhubl: [00:11:33] The part where I think we fell short on engagement that if we had the chance to do it over again, as I already mentioned, in the middle part of it. So after they enrolled, kind of while they're waiting to get their patch, maybe when they get their, immediately after their patch, just a "thank you," "did you have any questions," or any ... Those things I think, if I do it over again, I wish we would have had a very light touch engagement during that period both for the reasons of wearing the patch or just making sure that people didn't feel like "Oh, I wore the patch, now I'm done, you're done with me," kind of feeling.

Dr. Steinhubl: [00:12:12] The third part of engagement that I'm happy with, but we could certainly improve, was returning results to the participants. We told everybody at the beginning you get your results, but I heard from so many participants, who a lot had participated in clinical trials before, they had no expectation actually that we meant we were going to give them back their individual information. And they were, everybody who at least contacted me was saying how exciting that was, how much they really appreciated that, and how it made them want to participate in future clinical trials.

Lesley: [00:12:43] Oh, yeah. Thank you. That's great, and I like the way that you divided those into those three buckets. That's really helpful to think about. Steven, I want to thank you again for joining us today for Grand Rounds and for joining me today for this podcast. Please join us for our next podcast as we continue to highlight fascinating and informative changes in the research world. Again, Steven, thank you.

Dr. Steinhubl: [13::13] Thank you, Leslie.

Adrian H.: [00:13:16] Thanks for joining today's NIH Collaboratory Grand Rounds Podcast. Let us know what you think by rating this interview on our website and we hope to see you again on our next Grand Rounds, Fridays at 1:00 PM, Eastern time.