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The pitfalls of surrogate endpoints in cancer research

Prof Taylor: Thank you very much and good morning, good afternoon, and good evening from myself. So, it's a great pleasure and my thanks to the European School of Oncology for this invitation to give the session together with my dear colleague, Professor Oriana Ciani, on The Pitfalls of Surrogate Endpoints in Cancer Research. So, I'm just going to share my screen. Can I just check, Oriana, that's in full presentation mode?

Prof Ciani: Yes, yes, thanks Rod.

Prof Taylor: Thank you, okay. Well, maybe just a couple of minutes of introduction about myself, very briefly. So, I think perhaps the most important thing to say is I'm not an oncologist, but I certainly do have a longstanding interest in surrogate endpoint. So, as you can see from my title, I'm a Professor of Population Health Research and my specific methodological expertise is in clinical trial design and statistics. And in fact, I do have a clinical area of work, but it's actually more cardiovascular than oncology. But as I say, for the purposes of today's presentation, I'll be very much focusing on my joint interest with Professor Ciani in the area of surrogate endpoints. So, just in terms of declarations, I don't have any industry declarations to declare in this particular area, but I do want to mention that both Oriana and I are co-chief investigators of this study called SPIRIT-SURROGATE and CONSORT-SURROGATE which is funded by the UK Medical Research Council. This is a project that has recently begun. And in fact, we will refer again to this project later on in this presentation, and it'll become clear to you why this presentation is relevant to today. So, within this presentation, I'm going to try to address three broad issues. So, the first issue I would like to talk about is the whole area of what we might call definitions in surrogates. I think one of the challenges of this area is that people use different terminology here. So, let's try and see if we can bottom out our terminology at the outset. Then quickly get into why people are using surrogates and particularly, in the area of oncology where I'm sure I understand most of you are oncological clinicians. I am sure you'll be very familiar with various surrogate endpoints that we'll be talking about in the session. The meat in this language, in terms of the presentation here, if I can put it that way, is I guess the fact that surrogates while still benefit they do come with some risks. So, I will try and review some of the key-risks in this area. And then, last but not least, I think come back to your clinical practise and talk about what might be best practise for using surrogates in clinical practise or in future oncology research. And two principles that we'll pick up in this session are something we call surrogate outcome validation, but then, also, linking back to the funded project I mentioned earlier, the need to improve reporting and what we're trying to do in terms of the reporting of clinical trials in this area. So, that's the menu. Let's get started. So, this is a widely used definition. It comes from the FDA biomarker working group who have been really instrumental in moving this area forward. So, they say that an endpoint that's used in a clinical trial... a surrogate is an endpoint used in a clinical trial as a substitute for a direct measure of how a patient feels, functions, or survives. And we often call this latter outcome, a patient-relevant final outcome or PRFO. And, of course, in the area of oncology, a lot of, I guess, your therapeutic objective is the objective of prolonging patient survival. So, clearly, overall survival would be an

example here of a patient-relevant outcome. And what we'll be doing with the surrogate is to try and substitute for that. Importantly, as well as substituting for a surrogate, a surrogate also has the purpose of predicting the clinical benefit or harm that might arise from the treatment and the final outcome. So, these two elements, substitution, but also, prediction are absolutely key here to the definition of surrogates. And you can see we're very, very much focusing on the use of surrogates in an interventional setting. Some of you will see reference to surrogates and biomarkers in the area of prognosis, where they can be used, but we'll be focusing on treatment in this section. And then, the final thing is that we do need to have some epidemiological therapeutic pathophysiologic plus scientific evidence to support that prediction. And again, we'll come back to some examples of some of the statistical methods where we use to do this in the presentation. So, this is a slide that tries to illustrate then this definition. So, on the left-hand side, we have what is often commonly used as a surrogate endpoint called a biomarker. And a biomarker as defined here is any characteristic that can be measured as an indicator of response, in this case to an intervention. And what we are doing is using that biomarker as a substitute and predictor for a final patient-relevant outcome. And again, just to be clear, that's an outcome going back to this previous definition of how an individual might feel, function, or survive. And I guess the way to think about this is that if we have a treatment to the left of the slide, that treatment is having the impact on the PFRO effectively through the biomarker. We're collecting the biomarker because it's a substitute and predicts for the patient relevant final outcome. So, some examples just to try and maybe put some flesh on the bone here. So, as I say, my area is cardiovascular disease. So, if you have a lipid reducing, lowering drug or you have an anti-hypertensive agent, the ultimate final outcome would, of course, be cardiovascular events. So, things like hospital admission for a stroke, or R&D cardiovascular death. But of course, what we might want to do is to collect data using a biomarker as a surrogate and two biomarkers that are very commonly used in this area are systolic blood pressure and low-density lipoprotein cholesterol. So, they would be examples of biomarkers and, of course, if you think about it, you don't perceive those outcomes, do you? You don't perceive if you've got high blood pressure or low blood pressure, these tend to be asymptomatic and go back to our core definition of biomarkers. However, let's get into your area a little bit more. So, you're working in oncology. As we said, the ultimate outcome in many circumstances may well be overall survival, but two biomarkers that you will recognise hopefully are progression-free survival or objective response rate measured by some, for instance, radiographic measure of tumour response. So, again, these would be examples of biomarkers used to predict overall survival. Okay, so, hopefully, so far so good. But one of the things that we wanted to put over to you today is that actually there are other outcomes that can be used as surrogate. So, traditionally, we focused on biomarkers, but the sort of trials that I do, I'll give you a couple of examples in a second. We may actually have outcomes that the patient perceives, but we're still using those as surrogates. So, these are what we call intermediate outcomes. So, the endpoint tends to be further along the clinical pathway. It's more proximal if I can put it that way to the PRFO but it's still not the final outcome itself. So, what might be examples of this? Well, one example is exactly from my area of research. So, I do trials of exercise rehabilitation for patients with existing cardiovascular disease, particularly, heart failure. And a very commonly used surrogate outcome in my space is a primary outcome that would be exercise capacity, such as for instance, a six-minute walk test. And the reason we're using that outcome is we might want to be predicting, for instance, the final outcome, which might be health-related quality of life. So, increasingly in heart failure, for instance, objective measures of quality of life are now accepted by regulators as a final outcome. And indeed, I have some friends and colleagues and collaborators who do cancer rehabilitation. So, again, same idea. You have an exercise intervention given to patients either prior to their, for instance, breast cancer surgery or following their breast cancer surgery with the intent of not necessarily influencing survival, but definitely, trying to improve the quality of life of that individual. Another example, perhaps again from my area would be, let's say we had a lifestyle intervention like improving your diet. Now, the reason we might want to improve our diet, for instance, switch to Mediterranean diet, from the classic British high fat diet, is that we might want to ultimately improve people's cardiovascular risk, but by measuring an intermediate outcome, which in this case would be body-mass index, that would act as a surrogate, wouldn't it? So, I hope these examples are

