#396_ Leigh Frame, PhD – Nutrient Supplementation Trials_ RCT Design, Ethics and Placebo Groups

DANNY LENNON: And here we are, Dr. Leigh Frame, welcome to the podcast. Thank you so much for taking the time out to join me today.

LEIGH FRAME: Absolutely, it's my pleasure. I'm actually a big fan of the podcast.

DANNY LENNON: That's awesome to hear, and it's quite the honor, to be honest, and people will know why as we probably start getting through this. So maybe as a good way to start, can you maybe describe to people listening, your current work, your current research interests, and how you would typically define your current role, I suppose?

LEIGH FRAME: Those are great questions, and actually not as easy for me to answer I think as some people in my field. So I'm the director of Integrative Medicine at the George Washington School of Medicine and Health Sciences, and because of that, I end up getting my hands into lots of different pots in terms of research. My personal interest has always been in the role that nutrition plays in the immune system, and that started off with my first love of vitamin D, and how it's an immune modulatory hormone, so it's actually really important for your immune system, not just for nutrition in the traditional sense, when we think about bone health or

vitamin D. That's kind of evolved over time, and I've really gotten into the gut microbiome, I'm doing a lot of work with the microbiome and nutrition, and love doing all that. But I guess, my first love is still good quality research design, and that's how we get the answers to these questions, and it's very frustrating when you are trying to answer a question by looking in the literature and seeing that it hasn't been done right for one reason or another, we don't have enough funding, the studies weren't large enough or different placebo related study design issues.

DANNY LENNON: For sure, and I think that's something I definitely want to focus on today, and it's something I know many listeners have really enjoyed in previous episodes of the podcast where we have gone into some of the weeds on study design and being able to notice, well, what makes the difference between a good study and a not so good study. So I think that I've a lot to ask on that, but I did just want to pull back to something you mentioned about your love of immunology, and I noticed that your, I believe your master's degree was in immunology specifically. And then, to get to there, and then all these different areas around nutrition you mentioned is probably not the typical thing that people might have presumed. Can you maybe just kind of briefly chart out how did someone interested in immunology specifically end up coming to this kind of wacky world of nutrition science?

LEIGH FRAME: That's a great question, and I actually love talking about that topic because I think people have this idea that our life and our career is very linear and that you plot this path and you go on it, and you end up where you want to go, and I don't think that's how it works really for anyone – we all kind of go off on tangents or explore things that we hadn't originally intended. And I would say, for me, nutrition was actually always something that was really important to me, I understood the value of it, we had a garden growing up, I was very

engaged with my food system being from a more rural area, and just knew the importance of a quality diet. But I thought it was more of a personal wellness endeavor or a hobby, and I never really thought about it as being science. Obviously, I'm wrong, and I learned that, and it was in my master's in immunology that I really started to figure that out. We had a lecturer come in and talk about the Armandio model of tuberculosis, and how vitamin D was playing this crucial role in the pathogenesis of tuberculosis or mitigating that. And at that moment, I was like, wow, maybe there is some science to nutrition, and I started really diving into literature, and ended up doing my master's dissertation actually on vitamin D, and the immune system in the skin, and how it's really important for proper immune functioning, but also avoidance of autoimmune diseases or any other sort of hyperreactive immune functioning as well. And that's when I really saw that this is a pure science, I can do this, and decided to move my career in that direction, and did my PhD in nutrition.

DANNY LENNON: Fascinating. And so, just before we do get into our main topic, given your background on what you just said, and I know a lot of our listeners are either undergrad nutrition students, undergrad science students, more generally, post grad students, maybe early in their career, and often one thing that I think people find difficult is, okay, I know I'm really interested in this nutrition stuff, but I don't know whether academia is for me, whether being a practitioner is for me, whether going into the kind of clinical side and dietetics or medicine or into more of a general nutrition way of thinking, and I'm just wondering, based on what you've come to find out, is there any advice you might give or any red flags of don't go towards this for these reasons, or good reasons to pick up a certain path, if any of that makes sense?

