"I worry FDA Expanded Access will become a new way of bringing products to market": Talking with Jeremy Snyder and Leigh Turner about "stem cells for autism"

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Transcribed by Julie-Ann Lee

(Theme song – soft piano music)

Anne: You're listening to Noncompliant: The Podcast. I'm your host, Anne Borden King. Today I'm speaking with Professors Jeremy Snyder and Leigh Turner about direct-to-consumer stem cell clinics claiming to offer treatments for autism.

Jeremy Snyder is a Professor in the Faculty of Health Sciences at Simon Fraser University. His background is in Philosophy and his research focuses on public health ethics. Dr. Snyder's most recent book is *Exploiting Hope*, from Oxford University Press.

Leigh Turner is an Associate Professor at the University of Minnesota Centre for Bioethics, School of Public Health, and College of Pharmacy. Turner's current research addresses ethical, legal, and social issues related to stem cells and regenerative medicine products. He's the co-editor of *Risks and Challenges in Medical Tourism* and *The View from Here: Bioethics and the Social Sciences.*

Doctors Snyder and Turner have collaborated on research and writing about stem cell tourism, including direct-to-consumer stem cell clinics that claim to treat autism, and we'll be talking about that and more today. So, welcome to the show!

Leigh: Thank you!

Jeremy: Thanks for having us.

Anne: Let's start with defining some of the concepts we'll be talking about. I'll start with Leigh. What is **medical tourism**?

Leigh: There are a couple of different ways of thinking about it, one is kind of a marketing slogan or brand, the idea being that you have facilities that are advertising medical procedures, and they'll take advantage of local tourist attractions as part of their marketing pitch to try and draw people there. The idea being that you can travel to have a medical intervention, but also enjoy, you know, local tourist attractions. Another way of thinking about it is coming at it from a somewhat more academic perspective. We have different kinds of cross-border health related travel. If we going to use the phrase 'medical tourism' what exactly are we trying to say there? One way to think about it is to say 'this is only people who are travelling for medical interventions and they're typically paying as individuals, a cash on the barrel, out-of-pocket basis, as opposed to travelling as part of some sort of organized arrangement where there's a

prior arrangement with [for example] the Ontario provincial health care system to go and get care in Michigan. So, I think that's one way of thinking about medical tourism… somewhat individualistic.

Anne: Mm-hmm. Right. So, it could be [done] a number of different ways. What would make someone choose medical tourism?

Leigh: So, there can be a variety of reasons, and I think Professor Snyder and his colleagues at Simon Fraser have done a good job kind of laying out some of the reasons some people will travel for medical care. Sometimes there can be long delays in gaining access at local facilities, so people will decide to obtain expedited access by travelling elsewhere. Sometimes it's to obtain access to something that's not available in a local community, maybe because it's outlawed. So, some individuals have travelled to purchase, you know, kidneys, sometimes described as 'transplant tourism' – organ trafficking.

We're going to be talking about stem cells. There's a long history of individuals crossing borders, going to facilities marketing purported stem cell treatments. So it can be anything from fairly routine standard of care interventions, you know, orthopaedic procedures, cardiac procedures that are well within the mainstream of evidence-based interventions to something that's really kind of on the periphery, not backed by meaningful evidence at all. All kinds of factors can play a part in terms of why people decide to leave their local communities and go elsewhere in search of health care.

Anne: Interesting, interesting. So, you've both been studying how people use social media platforms to raise funds to do their medical tourism. An example would be like a GoFundMe or things like that. Jeremy, what platforms are people mainly using to raise funds for their medical tourism and how much money are people able to raise on these platforms?

Jeremy: There's really all sorts of different platforms, I mean it's nothing new in the sense that if you consider putting up a message on a church bulletin board or a classified ad in the newspaper asking for help from your neighbours, then crowdfunding in that sense has been going on for a long time. But, what we've seen is a movement to these online platforms like Facebook and Twitter, and the growth of these specialized online platforms like GoFundMe and other charitable crowdfunding platforms that people can use to try to reach a much wider audience than you might have in the older days where it would be much more limited to people who are close to you.

So if you look at GoFundMe, it's the largest platform for medical based crowdfunds in North America certainly, and probably the world. And they'll say that they're raising somewhere in the neighbourhood of 250,000 campaigns a year and about $750,000,000 going into that. And those are the numbers they were using before the COVID-19 pandemic, and since then it's going up quite a bit.

There are other platforms in other countries that are much more dominant. India has very large ones; China has very large ones and other social media as well. So, GoFundMe is not the only one, but certainly we're looking at probably well over a billion dollars. How much of that is for medical tourism – that's a little bit harder to say; the numbers don't usually get broken out in that kind of way. But we do certainly see a lot of people using them to travel outside of country, sometimes they're specifically given guidance on that. And it will sometimes depend on what kind of a procedure they're looking for. Things that aren't mainline and clearly curative treatments but much more experimental or unproven treatments. Those are the ones where you're likely to see much more of people going abroad for care.

Anne: Right, right. I was interested in a point that you made in a recent paper that crowdfunding campaigns can uncritically spread health misinformation to new audiences, in the same way that any social media posts can, right? Because these campaigns are social media content. Can you talk about that, Jeremy?

Jeremy: Sure. Obviously, misinformation or fake news being spread online isn't anything new, you know with a lot of people seeking out vaccines for COVID-19 right now, we're seeing tons of misinformation on Facebook and Twitter and everywhere else. But one of the ways that crowdfunding in particular gives rise to misinformation is that there's a really strong incentive baked into it to not necessarily *intentionally* misinform, but exaggerate the likely success of something and to hold back a little on any of the potential safety concerns. And the reason for that is they're *asking people for money*…

Anne: Mm-hmm.

Jeremy: You're asking them to help save a life or turn somebody's life around, and so you have every motivation, every incentive to try to show other people that their money is going to be well spent if they entrust it to you. And so, you know any kind of caveats that might have been on the website of the clinic or the provider that 'this may or may not work,' a lot of that is likely to go out the window when people are asking for the favour of money.

Anne: Mm-hmm.

Jeremy: And, you know generally – as we've seen a lot of times on Facebook and Twitter and other social media – there's not a lot of oversight of this. We're starting to see some of that, especially around vaccines. And even on GoFundMe there have been a couple of areas where they've started banning or restricting certain types of crowd funds for extreme right wing groups, or in some cases vaccine misinformation, that sort of thing. But for the most part there's really no screening going on, and you can say what you want to say. No one is going to fact check you. No one is going to demonstrate that that wasn't true.

Anne: Right. What about when people report it to the platform?

Jeremy: Yeah, that can be really opaque. I mean I've done that a couple of times myself…people raising money for anti-vaccine activities for example, where I knew that

GoFundMe had a stated policy of taking those down. I haven't necessarily always gone back to check, but I never got feedback. I never heard back from them. And if you think about that, you know if just in the medical area, you know, 250,000 campaigns, 300,000 campaigns a year – it's a huge amount of work to actually go through and screen these. It's one thing if you've got somebody like me reading through them and seeing these sort of things, but if you're largely sharing them with your own social network and friends and family and the people you're trying to raise money from, they may not be the sort of people that are likely to report you as spreading misinformation.

Anne: Right, right. Now, people crowdfund for medical tourism to receive stem cell infusions and I just wanted to define here, for listeners, what stem cell infusions are.

[9:50]

Leigh: People engage in crowdfunding and one common campaign you can find is individuals crowdfunding for stem cell treatments, and those stem cells--I should add a qualifier which is at these facilities people aren't necessarily having stem cells administered, but that's kind of the pitch. And, when stem cells, or whatever, are being administered to somebody, it can be done in different ways.

So, one is an **injection**. Just a site-specific injection. Another one is an **infusion**, and that's typically going to be intravenous infusion, different ways of doing that. Some of us may have had family members or friends who had cancer for example and it's possible to use a central catheter where you use a vein in someone's chest cavity, and that's done, and many of these clinics, that's not how they'll do it. It's going to be an I.V. infusion, maybe in someone's arm, something like that.

There's also some businesses that will **nebulize**—with *the claim* to nebulize stem cell products or **exosomes** and so the idea is that's almost like using an asthma inhaler… that you're inhaling it and that's going to have some kind of a therapeutic effect. That's not the most dominant way of doing it. But these are some of the different ways that businesses will claim to administer stem cells.

Anne: And what are some of the risks associated with the stem cell infusion process?

Leigh: Well there's different kinds of risks. One is that in many facilities, it's not really someone who's a qualified practitioner specializing in a particular area. So, you could have individuals operating far outside their expertise, their training, their specialization, so they don't really bring a wealth of knowledge or a background understanding to treat the individuals they're seeing. Another problem is that if cells haven't been properly manufactured and processed, there could be contaminated products being administered to individuals.

This isn't just a hypothetical, theoretical possibility. This has happened already.

Another possibility is that cells are being administered, but that all the careful pre-clinical work hasn't been done carefully in the context of clinical trials and so you could end up with very serious adverse events – complications occurring where someone has been told they're getting this risk-free, safe, efficacious intervention and instead they end up suffering quite serious adverse events. That could be a pulmonary embolism, it could be a stroke, it could be they end up with some sort of a undifferentiated mass – what some of us might think of as a tumor. So, there's a whole spectrum of possibilities from relatively minor, relatively inconsequential in the grand scheme of things, to really life threatening, life altering complications. Some of the more well known case reports involve women in their 60s, 70s, and 80s who ended up being blinded by purported stem cell procedures. So, the risks can be quite serious.

Anne: And there are a couple of different types of stem cells that different people use as well, is that right?

Leigh: There are many different types – and if you look at companies and the kind of advertising claims they make, a lot of them, especially in the United States, will mention **autologous** stem cell products – here, bone marrow aspirate is being taken from someone or liposuction is being performed and fats are being taken and processed and put back into them. