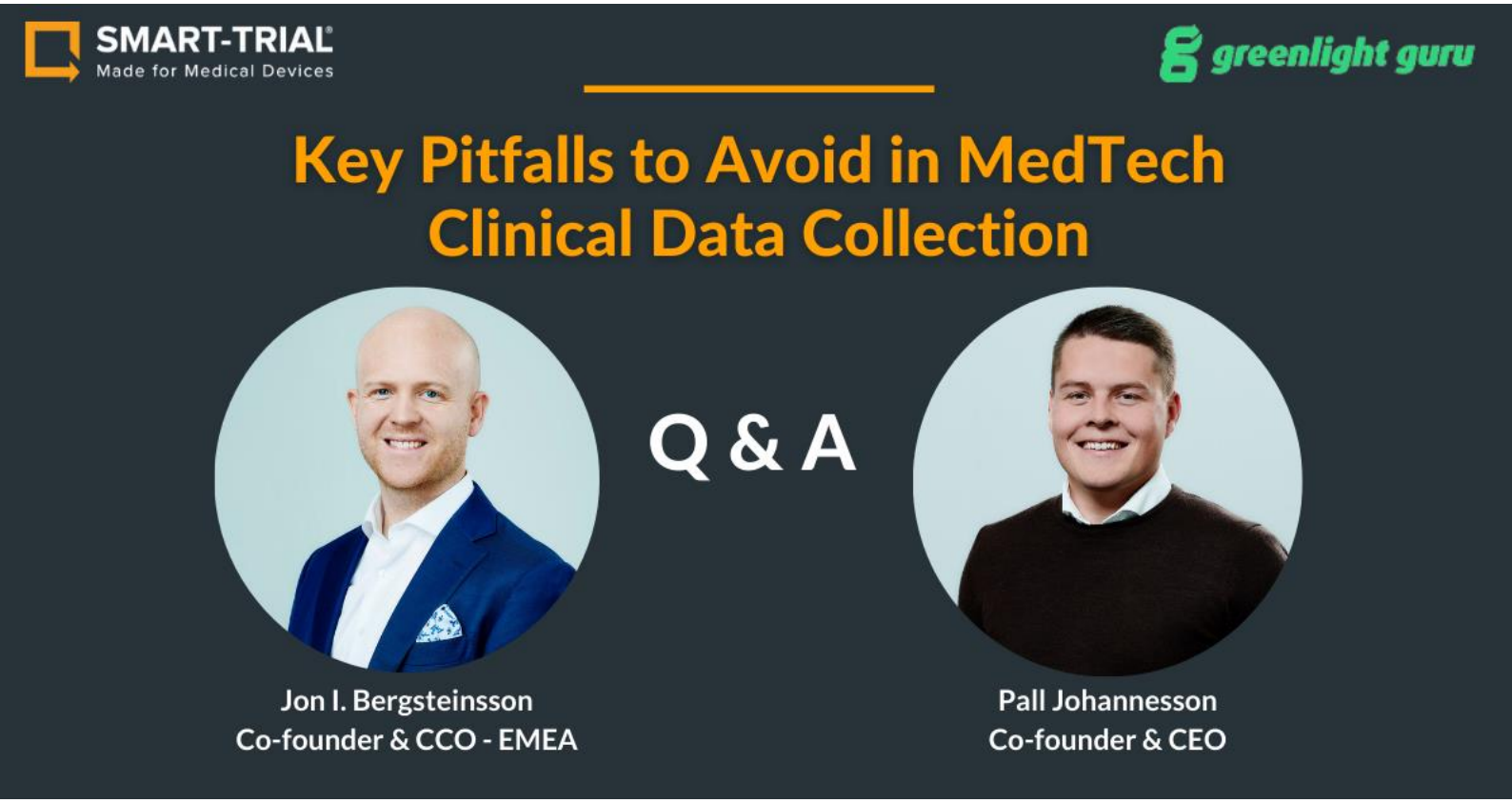

Question Overview

1. **How to conduct a clinical development plan specifically for a device that has been CE marked?**

***Jon**: It depends on device classification, the risk category, and whether there are existing devices out there on the market. Believe it or not, you can still claim equivalence or similar predicate device in Europe if you have access to the technical files and clinical data on that device. The clinical development plan in Europe follows somewhat of a standard. Of course, like always, you need to produce some initial data on safety, you need to have initial data on performance and whether you produce that yourself or not depends to an extent on the factors mentioned above. Then you have post-market clinical follow-up activities that need to cover data and clinical information that's gathered on your device throughout the device lifecycle on the market. So, the clinical development plan is not only the regulatory pathway and all that's related to that within the market area you're trying to access, but also the strategy that you're going forth with.*

***Páll:** When it comes to a device that's already CE-marked, especially considering the strategy part, if for example that says, we'll start in one therapeutic area or for one specific diagnosis, then you can move your way through, I would say, different clinical areas or different diagnosis of different configurations of your device, and that would then be reflected in your clinical development plan.*

2. **What about the CRF? If you're not filling those out, then you are out of compliance, and maintaining those forms is a lot of work. That's the minimum that you must do as part of data collection. Are you suggesting cutting down on the CRF so that you don't collect too much data at the end of the study?**

***Páll**: Basically, yes. You still need to keep your eyes on two things. So, depending on what your claims are for your device on safety and performance, you need to make sure that you're meeting those endpoints. So basically, you can support those endpoints with clinical data from your CRFs, but we are advising that you do not collect data that is merely interesting, so to speak. We see companies that end up collecting unnecessary data because now we're already there, so we'll add 30 different variables that might, at some point, become interesting to us but are not necessarily a requirement for us right now to maintain our pathway to market or to be able to make*

these claims that we want to make when we go to market. So, keep an eye on what you need to do first and stick to that.

Jon: *Another thing regarding getting the data in there, that is also somewhat related to not only just designing a nice CRF or a nice data collection form or not having too much data, has a lot to do with motivation too. I know personally, when I first got into this industry, I was working as a data and staff member for a clinical trial, and what frustrated me was the lack of appreciation that I was getting. The same goes for clinical staff. I've been at clinical sites sitting next to a nurse who was entering data, and she just keeps rolling her head around because it's not motivating enough. Others are head over heels about the study that you're driving because it's so much fun. So, it also has a lot to do with how you communicate with the people at the site. Are you motivating them well enough? Are they even interested enough? Have they been presented with the values that they're providing to this study? Everything impacts your data collection. Yes, cutting down on data points can help, but like Páll just mentioned, there's a thin line there and that's some of the things that we tend to be experts in, and we tend to share that experience with our customers. When they design their studies, we tend to provide feedback on that part so that people can take that in and then decide what they want to do with that.*

3. Can you clarify why a good study design is not equal to quality data?

Páll*: If you designed a study, it does not mean that you can produce high quality data because that depends on several different factors. Quality of data can, for example, be defined by the type of variables you're collecting. So even though your endpoint might be very clear, that endpoint can be collected in different ways. If the way that you choose to collect your endpoint results in challenges for data analysis that can generate low-quality data. If the data has errors or hasn't been validated, or the form isn't designed well enough, the information that is put into the system might not produce the results that you're expecting. Data quality can be affected by for example, typos or even just a lack of testing simply because the form that you wanted them to answer now got forgotten, because it was not placed at the right time, or it wasn't seen within the system because it could have been looking differently. You could have the greatest protocol ever, but there are so many factors involved when it comes to the data collection itself that can impact the quality of data.*

I guess also what counts is, what you consider when you describe a "good study design". If that is a reference to the protocol, then the points I have just made are valid. If you are taking a more holistic view and thinking about "good study design" as including CRF design along with all your other plans, such as your risk-based monitoring plan, your safety plan, etc., then a good study design will produce good data.

