Johner Institute

Sample Size Planning for Clinical Trials of Medical Devices and IVDs

With Dr. Thomas Keller, Prof. Dr. Christian Johner

Transcript

00:00:05 Speaker 1

Medical Device Insights, a podcast by the Jona Institute for medical device manufacturers, authorities and notified bodies.

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The Medical Devices Directive and the In Vitro Diagnostic Medical Devices Directive place ever higher demands on all of us and the likelihood that we will have a

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clinical trial or performance study.

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Unfortunately, this probability also increases.

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And in this context, it is interesting to find out what number of cases we have to operate with at all, among other things in order to be able to estimate the duration and costs of these studies.

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And it is precisely this case number planning that today's episode of our podcast is about.

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Because the topic is so demanding, I have 2 guests with me today,

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namely, once Doctor Keller, a biostatistician, and once my colleague, Doctor Katharina Bertram.

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It's nice to have you with us.

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Hello, yes, good afternoon.

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Hello, greetings, Christian, thank you very much.

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Yes, as I have just indicated, case number planning is an important point.

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Which manufacturers have even been discussed by this sample size planning?

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So, he has to plan for case numbers here, does it affect all manufacturers?

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Yes, that's how I would see it, that's how I would see it, and every time you do an experiment or collect data in any way, you should deal with the sample size.

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This takes different levels of effort.

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Sometimes there are precise specifications in guidelines and sometimes you have to make your own considerations.

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Yes, in the end it is about avoiding that on the one hand you make the mistake of

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to come to false negative or false positive results of the studies in the case of too small sample sizes and, on the other hand, to waste resources in the case of too high a number of cases.

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And of course we want to avoid both.

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You have just mentioned the key point or the keyword of the regulations.

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Katharina, you also deal a lot with this, what regulatory requirements do we have in the context of case-load planning?

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The IVDR applies to in vitro diagnostic medical devices and for medical devices we have to look at the regulation for medical devices, the MDR.

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And yes, there is indeed such an arc of tension in the regulations.

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At the beginning, the definitions already explain about performance studies and planning that statistical considerations must be considered and defined.

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And especially when it comes to clinical trials or, in the case of in vitro diagnostics, clinical performance studies

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, the appendix to both regulations then stipulates that the performance study planning or the planning of the clinical trial must take into account the design of the study and also the statistical methods for the evaluation.

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That is, we don‘t have a number obviously that is set by it yet, but the

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the demand, if I had understood you correctly, to include exactly these statistical considerations.

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This seems to be a bigger deal now.

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I still ask myself, what is so complicated now and what is it taking so long?

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So, isn‘t there now somehow a computer program where you hammer in these parameters and then somehow have the result a few seconds later that tells you how many test subjects you have to work with here?

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So, what‘s so complicated about it, Mr. Keller?

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Yes, on the one hand, the requirements that are in the guidelines are not so easy to understand at first.

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So, I now also have this new variant or new version of the ISO 14.155 standard in mind.

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In Appendix A7, it describes very precisely which points have to be considered when calculating the number of cases.

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But I don‘t want to offend anyone, but I suspect that not everyone understands that.

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So first of all, there is a problem of understanding the statistical background and the terms.

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But even if you can explain these points, it doesn't get any easier.

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Because the situation is as follows: You can summarize it as a paradox, so to speak.

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When a customer approaches me and a

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then instead of an answer, he is actually asked counter-questions, namely what should come out of the experiment or the study, quantitatively.

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In other words, when we carry out a case number determination, we already want to know the result of the study, which you want to plan first.

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Yes, there are 6 main points that need to be clarified in advance and other technical questions.

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for more complex designs.

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Yes, to answer your question, so once all this has been clarified, then a case number software often helps and this step can actually be done in a few minutes.

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I would like to add that the result is usually not a number of cases, but these are scenarios in which the number of cases is tabulated depending on factors and these are then discussed

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together with the customer in terms of uncertainty on the one hand and feasibility on the other.

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K., so it's not so easy, also that not only one number comes out, that would probably have been too easy.

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You have already described that these are different things that flow into it.

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So what parameters are these or vice versa, to which questions do you then put back, as you have just

described,

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Do you need the answer in order to actually be able to feed your software and have it brought to a result?

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Yes, these are, as just briefly mentioned, 6 main points that have to be clarified beforehand and then, depending on the complexity of the design, you have to look at other technical questions.

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So, let's start with the endpoint first.

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So, this is the variable that we use to determine the study objective

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or to provide evidence in accordance with the study objective.

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This can be a quantitative quantity, for example the size of a wound area or a proportion, for example the proportion of true positive test results, i.e. what the sensitivity is in the IVD area, or the proportion of patients with a complication.

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That would be proof of safety in the field of medical devices.

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In the analytical as well as clinical performance evaluation of IVDs, the endpoints are predetermined to a certain extent.

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In the area of analytical performance evaluation, bias, precision, stability, limits of detection and quality, and in the clinical field, sensitivity and specificity.

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In the case of medical devices, endpoints must be chosen that assess efficacy or benefit on the one hand and safety on the other.

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on the other hand, but there the field is wider.

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Yes, Ms. Bertram, what does that look like from your point of view?

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Yes, the endpoints, you are addressing a very important aspect that the

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manufacturers should actually consider and specify directly during their product development in their product requirements specification.

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So, what is the acceptance criterion for precision in analytical performance evaluation or diagnostic sensitivity and specificity?

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and this in turn depends on the purpose that the respective I.V.D.

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and which is intended by the manufacturer.

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And the state of the art is essential, since we determine the risk-benefit ratio of the product, the I.V.D. or the medical device that is to be placed on the market.

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and that the benefits should outweigh the risks, we can and do only want to put products on the market that are no worse than other in vitro diagnostic tests already on the market.

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And here, too, we can meet the acceptance criteria for such

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Parameters that ultimately represent, derive and also justify the endpoint in the study.

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If I may summarize this very briefly, so that you can briefly confirm whether I have understood it correctly, so the first answer to the question of which parameters flow into such a case number calculation was more or less the dependence on the number of these

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endpoints, you have just given us wonderful examples of what such endpoints could be.

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So, you talked about percentages or absolute values, like this size of these wounds.

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Then you, Katharina, added that although it is important to determine these endpoints precisely, one is not completely free in the choice of them, because we have to be with this consistency, so to speak, because they have to be derived from the intended purpose.

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And second requirement,

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they really have to reflect the state of the art.

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Have I understood that correctly so far?

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Yes, very nice.

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Do we now have other clusters of parameters besides the endpoints that we should consider?

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Maybe now just the coarsest ones again, Mr. Keller, because I think I had interrupted them or not all of them are mentioned yet.

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Yes, so the second point is then

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the statistical test or method used to prove or describe it.

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Because if we want to keep it a bit tight, then the third and fourth points are the most difficult points, namely we expect

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Information on how large the quantitative effect is.

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So, when we look at a difference in proportions, we want to have quantified this difference, for example 20%, and we also want to know the variability of this effect.

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That's just a difficult point.

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Literature research, the research of comparable studies can help here

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or requirements for the quality of the result.

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There is talk of minimally interesting differences, which a product must have compared to certain criteria.

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Yes, they are, they are, those were the third and fourth points.

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And then there are the two mistakes I mentioned at the beginning.

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So that would be 2 risks, so to speak.

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Namely, on the one hand, the risk for the manufacturer that the study will not reveal an existing effect and the risk for the general public that an effect will be proven in the study even though it does not actually exist.

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These are the so-called beta and alpha errors and there are usual values for them

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from 10 to 20% for the manufacturer and 5% for the general public.

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Yes, and finally, as a sixth step, you have to look at whether losses could occur in the study.

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For example, that in some patients a test result of an I.V.D.

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cannot be achieved.

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or whether patients are eliminated in the pursuit.

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So this rate of dropouts must then be added additionally.

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Yes, and then I mentioned design-specific additional points, which I want to mention very briefly.

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The first would be the allocation ratio, i.e. the ratio in which patients are assigned to the study groups.

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This is usually 1 to 1, but there are also other ratios.

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then there is the point of multiple testing.

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So if you look at several endpoints in parallel, the error of these alpha errors increases, i.e. the risk for the general public that there will be a false positive result and this must be taken into account accordingly with the number of cases.

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In the case of I.

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it is almost always the case, because here you are investigating 2

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Sizes, sensitivity and specificity.

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In this case, you have to correct the beta error and that then has a fake-increasing effect.

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However, multiple testing is also very common in another context, namely in interim analyses.

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Very often, companies want to know during the study, than the sponsors, during the study, where they stand in the study.

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And in pure statistical theory, this has an increasing effect on errors.

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because then we also get into such multiple test situations.

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And the question I always ask is what consequences these so-called interim analyses should have.

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Should the study be discontinued or should adjustments be made?

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And that has to be discussed in great detail.

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There are also guidelines here, for example for adaptive designs from the F.D.A., but that then becomes very complicated and I have not yet experienced it in practice.

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As far as these interim analyses are concerned, one usually finds a practicable way, but strictly speaking they are not permissible without a corresponding increase in the case.

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Yes, and one last point, which Ms. Bertram has already addressed, is the determination of the acceptance limits, and that is also a broad field, both in analytical performance validation, when it comes to permissible limits.

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as well as in the field of diagnostic quality.

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There is an example, namely the idiological test for blood in the stool.

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This is a screening test for colon cancer.

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There is actually a requirement of the G.

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A. that the sensitivity should be 25% and the specificity 90%.

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But you are not always in this comfortable situation.

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Again, I dare to make a summary, so that it can be used again

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whether I have understood it correctly.

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So I think we've all already understood that it's a more complicated thing and that different parameters go into it.

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A parameter group perhaps out of context, what do we have in terms of signal-noise ratio, because probably the worse this ratio is, the more higher the number of cases you need.

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I think that was such a group.

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The next thing, if I understood you correctly, was the reliability of the statement you want to achieve.

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You talked about alpha and beta errors and then another parameter was the influence, the number and this linking of the endpoints and also the wish or whether you want to fulfill the wish that you can already use interim results in order to be able to decide on a redesign or, in the worst case, on the termination of the study.

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have I understood and mentioned the most important points correctly?

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Yes, thank you, wonderful.

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Yes, I think everyone now understands, how time-consuming something like this can be and that it's just more than just, I'll enter a few values into the computer, but that there is a lot of strategic

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decision.

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So this not only has something to do with medical devices law, but also almost business considerations come into it, risk considerations for the project, so to speak, and not only for the patients.

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How will something like this be designed in practice?

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So if the manufacturer is at the point, so to speak, that has recognized, with only literature data, if it is allowed at all, I won't get anywhere.

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I have to go into a clinical trial or a performance study,

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what would this ping-pong be, which typically takes place between the ruler or the sponsor on the one hand and perhaps you on the other?

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So, what does it look like and how long does it take?

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Yes, so usually the cooperation is such that I take the first serve.

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So the customer tells me his idea

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and then I try to determine the above points in his sense.

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So, I don't proceed in such a way that I sit back and say, yes, dear customer, now deliver everything first, but I try to make an initial suggestion and then the customer usually receives such scenarios of case numbers depending on various factors

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and then it goes on interactively, then it's just feasibility versus yes, the uncertainty to negotiate, so to speak.

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And the whole thing usually takes a few hours, but these are spread over a few days, depending on how quickly the feedback works.

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And in the course of the study, are you also involved, then or do other statisticians, who then make interim evaluations and, if necessary, help decide on a redesign or adaptation of the study.

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Yes, of course I wish that I am always part of the party, from start to finish.

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Yes, in the pharmaceutical industry it is directly stipulated that a statistician should accompany studies from start to finish.

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In the

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In these areas that we are looking at today, it can already be found from time to time that there is selective, I only act selectively, but in the ideal case and in many studies I am involved from start to finish.

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It is indeed advisable to involve statisticians from the outset.

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The only point where one is actually forced to include foreign statisticians is when it comes to such statistics.

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adaptive designs, because then the study is unblinded and I, as the main statistician, am not allowed to gain any insight.

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Yes, but these are very special, very specific points that I have not yet become acquainted with in the area we are discussing today.

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Yes, because of course we are now discussing mainly the field of medical devices, in vitro

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Diagnostics, now less the pharmaceutical sector, pharmaceutical sector, one can draw big differences, for example, in the number of cases or in the effort of the calculations between I.