LEIGH FRAME: Yeah, definitely. First being that just because you start in a path, doesn't mean you have to

stick with it for one. Right? So I did a PhD in research, but now I end up working in more of a clinical and educational setting. So there's always ways to sort of pivot, so don't worry too much about that. But the other thing being that you really have to figure out what sparks joy for you, you have to get there and experience it. And if you think it's clinical care, then you need to spend time with a registered dietician or a certified nutrition specialist and see what that means to be doing clinical care. I actually originally thought I did want to do clinical care, I thought I wanted to go and get my MD, and when I spent time working with MD PhDs, I found how torn they were between not having enough time to do their research, not having enough time to spend with their patients, and that for me really made a decision that I wanted to stick with the research path, but I wouldn't have known that if I hadn't spent that time with the MD PhDs. So I think giving yourself the opportunity to interact in the world that you think you want to work in is really important, and sometimes that might mean taking a year or two off, working as a research assistant or working in some capacity to just get that experience. And I personally find that to be very valuable as an individual, but also as a program director of a graduate program. I think when someone has had those types of experiences, they are better prepared for the graduate programs.

DANNY LENNON: Fantastic. I appreciate that. So let's get into some of the weeds on our topic today, and generally, what I was hoping to ask about is RCT designs, but specifically, looking at things like ethics and placebo groups, because you've written quite eloquently about this, which we will link to, for people to go and check out as well as we'll probably discuss in a moment. But I think it's really interesting because most recently in the podcast, people will have heard us maybe discussing about vitamin D specifically, and this is a good example, because it's something that clearly has an impact, our vitamin D status with overall

health, but yet, when we were discussing some of the nutrient supplementation trials, you sometimes actually don't really see all that much. And that might be down to how some of those comparisons are being done, which we'll probably get into. And I know you've used vitamin D research as a really good example as to how we should think about placebo groups and their use within nutrition science and specifically when we're using something like a micronutrients supplement, let's say. So, before I get into all the questions I have, can you maybe just give an intro to this and explain some of that idea that we just touched on, because you've done a far better job than I've been able to raise here?

LEIGH FRAME: I think, as researchers, we have two responsibilities, the first and foremost being to science and answering the question and finding the truth. The second one is a responsibility to the participants in our research study, and to society at large to provide value, minimize risk and maximize benefit. And sometimes those are at odds with each other, because answering the question might be easier if we use, say a placebo, because that effect size difference between the control and intervention will be greater. And that may speak to some of the issues that you're talking about with some of these studies. The other is, we want to make sure that we're not harming our participants who are in our research studies, and some of them for long periods of time. So if we're talking about a short research study for a couple of weeks, having a placebo control, almost always, is going to be okay. Right? Two weeks of not getting enough vitamin D is not going to kill anyone, probably not even going to cause really any undue harm. However, when we're talking about longer trials, where maybe over a year, we're following these patients and controlling their nutritional intake to deny them sufficient amounts of vitamin D – and I'm using the word sufficient in very non-technical term there, that's when we start to have to wonder, are we causing harm, and is

this unethical to the research participants, particularly if they don't fully understand what they've consented to in terms of what the potential harms might be.

DANNY LENNON: And for perhaps people listening, that aren't familiar with academia and how trials are not only designed but then have to pass through an ethics review board, let's say, can you maybe just outline that process, and not only why we have ethics, as you just demonstrated, but what that actually looks like for someone on the frontlines doing research?

LEIGH FRAME: Yeah, so as a researcher, you typically have a research team, and you're going to work together to put together a study protocol that clicks all the boxes on the science side, but is also making things as easy as possible for the participants. You're trying to decrease burden, you're trying to make things relatively simple so they will hopefully actually complete everything and won't be lost to follow-up; you're also trying to incentivize them in some way, but not cause undue incentivization. So if you're offering large amounts of money, then people might consent, even if they don't think it's safe – maybe there are a vulnerable population where that money would be really particularly enticing. So you have to balance all of those things together, and you try to put this protocol together to the best of your ability; and then you send it off to your institutional review board, and a whole team of people review it there. And a lot of times, they're going to come back with questions or comments or suggested changes to improve it, and the IRB really focuses a lot on the ethical side of things, they are there to protect the participants as well as the researchers, and they may not understand the science behind it. So that's definitely the responsibility of the research team to communicate the science and why they've chosen to design the study and the way that they've chosen. So there is this whole gatekeeper aspect, you don't get to just do research anymore. Historically, we would just

start doing research studies, like, 60 years ago, there was no board to review it, and frankly, we just did the research on ourselves, because we're handy. And we're not doing that anymore, because not only is it not ethical, but it's not actually great science either. Right? We need a diverse pool of people to get a better answer that will be applicable to the diverse populations that we're talking about.