4. Do digital health devices have other clinical trial pitfalls besides the ones you have listed?

***Páll**: Some of them, yes. Interestingly, we've even seen digital device companies starting on paper, although it will be way less common than starting on a digital solution. But one of the pitfalls that we would see for them that we don't necessarily see for all the others is that they're much more prone to think that they can actually build their own system, build their own database, and they can just use that because they already have the resources or the skills in-house. I would say - Build a validated solution for the data collection project. But that is a pitfall we see because then they end up trying to maintain something that is not really their core business, and it ends up getting washed away in the end because it's not as important as everything else that they're doing. We can actually just make our own data collection tool next to our digital health device or digital health product, we can add our own forms in there or something like that. And we do see that there, but that would probably be the most common one.*

***Jon:** I also think that the amount of data to be collected is very common for this type of devices. Again, you would think that the most important parameter ever is the measurement that your devices may be producing or the result itself or the outcome itself. Again, going a little bit back to the fact that you have to think a little bit further than that because if you're going to be selling your device in one way in one country, and another way in another, shouldn't you think about some of those parameters that you need to prove the value of the product in those different countries in your clinical study as well, without focusing too much just on the results that are generated by device itself?*

5. **What would the documentation look like when we ask it from vendors? Is it some sort of compliance report?**

***Páll**: Yes. So, it looks mostly like the documentation you would expect yourself to be making basically. So, you know the documentation for medical devices, you need verification, validation reports, it needs to be signed and stamped. And in most cases, when it comes to compliance, it needs to map out how that solution is compliant to a given set of regulatory requirements or standards. That mapping can be done differently, sometimes we see it done in an Excel spreadsheet. We sometimes see it done on a designed PDF or in another way in a report, but you would expect that report to be fairly thorough and fairly easy to read when it comes to explaining how this tool facilitates compliance towards a specific standard or regulation.*

***Jon:** In section 7.8.3 of ISO 14155:2020 there's a list - a bullet points list that actually defines what kind of documentation requirements a software would need to fulfill what you're going to be using for clinical data collection in the digital matter. And it goes through everything from verification, validation, documentation, to other facilitation documents, so you could actually look at that section specifically to get a feeling of what's required.*

6. **When you're gathering data, you sometimes realize that there are questions that shouldn't be there, and new questions that need to be added. In that case, do you have to scrap all the previous data anytime you make those changes?**

***Páll:** You don't have to scrap what you already did. It's common that you submit protocol amendments where you request authorization from the authorities governing your study, to make changes in it going forward. When you do so, try to make sure that you don't do many of them. Try to gather further evidence, and proactively seek out any other issues that might be related to your study and make a single amendment rather than multiple amendments. That's because it might affect the way the clinicians are working with your device, or the data that they or the patient are giving. So, it changes some of the workflows, the endpoints. Again, you don't have to scrap what you have already. It's important to keep the 'old' data while collecting new data so that you can always document what the previous and new versions are. Test before you release the new version of your study for clinicians and patients.*

7. With the new medical device regulations, some companies are not going to renew their CE certification in Europe. Can those be used in clinical investigations in Europe?

Jon: *This question could be asking two things – firstly, that the device will lose its CE marking as it has not and will not be renewed under MDR. In that case, it becomes an investigational device and can only be used in clinical investigations when considered to be investigational. Secondly, and I suspect this is the case as it is a very common scenario, this may be a device that does not have the required evidence to keep it on the market in Europe, for instance where a device has been up classed from, say IIa to III. The most common pathway now is to generate the required evidence to obtain a Pre-market Approval (PMA) or Pre-market notification (510(k)) in the USA. In this case the clinical studies may have European sites and may be using the device as a CE marked device for part of the trial, and an investigational device for the remainder of the investigation. Ultimately the device would gain clearance or approval in the US and would then be CE marked in Europe – presumably if the device was valuable enough to go through the FDA process, it would have similar value in Europe.*

8. I was wondering if you have any idea about how to calculate an estimation cost for trials before it happens. Can you provide any resources for budget planning in advance?

Páll: *If you don't have the experience of running studies yourself, reach out to for example a clinical research organization (CRO). They will be more than happy to cost it out for you and give you a budget for it before you make the commitments necessary to move forward with it. You can use that as a benchmark. If you want to do it yourself, it's all about writing down the plan of what you're expecting to do, what the bare minimum is for the data that needs to be collected in order to document the feasibility of your device, or feasibility of going ahead with actually pushing the device forward to the next steps. Use the insights and feedback from the CROs, and from your own experience and insights into your own device and apply all these in the area that you're entering to build out the budget. But there's not really one true story to this, because it will depend a lot on the therapeutic area. It will also depend on the location of where you'll conduct the study; access to clinicians can be very difficult in some locations, as compared to others. There's no true answer to this aspect, as there are*

many things to be considered, but you could probably get close by asking CROs to cost out the study and make out a plan for you.

Jon: *In Europe, there are also a lot of individual research units in hospitals. For example, in Scandinavia (Northern European region), some of the larger research hospitals here that are connected to universities, often provide what you could call 'full service clinical research organization'. That is because they have physicians, research staff, they might even have a platform like SMART-TRIAL managing all their studies. So, even there you could get a second opinion. But a big cost factor is, like Páll explained, the sites. The CRO might be able to provide you with the cost estimates for producing the protocol and everything they need to plan and initiate the study. There's also the cost of the staff who conduct the study, and for that you would need to contact ta site or request that the CRO contacts their sites to get a cost estimate.*

9. Do you recommend using a CRO?

Jon: *I would say it is case-by-case. Some companies for example prefer not working with a CRO because they might have their own strategy to build their clinical operations. And that can be a good this, because it can greatly reduce the costs, or improve your knowledge and know-how of your own device, clinical data since you handle everything. So CROs are a good option for some companies, and not for others.*

10. What pitfalls have you encountered in MD field which involves single solution comprised of physical sensor unit and software parts?

Páll: *Many products now have both physical parts and software parts making up their device, even implantable devices in some cases. In general, the pitfalls are common across device types and so having this combination is not necessarily different. I think the most likely pitfall would be not making sure that you have a method of bringing in your device data into the study. For example, if you bring in device data using our connected devices module, you can see the data alongside the other study data as it is being generated and can see the impacts this has on the patient in near real-time. If you only merge the data post-hoc, for instance after study completion and database lock, and analyze it during your statistical analysis phase, you may have missed important safety and performance data.*

11. When you speak about the data collection plan, is it sufficient if part of the CIP is part data management?

Jon: *A data collection plan is a part of your clinical investigation protocol. It's everything from your sample size to study design and basics, designed to data collection requirements, visit windows, etc. These all make up your data collection plan together with, for example, the data management plan as it also incorporates how you want to export the data, how often, who's responsible for that, and if there are any standards of data you'd like to be presented.*

12. Once at a site, can you elaborate possible downsides of not collecting some variables data as interesting to potentially use to build real world data and perhaps learn from it somewhere down the road?

Páll: *The reason we say, "avoid just collecting data that's interesting," is because it puts extra workload on the clinicians. It will increase the cost of your trial and it might end up making the key elements of your study fail because it's too heavy. They can't do all the work or they're not as motivated because they're having to do other things that they can necessarily see as relevant for what they're doing in the study. So again, it's not because you can't do some of those things, but just be careful not to make 50% about what the key endpoints of your trial are, and the other 50% of the data you're collecting is maybe useful down the line. I recommend you split this up and do two different projects at an investigational level. This would be more of a soft research project on the things that might be interesting. You can also do some of those things post-market. You can still do post-market follow-up studies. Especially in Europe, it's required for class III devices. You can also do those activities, and thereby collect data that you did not necessarily need for your certification, but that might be interesting going forward.*

13. Do you have any experience with registry database design and study? If so, can you please comment on some similarities and differences with clinical trials?

Jon: *I actually shared a post on LinkedIn about this a couple of months back. The definition of a registry is very different from one therapeutic area and one device to*

another. But in essence, a registry can either be a single observational-like study that is conducted by a manufacturer, or it can be a set of many studies that are conducted by a manufacturer on maybe a portfolio of devices that have a similar outcome measure. And a registry is really just a term for gathering observational data. So, whether that is done with an observational study or a tool that folks will produce as case series, or in addition with some kind of survey tool that can help you support some outcomes. It really comes down to the device itself, but the term registry is basically just a synonym for what I would consider an observational data collection.