now helping to cement what we mean in terms of surrogacy and biomarkers, intermediate outcomes, and final outcomes. But if there's any lack of clarification, don't hesitate to put a question in the chat and we'll pick up on that later. So, I hear you saying, well, all very interesting, Rod, but why do we use surrogates? And of course, from my perspective as a trialist, the main reason is to just be able to do trials more efficiently. So, if you think about it, if we look at, for instance, if I take one of the examples, anti-hypertensives. To be able to demonstrate a reduction in blood pressure, you could maybe do that within six months follow-up whereas if you wanted to demonstrate a reduction in heart failure admission, you may need two- or three-years follow-up in the trial to have adequate power to demonstrate efficacy on that primary outcome. Of course, the other implication is you might also be able to reduce sample size and then, ultimately overall cost. And as you probably are aware, and it was very interesting during the pandemic, wasn't it? Where we cracked on a society and very pragmatically delivered high-quality randomised control trials using routine data. This idea about being more efficient in trials is I think a really important topic, not just for researchers, but actually, for society in terms of how we more efficiently do research and use public resources and obviously, industry want to do this efficiently as well. One thing to think about, though, is that we do need to be somewhat cautious about this. So, as I said to you, the ultimate goal in oncology might be overall survival, but there are problems with overall survival. And this might be another reason. For instance, we might want to use other outcomes that may be less prone to bias. So, for instance, if you think about it, if you have a metastatic cancer or a first-line therapy, you randomise people to either receive the active or placebo. What tends to happen in those trial is that patients may be assessed at follow-up. And if they haven't responded through, for instance, tumour response, there may be a therapeutic incentive to introduce a second-line treatment or cross the patient over, for instance, to a rescue therapy. And of course, that may be asymmetric. So, it may be more likely in those receiving placebo that they don't respond. And can you therefore see the issue then, measure overall survival, for instance, maybe two years follow-up, that may be biased by treatment crossover. So, actually, OS although it's a clinically good outcome in oncology, can be tricky to interpret in a trial setting, particularly, for first line of metastatic disease. And then, the last thing to say is, and if you think about a lot of behaviour in terms of clinical trials is driven by industry. They're big funder of trials, is that regulators, so, if you're a company and you want to have your new oncological agent have a licence, FDA, the U.S. Food and Drug Administration Agency and the European Medicines Association, EMA, both now have introduced what they call accelerated pathways or in other areas such as orphan medicines, if you had a rare cancer, for instance, have now introduced pathways where they will formally approve a product, not on the final outcome of interest, such as overall survival but based on the surrogate. And, of course, that stimulated focal behaviour of using surrogates in industry. So, this is really mushroomed from what might have been, I think the FDA said one in 20 submissions about 20 years ago, we're now seeing almost 50% or higher of oncology submissions are being approved on the basis of a surrogate. And indeed, with that in mind, FDA probably about 10 years ago now, published this table on their website, which is a table of surrogate endpoints that they indicate or are indicating might be suitable for use within clinical trials. And I think the thing I just want to note is just, first of all, look at all of the various types of surrogates that exist in your clinical field. So, a real number of them. And again, I think that's one of the challenges for you is just wrapping your head around these different surrogates. And then, I guess, the other thing I'll notice is that many of these surrogates are what I call generic surrogates. So, for instance, if we took ORR and progression-free survival, FDA says that you can use those in any solid tumour cancer or any haematological indication. They've got plausibility in all of those settings whereas, for instance, disease-free survival tends to be limited to solid tumour and particularly, in the adjuvant setting, similarly, metastasis-free survival is the term its suggests. In fact, they've even limited that to non-metastatic castrate-resistant prostate cancer, but obviously, a lot of surrogates in your area. So, hopefully, you're comfortable now with the definition of what is a surrogate and why we might want to use them. What I'd now like to go on and talk about is the risk of surrogate outcomes. And I broadly assess these under two headings. So, one is what we might call over-estimation of treatment effects. I'll come back and explain this in a second but then, something that's perhaps more, if you like worrying, which is what we might call surrogate failure, which is basically where we have a surrogate that

actually turns out not to have any benefit on the final outcome or more worryingly, it actually has more harm than benefit. And if you want to read more about this, this paper by Tom Fleming and Dave DeMets from the USA, is an absolute citation classic. I think it might have been the first paper I shared with Oriana when she came to do a PhD with me in Exeter. and said, well, have a look at this paper. And they define a whole litany of approved decisions of the FDA back in the early 90's, that led to being what they say misled by surrogate. It really is a beautiful paper. So, why does this happen? So, I guess I just wanted to do... I'm not a clinician, but a little bit of disease pathway with you on this session. So, here's the disease, in this case cancer, we introduce an intervention and, of course, what we want in a perfect surrogate world is for the intervention to impact on the patient-relevant final outcome directly through the surrogate outcome following the red arrows. So, in other words, using my language, the intervention effect on the final outcome is entirely mediated through the surrogate. However, if life was only so simple, interventions, of course, can actually have other effects. So, they may have direct effects on the patient-relevant final outcome, or they may have other effects on other pathways that then effect. So, in other words, you can very quickly see that even although an intervention may have a post-effect on a surrogate, the final outcome effect may depend on the net of these other pathways. Hope that makes sense. So, this is just a slide to remind me that if you do have any questions, do put them in the Q&A. We've got a discussion session that Oriana's going to be leading at the end of this session. So, please do feel free to contribute your comments. So, back to over-estimation. So, speaking of Professor Ciani, well, here's one of her papers. And this was a paper that she published during her PhD in the BMJ and this was a really interesting study, what we call a meta-epidemiological study where she took randomised control trials, published in a number of top journals such as the BMJ, New England, The Lancet, JAMA, and asked the question of "are those randomised control trials with the prime outcome a surrogate outcome, or was it what we would call a PRFO, a patient-relevant final outcome?" And then, she looked at the treatment effect in those two groups of trials and compared them and compared them using what we call the relative odds ratio or the relative risk ratio. Won't worry too much about the statistics, but we're basically doing a head-to-head comparison between the two. And the thing to note here is that no matter which way you look at the data, Oriana concluded that you overestimate the benefit of a treatment by anything up to on average about 47% and indeed at the upper end of the consent, you could even be doubling the treatment effect. So, that's interesting, isn't it? Because if we were, for instance, looking at the cost-effectiveness of a treatment and all we had was surrogate outcome data, could you see, we may be over-estimating the cost-effectiveness of that treatment and for bodies such as NICE in UK or other payers in Europe, that would be more relevant for you given where you're located. This is again, a bit of a worry. Now, what about an example of treatment failure? Well, I had a little look around in preparing for this lecture and I came across this very interesting story. So, this is the story you might be familiar with which is the use of Bevacizumab, commonly known as Avastin in breast cancer and specifically, breast cancer. Now, I'm out of my comfort zone here. So, I'll just kind of read the slide. Breast cancer in HER2-negative women or men who have not received prior chemo, so, I guess they're treatment-naive. So, what's the story? Well, if we go back to 2007, this randomised control trial was published in a New England Journal of Medicine. You can see the numbers randomised here. The randomised either Paclitaxel plus Avastin or Paclitaxel alone. So, Paclitaxel, if you like, was the standard of care at this point. Roughly about 300 patients in each arm and then, they were followed-up over... well up to 54 months, by I think a median of, yeah, maybe, about 24 months follow-up and the primary outcome was progression-free survival. And as you can hopefully see from this Kaplan-Meier curve, there was a very clear signal of benefit, such that the median PFS was 11.8 months in the Avastin group compared with 5.9 in the comparator group. In other words, an incremental gain of about six months progression-free survival, and obviously, highly statistically significant. And when the FDA saw this, and this was part of the company's submission, they approved this therapy for this indication. However, given it was a surrogate outcome, the FDA did encourage the company and clinicians to go on and do more research in this area and about two, well, actually four years later to be precise, this trial was published in the Journal of Clinical Oncology, 2011, the RIBBON-1 trial. And, in fact, there is another parallel trial. I can't remember what it's called, but very, very similar design. This is a slightly more complicated trial, in that's it randomised

patients to receive two active comparisons. So, capecitabine plus placebo or capecitabine plus Avastin or docetaxel plus placebo or docetaxel plus of Avastin. So, we've effectively got two active comparisons here. And the thing I want to first of all notes is that again, here is progression-free survival. And by the way, that was, again, the primary outcome in this trial, slightly bigger trial. If you count up all the numbers in the four arms but look at the magnitude of the PFS benefit. Can you see its only in this case now, just over whole, in this case, it's about 2.9 months, whereas here it's only 1.2, but it's considerably less than we saw in the previous trial, isn't it? And perhaps more concerningly is that these trials hadn't what we might define as more mature overall survival data, and these are the hazard ratios. And hopefully, you can see that the hazard ratios cross one. And in fact, we do not have evidence that this leads to an improvement in overall survival. In fact, if anything, it goes in the wrong direction, in the docetaxel comparison. And as a result of that, in July, 2010, the FDA was through approval. They thought that this treatment did not demonstrate any benefit, but interestingly in Europe, our regulatory agency continued with their approval. They kind of came to the judgement that on balance, there is still some evidence of a PFS benefit here where we don't have any strong evidence of harm, all the upper end of the consequence was up there, but we think it should remain licenced. So, for instance, in UK, NICE recommend, interestingly, their recommendation was not to go with docetaxel but to stick with paclitaxel and if you remember paclitaxel, was the taxeme used in the first trial. So, they kind of extrapolated off of that first trial that I showed back, but it's an interesting story. I hope you agree. Okay, you'll be glad to know we're getting near the end. So, what are we going to do about this? Well, one of the things we need to think about is that we need to select surrogates very carefully and we do that typically on the basis of three levels evidence, clearly there needs to be some biological rationale, but as I'm going go through now in some detail, we also have to have evidence that there may be an observational association between the surrogate and the final endpoint or a treatment-level association between the two. And just to illustrate this and really to say we could spend a whole lecture talking about the statistical methods for this validation, but essentially, really, I guess, for the purposes of this session, a lot of them are correlation-based often using meta-analysis. In the observational, we may be looking at individual-level associations and for intervention, we'll be looking at what we call trial-level, and we'll often do this with several RCTs so hence, a meta-analysis. So, again, let's have an example to try to put some flesh on the bone. So, here's an example, cross-sectional data where we may have PFS on the x-axis, overall survival, we plot the two. And in this case, we can look at, let's say, its experiment's correlation, not a particularly strong one at 0.48. Obviously, if we squared that we'd only be explaining 16% of the variance, but it is statistically significant. So, we've got a weak association observational here, haven't we? But remember what we want, the highest-level of evidence, level, the third level of evidence I showed you on that previous slide is this. What we want to see is the change in progression-free survival relative to the change in overall survival and each of these dots is a trial, this is a meta-analysis where you're comparing, and these are I believe placebo-control trials. So, of course, some trials may show that the majority of them are positive result. In other words, an improvement in progression-free survival and also, overall survival, but some showing that the control does better and hence, the negative. But the point is, we would want to see the data going through the origin and also, to see them clustering around what would effectively be a straight line or a strong correlation. So, with that in mind, how do surrogate outcomes and oncology stack-up? Well, this question was looked at by this heroic systematic review that was done in 2018, 164 meta-analyses were reviewed in this review and what they were looking at was the treatment level association. So, that third-level of evidence and they categorised the association as being high if the treatment correlation was 0.7 or an R squared of 0.50. So in other words, at least 50% of the variance was explainable based on the association between the surrogate and the final outcome. But of that 164, how many of them achieved those criteria? Answer, only 12, so less than 10%. And you might be interested to know clinically what were the surrogates that came up to master and the answer was essentially two surrogate groups. So, disease-free survival and progression-free survival. And I think what's interesting is that disease-free survival tends to perform well as a surrogate in the adjuvant setting. So, in other words, situations where we may have a surgical intervention and patients have therefore got relatively good survival and PFS, again, did appear to perform well but typically, in a more

metastatic early line of treatment. At least that's my understanding as a layman of that slide. So, again, an interesting point that different surrogates appear to perform differently in different settings. And we can't transfer that evidence across different settings necessarily. So, you'll be pleased to know this is pretty much my last slide. And what might be the conclusions we can draw? Well, I hope I've been able to show you that surrogate endpoints, particularly, for overall survival have been widely used in interventional trials in oncology and I suspect will continue you to be, that's not going to change, but hopefully, as you picked up, there is a trade-off here and it's a trade-off between trial efficiency, perhaps speed of access. We won't do effective therapies to get to patients quicker but remember we might be able to do the trial quicker, but we might, as a result of using the surrogate, introduce something that Oriana and I would call and sorry, there's a typo here, provision decision uncertainty. So, if we're using the surrogate, we are not so sure of those benefits as if we observe them directly on the final outcome. And we need to think about that. What we need to do going forward then is focusing licencing coverage and clinical practise on surrogate endpoints that have strong statistical evidence of validation. So, we shouldn't be using putative surrogates that aren't validated. Challenge in this area is OS can be confounded. And then, I think the other point as I made in the previous slide, is, if we are looking at surrogates, we need to think about them as being setting specific, they're specific to the treatment regime. First-line, later line, they are specific to the cancer type and also, the cancer stage as well in many circumstances. And I think maybe moving to what might be the future in this area. I don't have a crystal ball, but I think certainly, one of the observations I would make, and you can maybe pick it up in discussion, Oriana, is the focus has been on overall survival as final outcome. What about quality of life? That's an important outcome for patients. Should we be using that as a relevant outcome here? Clearly oncology is a very, very fast-moving area and new surrogates are appearing. Should we be reacting and validating them in the same way? And then, I guess the last point for me is if we are doing trials using surrogates, we've really got to be better at reporting those. I haven't shared with you this evening, but there have been probably two or three audits now of trials on the surrogate outcomes, not just oncology area. They tend to be a little bit ropy, if I can use that expression, in how they report. So, last slide for me is then just to put a plug for this project that Oriana and I are leading. So, we are working together to put together extensions. You hopefully will be familiar with SPIRIT and CONSORT. SPIRIT is the reporting guidance for randomised control trial protocols. CONSORT is for randomised control final reports and what we are doing through a detailed literature review process, but also, a Delphi survey, we want to involve a number of stakeholders, including clinicians in helping us put together this extension. And we're going to be doing this over, probably starting in the summer and certainly, going through to the end of the year. And I'm just going to end with this link. And if you are interested in participating as a clinician in this area, so, we've now put together this link. I know you can't click on it now together with a QR code, but we'll make the slides available after the presentation. And if you would like to participate, there's an expression of interest form that this takes you straight through and we would be very pleased if you would like to put yourself forward. There's a couple of questions we would ask you to look at to help us screen our final clinician numbers going forward. But if you're interested, please do participate. And perhaps, without any further ado, I will finish there. Just remind you if you have got any further questions, put them in the Q&A and I thank you for your attention.