DANNY LENNON: Awesome. So if we start thinking about different types of placebo groups, and I know you outlined a number that we'll probably talk through in a bit more depth in the moment, but really, as you just outlined when we think of things, both trying to balance the ethics here towards participants, but on the other side, trying to get really good data from the science side, there's kind of two extremes that make things difficult for each one of those. And the way that we, for example, that you mentioned that we could have the guaranteed of what we're doing the least harm to people, would be to make sure, well, we don't want anyone to have a vitamin D deficiency, because that's bad for their health. So if we screen people and see that they're vitamin D deficient, let's treat that immediately, but then what we're losing then is we obviously can't compare people who are actually deficient, that are walking around the population to see what would happen. So we're kind of losing some of that. Can you maybe talk about the balance and those two different extremes that we might see if we go one way or the other in setting up a placebo group?

LEIGH FRAME: Yeah, that’s spot on. It is definitely a balance of these two extremes, taking care of patients the best we can is what we do in healthcare, that's not necessarily what we do in a research study. So that's the first thing is we're realizing this is not standard patient care. They're not coming in to see us form their medical care. They know they're participating in a research study, and they should have undergone informed consent to understand the risks to the best of our knowledge, which is also a problem. We don't

necessarily know what a lot of the risks to mild vitamin D deficiency might be. We're still learning that. So that is a little bit difficult for the vitamin D world. But really, we're trying to get the right answer, and we're trying to do it without hurting these research participants, and there is a happy medium, but that happy medium is going to be different for every population, and for every research study, because the factors are going to be different. For instance, if we're doing research in women trying to conceive, there's a distinct period of time in which that nutritional deficiency may affect, A, their ability to conceive and, B, the child's development. So it's a much larger burden on us to protect the research participant there than there would be in, say, a healthy population. If you have a general healthy population, a lot of the research studies are done this way – we have grad students, we have undergrad students who come in and participate in the research studies, and it's okay to deprive them of these nutrients for a longer period of time, because they probably aren't deficient. But to your point, the largest effect is going to be seen in patients who are deficient. Right? If we have someone who doesn't have enough of a nutrient, say vitamin D, and we deliver these different doses, we're going to get a much bigger response, if we're taking a patient from deficient to now sufficient or optimal various different levels. And that's really the question in most cases. So how do we do that in a way that we can answer that question, but we're still not putting people in harm's way.

DANNY LENNON: Awesome. So maybe let's talk through each of those types of control groups that you had outlined in that particular paper, two of which we've just touched on here, but to name them, you first have this active control, and then you also compare that to kind of not necessarily the opposite end, but towards an opposing end of what we're discussing here, a placebo control with restrictions on someone's ability to supplement, so people are not allowed to

supplement and they're in a placebo group. Can you just, again, outline what those two types of groups are, and then the issues that may occur if we use one or both of those – and we can even give this specific vitamin D example, if it's more useful.

LEIGH FRAME: Sounds good. So I'll start with the placebo control, because it is really what is kind of the gold standard. When we talk about an RCT, a randomized controlled trial, it's often double blind, placebo controlled. That's what a lot of our guidelines are based on. In fact, a lot of times they won't even look at research that doesn't fall into that category. So this is why we feel very much compelled to, one, user placebo, and, two, do it in the most highly controlled way, which is to not allow them to supplement otherwise. So they can't have a multivitamin or any other vitamin that contains that nutrient of interest. And with vitamin D, we would say, okay, that means you are getting one of these three doses, or you're doing a placebo, and you aren't allowed to get any other vitamin D. However, they can go outside, they can get some vitamin D, they can't get it from their diet. We're not totally excluding vitamin D from the diet in that sense, just not allowing them to take any supplements. However, if they're deficient, then they probably need a supplement. So that is the concern on that end – are we putting them at risk of deficiency? But we're also probably going to get some of the better data by looking at the patients who are deficient. So really big pluses for science and maybe not the greatest aspects in terms of reduction of harm; opposite end of spectrum we have the active control. So in this group, we'd have maybe the same doses we were going to give in that first version, we'd have three different doses we're going to give, and instead of that control, we would use a really, really low amount of vitamin D. For instance, the estimated average requirement is probably a good one to go with, because it's the bare minimum that you need to kind of exist, and in vitamin D, that's 400 international units. So if

we give that and then, say, the next dose is maybe 2000 international units, and then we have 4000 and maybe 6000, so there's a pretty large difference between those doses in the hope that there's actually going to be a difference in the effect between the 400 IU and the 2000 IU, that lowest other dose. That's really what you're doing in trying to optimize the ability to measure that change, but also try to minimize harm by using the active control. And in some populations, that may work really well, because you're actually looking for a relatively large effect size, and the difference between 400 and 2000 IU will be really relatively easy to find, or maybe have enough people who are participating in the research study that your power is really strong in that way.

DANNY LENNON: So if we think about one of those other types of groups that you outlined, was something that might be counterintuitive to people because you've just mentioned there that oftentimes when we use a placebo, we would require people not to then go and take other supplements that contain the certain nutrients, because then essentially that's going unaccounted for to some degree, or, even if it's not, we're not able then to have the same level of intake in this whole group. So typically, we think, well, that's clearly a good idea from a design perspective. But now, more recently, we've seen the use of these placebo controlled groups without these supplementation restrictions. Can you maybe talk about what that looks like, but then also the benefits to using such a strategy and where that might be best served to be used?

LEIGH FRAME: Yeah. So this is in line with the use of the placebo control, like, we're trying to stick to that gold standard. But now we're maybe taking a step away from that and moving towards harm reduction, by allowing them to take whatever supplements they already were taking, that's typically what it is, it's whatever they were already taking, because that, in

theory, shouldn't change their nutritional status, because that was whatever their baseline status is, was based on taking those supplements, rather than excluding patients who previously took supplements, which is what you often do in the placebo with the restrictions. You say, you can't take supplements for within the last 30 days, something like that, but here, we'll say, okay, you keep taking supplements you were already taking, and we're just going to add this on top of that. So we know where they were nutritionally, we've got their baseline information, and now we're saying, what happens if you add this much. So the question is quite clear, and you know what you're doing. I guess, the negative is that the precise dose that is being delivered is going to be different for each individual, and that does make it a little bit difficult; and perhaps you want to stratify by whatever their starting nutritional status was to make things a little bit more clear in terms of what the effects are, but that being said, it's something we can do, and we can analyze it that way. And if it's going to help produce the harm for individuals, that's probably beneficial. But I think more importantly, it's realistic. This is sort of how the world actually works. We wouldn't have someone stop taking supplements, and then start something else. When they come in for patient care, you're going to see where they are now and say, okay, we need to increase that by 1000-2000 international units of vitamin D, and then check again and see how that is. So I think it actually is more of a pragmatic research study design.

DANNY LENNON: Yeah, and it's interesting how there is starting to be a bit more focus looking at doing pragmatic RCTs within nutrition, which wasn't always typically done. So that's also an exciting area that probably good data can be taken from in the future.

LEIGH FRAME: Yeah, I agree, I think historically, we've tried to be very reductionist in our study of nutrition,

which makes a lot of sense, scientifically, we can only study one variable that's changing. But again, it's not overly reflective of how people actually function. And so, when we then apply that understanding to the real world, it doesn't always translate exactly how we expect it to be, because of those pragmatic issues of people being real people, and living their real life. So I think there's absolutely benefit to all of these approaches, and I think that's what is going to be really exciting about research moving forward is that we're going to see both the mechanistic-reductionist work to continue, but we're now going to see these pragmatic trials, okay, well, how do we apply that, and that application, I think, will allow, at least, healthcare providers, and hopefully, individuals, informed consumers, to better care for themselves.