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s and classic medical devices?

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Yes, that is, in the I.

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area you have it a little easier, the case numbers for the analytical performance, which are for example in the C.

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Guidelines

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or there, there are instructions and there is usually my job to make adaptations if the experiments suggested in the guidelines do not fit 1 to 1 to the product and you have to make adjustments.

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The calculation of the number of cases in the area of clinical data in I.

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D., she is also

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it's not trivial now, because there can be different endpoints.

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You can estimate sensitivity and specificity, i.e. determine with confidence and ultimately measure easily, or you can provide evidence against borders or you can make comparisons against other in vitro diagnostics.

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So that's different, but in the end it's a limited area.

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While in the field of medical devices it is just more diverse, especially on the rails,

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Leverage effectiveness.

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No, so you can, I briefly took the example of a wound earlier and let's imagine that we have some means to improve wound, wound healing, i.e. some special plaster, then you can think of a wide variety of endpoints, i.e. the size of the wound at a certain time or the time it takes for it to heal.

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Or patient-reported outcome, where the patient can assess his pain and the cosmetic result.

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So there is a large panel of possibilities.

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Yes, and then on the topic of safety, i.e. medical devices and safety, that is actually the most critical point when it comes to case numbers, because there it is often a matter of showing that certain, i.e. rates of complications or adverse events below certain limits

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and these are small limits.

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So, for example, if you now have a rate of 2% and you want to prove that it is less than 5% of that rate, then you need over 300 patients.

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And if the true rate is 3% and you want to show that it is less than 5%, then you need 800 patients.

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So here we really go into large numbers of cases.

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Yes, and that then represents in the

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yes, in the situation that medical device manufacturers now suddenly have to carry out studies, these are major obstacles.

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The next question, yes, may now lead a bit into the temptation to speak too much in favor of Patriot, but I'll ask it anyway.

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Are there situations where you would say that a manufacturer can sometimes dare to do such planning on its own?

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Yes, so a manufacturer can

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can act on his own if he, i.e. if there are guidelines that give clear indications, so the CSI Guidelines in the area of IVD are definitely very helpful.

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He can also act alone, if there are well-described studies in the literature that in principle correspond 1 to 1 to his concern, then he can simply refer to these studies.

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So it's certainly not a

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it is not a must to bring in biostatistical expertise from outside, as is virtually mandatory in the pharmaceutical sector.

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Yes, thanks for the frank answer.

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What would be such typical next steps that should perhaps be taken, Katharina, perhaps also for you?

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Yes, since we have already addressed the various interfaces, it is certainly very important that before you start planning a study, performance study or clinical trial, you have defined the intended purpose of the medical device or the in vitro diagnostic device and also think about the patient population.

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The broader the scope, the more extensive the study population that is required, and straight, usually becomes.

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as the M.

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and also the I.

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to create technical documentation that contains development documents and the said product requirements, the better it is to think about this before you go to an expert like Mr. Keller, yes, you are prepared

and can also directly enter into the exchange

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in order to be able to answer the questions that are then asked by Mr. Keller directly.

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And these are things that exactly you do, to interact as an interface, to make sure that everything is prepared in the best possible way and, of course, also coordinated with all the rest of the technical documentation.

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Did I understand you correctly?

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Yes, exactly, so

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We have found out with Mr. Keller that we really have a wonderful interface.

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We, i.e. me as a team, i.e. as part of the team that takes care of the support of in vitro diagnostic manufacturers and accompanies customers in the preparation of the technical documentation, product file, risk management file and in particular

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strategic planning, how such an analytical and clinical performance evaluation can look like and then use the synergy with Mr. Keller, because that's where my competence is at the end.

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Yes, as always, it's also teamwork, not only with the manufacturers, but also with us in the team.

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Yes, thank you so much for these insights.

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Of course, you can't answer the topic of case numbers comprehensively in just under half an hour, and certainly not replace a statistics degree.

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But we have created more articles anyway and linked them at the bottom of the description of the podcast.

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Just like the contact details of everyone who was now in the call.

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Yes, to you, Dr.

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Keller, dear Katharina, thank you very much for being there.

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Yes, thank you very much from my side as well.

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Yes, thank you for the opportunity to discuss this exciting topic.