14. How to quantify the benefits and risk to establish a baseline in the state of the art and how to establish performance and safety endpoints over state of the art?

Jon: *First of all, you need to justify what the state of the art is. So, what that really means is that state of the art is not something that you pull off the shelf or you find in a publication, state of the art is something that you need to document or justify what you would consider to be the state of the art based on scientific justification. So that can be, for example, references to publications, references to your own clinical data from maybe similar devices, references to data sets coming from registries from other similar or equivalent devices. It can be many ways that you can justify state of the art. It's up to you to justify what you would consider to be equivalent performance and safety to the state of the art. Every single time I hear a question like that, and I hear a notified body's comments about it, or an experienced medical expert, they always say the same thing: it depends on you, how you justify it. And the reason for that is because the people that are looking at this, whether it's the FDA, competent authorities, notified bodies, will be listening to you. They cannot listen to anything else that you apart from what you present and justify in your own documents. You're the experts in certain aspects, as we are experts in other aspects, and device manufacturers that produce for example technical files are the experts on their devices. The people that are reviewing these technical files are listeners, so it's up to you, or in this example device manufacturers, to sell it to them.*

15. Can clinical evaluation involve cost benefit analysis? The sample size would be too small.

Páll: *I would say that, yes, the clinical evaluation can include a cost benefit analysis. However, it's not required. You might still want to do it, or your device might be in an*

area where it will be required from buyers. So even though it's not necessarily required to obtain the approval to go-to-market, you're not going to be able sell your device without the evidence on cost effectiveness or cost utility or cost benefit. And so, this is back to one of the pitfalls. Look a little bit further ahead than only the clinical evidence. Make sure that if you need other items to actually succeed, rather than only safety and performance, make sure to include them in the clinical evaluation report based on the clinical investigation.

16. Are there any device specific templates or standards available for clinical data collection?

Jon: *ISO 14155:2022 covers the requirements from a good clinical practice standpoint, for what you need to fulfill or accomplish in terms of documentation when it comes to clinical data collection. Then there are other standards and requirements, such as data privacy regulation standards that you need to ensure are also taken care of. There might be data standards that are required for data analysis. How are you going to analyze your particular outcome measures? There might be a specific way to do that and structure it because when the statistician receives the data, they may need to look at it in a certain way. There might even be data standards, such as defining, coding adverse events, which can happen during a study or out on the market. There are several standards that are applicable. One of the things that I've learned throughout my now almost a little bit more than a decade, within this industry, is the fact that none of the standards, or regulations, tell you what to do. They tell you what you need to include, and present, but not how to do it. So, you're freer than you think to produce what you believe is compliant with what is required by the regulations.*

Páll: *In terms of templates, what you could find are templates which are more generic than others, e.g., adverse event reporting or safety reporting, something like demographics. You are most likely also able to dig out templates for inclusion, exclusion criteria for specific therapeutic areas, and then amend those templates. They might not necessarily be directly transferable to your study, but you will most likely be able to find bits and pieces that you can pull into your studies.*

17. Is there a difference between the regulations on clinical data between the US, EU, and the rest of the world?

Jon: *Almost all regulatory bodies around the world, require you to follow good clinical practice. And the International Standards Organization, ISO 14155:2020 is often looked at as the gold standard for how you should do clinical investigations. That covers United States, Japan, Canada, Europe, and many other countries. There are data standards that are applicable for both Europe and the US, such as GDPR in Europe, and acts in the different states in the US but also general HIPAA around the hospitals for information protections and FDR, FDA, CFR 21 part 11 regarding e-signatures and systems used to gather information trials. But looking at the two (US, Europe) and comparing them together, they're very similar when it comes to clinical data collection. They do expect the same kind of level of standard for data. The regulations themselves might be called differently, but they require the same quality level.*