DANNY LENNON: As you alluded to earlier, with a number of nutrients, we often see that most pronounced benefit going from a deficiency state to something that's more sufficient, and given the kind of ethical challenges that you've outlined earlier, one of the potential solutions that you've discussed in your writing is the use of rescue repletion therapy. Can you maybe explain what that looks like for people who haven't come across that before?

LEIGH FRAME: Yeah, it's definitely not common in the nutrition world, it's really common in other sorts of research – asthma being one of the major ones, where they're using a treatment, and it gives them sort of window that the treatment has to work in, and if it doesn't, and they have to use a rescue therapy, then that's basically a sign of failure of the treatment. It wasn't sufficient, and that's really more of the outcome, as opposed to looking at different nutritional status, which is a little bit more difficult. But we could do something very similar in nutrition, we could measure where they are at baseline, give a certain period of time in which they're going to be on this assigned dose; and if, at that point, they are

still deficient, then we can deliver a defined protocol to rescue them and what that looks like would definitely depend on the population and how long this study is going on. Right? So if it's a relatively short study, then maybe you don't need to have a large bolus dose; but if this is going to be over a long period of time, and you'd like them to go back to whatever the other study dose was, then maybe you do need to give a fairly large bolus dose. And then how do you correct for that or are you just using that, as they do in the asthma studies, as a sort of a marker of treatment failure, and do some sort of analysis looking at how many patients in each group failed. Because the number of deficient patients, and hopefully, if it's randomized, probably should be relatively similar between groups, right? You should have roughly, say 20% vitamin D deficiency in every group, so if there's more treatment failure in any one group and treatment failure being that bolus dose, then that is meaningful.

DANNY LENNON: Given that we are talking about placebo here, it'd be remiss of me not to bring up the placebo effect, which I'm sure everyone has heard of, and I think it's been really interesting to see, in recent times, the methodology of using open label placebo trials as potentially one way around this, so this is where participants are given a placebo, but kind of told upfront that it is a placebo. In relation to that, as a potential methodology within nutrient trials, how do you think we should consider that, and its place and where it may be efficacious within the nutritional world?

LEIGH FRAME: That's a great question. Well, so we know the placebo effect is just that, it's an effect. Right? So it's not an absolute zero baseline, which is basically how we treat placebos when we do these randomized control trials. We treat them as if that's the baseline, but it's truly not, if they're receiving a placebo, and they think they might be receiving a therapeutic. That being said, there is still some residual effect, even in patients who know that it is a placebo, so we're

still not going to true baseline there. And with the concerns of potential bias from investigators knowing what the subjects are receiving, it makes me a little bit uncomfortable about the unblinded placebo, because it seems like it's sort of missing a large part of the point, which is that the research study team doesn't bias their collection of data or anything else. That to me is actually almost more important than the other aspects of bias to the actual participant themselves. So unless there's some way we can get around that which it's possible, we could have two different aspects of the study team, one that's blinded, one that's unblinded, to eliminate that. But I just think that there are a lot of factors to consider, and how we move forward with that is going to be, as with all of it, it really needs to be done on a case by case basis, to see what is feasible – because a lot of times with research, we have to think about what's feasible, do we have enough distance between study team members that we could have a blinded and an unblinded group. If it's a study team of two, that's probably not going to work; but if you're doing large epidemiological trials, and you have this massive study team, then yeah, that probably could work, and that's a realistic feasible method.

DANNY LENNON: Yeah, and that issue you just mentioned, I think it was a paper on IBS I was reading recently, and it was an open label trial, but exactly that you see more of an improvement in that placebo group, even when they know it's a placebo, and I think you tend to see that in pain science trials of back pain and stuff as well. So it's just fascinating, but obviously, it still just means that there are more challenges to overcome. So going forward, in order to have better quality nutrition trials with the correct use of placebo groups, what would some of your recommendations be, or, what would you like to see happen, and in kind of ideal world, how we can start conducting better quality nutrition trials, even generally beyond what we discussed here?

LEIGH FRAME: Well, in an ideal world, I would love there to be guidelines that people can refer to, because I think it's a little bit difficult for every individual researcher to tackle this problem on their own. Now, granted, like I said, it's got to be done on a case by case basis, but there are some general guidelines and principles we could put out there as a maybe consensus statement from the nutrition science community saying, this is how we see this working and how it can best be managed. That may or may not happen. And so, in the meantime, I really encourage every research team to make this part of their study protocol development, and actually have it be a discussion, a really full-fledged conversation about the pros and cons in each element, and why we're making these decisions. Because a lot of times, to be honest, we make decisions, it's because it's what we've always done. Right? There's a lot of tradition behind it, that's how all the other studies were done, and we want to be comparable to the other studies. And if we change our protocol, then you can't directly compare what we're doing to these other studies. That has value, but we need to know that's why we're making that decision, and that we have, conversely, not made a decision to change that maybe would make it slightly more ethical.

DANNY LENNON: For maybe those of us who are not producing research, but more interested in reading through the literature and trying to pull some conclusions from that, given that there isn't maybe guidelines here or there's certainly not a consensus about some of these things of the best way to go, is there a framework you'd kind of recommend for, how can we, when we're reading through a research paper, work out how is this particular placebo group impacting these results, particularly, or, is this a good design the way it has been set up – is there any way we can start trying to integrate that? And obviously, that's a difficult question itself, but if we presume someone has already a level of competency to read research, is there

something on this particular question that might be useful to keep in mind?

LEIGH FRAME: Yeah, that's a great question too. I think probably the most important thing is to look at the difference between whatever the control, be it an active control, be it a placebo is the next lowest dose. And does that seem like something you would intuitively expect to be significantly different? We talked about 400 IU as an EAR dose, versus 2000 IU has to be more of a therapeutic dose. Those inherently jive with me as being different, but if we were looking at, and there are studies out there that we've got 400, 600, 800, those are not inherently different to me. And so, I would be worried that we don't have enough difference to actually measure an effect size. So if we have a null result from that study, that to me is not necessarily a null result for the question, in general. It's just in that study with that study design. I think that's the most important thing we can look at, because, particularly in vitamin D, that's where a lot of studies fall is, whatever their baseline was or the amount they're giving in terms of changing their blood concentration of vitamin D, just wasn't enough. And so, that null finding is null for the study, but not necessarily null for the question in general.

DANNY LENNON: Yeah, perfect. That makes a ton of sense. I think, hopefully, for everyone listening, they'll be able to connect dots previously on the podcast where we've discussed having appropriate exposures between groups. And we've talked about in the context of maybe some epidemiology, but I think that fits, obviously, quite clearly here, as important within RCTs as well. So before I get to the final question, Leigh, where can people find you on social media, on the internet or anywhere else that you'd like to send their attention?

LEIGH FRAME: Great. So my number one platform is Twitter, I'm @PhD_Leigh, I'm also on Instagram, same handle, I have a Facebook page, and you can follow me on LinkedIn. But also, please check

out the GW Integrative Medicine Podcast where we talk about these type of topics quite often.

DANNY LENNON: Awesome. And for everyone listening, all of that will be linked up in the show notes, and I recommend you go and check all of that out, and make sure you follow along this work. And with that, that brings us to the final question that I always end the podcast on. So if you could advise people to do one thing each day that would have a positive impact on any area of their life, what might that one thing be?

LEIGH FRAME: So I knew this was coming and I still struggle with it, because, as an integrative whole person health provider, I like to look at all the different aspects. But if I could say just one thing, and with my background in nutrition, I have to go there, it would be, get a diverse, colorful diet, not just for you, but also for your gut microbiome. It seems to be the one thing we can say very clearly about the gut microbiome is a diverse diet leads to what seems to be a healthy microbiome.

DANNY LENNON: Awesome. A brilliant way to end. And with that, Dr. Frame, I want to say, thank you so much for taking the time to come and talk to me today, and also for the great information and the work that you continue to do, it's been an absolute pleasure.

LEIGH FRAME: Absolutely. Thank you so much.

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