Prof Ciani: Well, thank you very much for this overview of the pros and cons of the use of surrogate endpoints in oncology research. I will ask directly one of the questions we are seeing in the chat. So, this is about, again, the issue with using PFS in oncology trials that might be collected in four-eight months while OS is in the order of two years, maybe a follow-up. So, the patient lives more than one year after the end of the treatment under investigation. And this might explain in part the lack of correlation. So, again, as you said, the problem of post-progression therapies and up to you Rod.

Prof Taylor: Yes, no... that's a great point. Of course, part of progression-free survival is compass outcome, isn't it? It contains one element that is around progression and the other element is whether the patient dies or not. So, I think that's a very reasonable comment. I mean, ultimately, I really do think that overall survival can actually be really quite difficult to interpret here because if we're going to go on, particularly, with an

early-line therapy and assess overall survival, for instance, at two years, and you are in the control group or even in the active group and you fail to respond to treatment, for instance, at four to eight months, can you ethically argue that we leave those patients in their current treatment area without further rescue therapy or switch what might be second-line treatment? And I think it's very difficult and it certainly can confirm and explain this lack of correlation as you say, yeah. And this has been commented on a number of times. I get the impression, Oriana, and I'd be interested to hear from what you say. I think regulators are aware of this problem but I don't think there's a solution out there. We have these statistical methods that try to adjust for switching, but my reading of them, A is they're very difficult to implement technically and B they're even more difficult to interpret if you are a clinician or a panel member, for instance, on a regulatory committee. I don't know if you've had any experience of that.

Prof Ciani: Yeah, so there exist methods now, as you say Rod, like inverse probability of censoring waiting or another one is the... It's called rank presentation structure of failure time. Anyway, something for statisticians to implement. But the point that is made here is also in my view that there is a different, let's say, approach in the evaluation of surrogates as we know from the regulatory agency and maybe, from the clinicians as well, because the clinicians and the regulatory agency want to know whether the treatment works. So, we look for endpoints that express whether there is treatment, is there a treatment activity, but then, when we get to the payer perspective, we want to prolong life and improve quality of life. And are we going to achieve this if we only inverted common, increase the progression-free time and not the overall life expectancy for those patients? And this is where we have a debate as we know quite active in the literature. I just wanted to ask another question, Rod, because we might have some people interested in the methodology here. So, how do you think this issue of surrogacy and surrogate endpoints is captured in systematic review and let's say like the interpretation of the evidence, for instance, from the great framework approach?

Prof Taylor: Okay, I think I understand your question right then. I mean, the first thing I would say is that if we were to take, for instance, Cochran reviews and Cochran methods, my understanding is that the grade recommendation structure. So, in other words, how strong is the evidence to recommend or not recommend a treatment? I don't think it explicitly takes into account surrogacy. There is this expression of is the treatment effect direct or not? But it doesn't, my recollection is that that directness does not necessarily explicitly link back to surrogacy. So, I'm not answering the question very well, but I think what I'm perhaps indicating is that there is some opportunity to think about the use of surrogacy through grade. But I would imagine that most people tend to think of directness when they're thinking of the comparator. Is it the appropriate comparator? That's the appropriate, showing the directness of the evidence rather than what we might call directness. In other words, have we seen the effect on the final outcome? Was that what you meant here? Sorry.

Prof Ciani: Yeah, yeah, yeah. And I think I agree with you that this issue of surrogacy is captured through the element that is called directness. And so, if you don't have direct evidence on the patient relevant final outcome, but only to the surrogate, I think that reduces a bit the level of evidence that we have got. I think I agree with you.

Prof Taylor: Yeah.

Prof Ciani: I think we have reached the end of this session. I thank you Rod for your presentation and all the attendance and you will find the recording and the slides available on the platform. Thank you, thank you.

Prof Taylor: Thanks very much, everyone. Thanks, Oriana.

Prof Ciani: Bye.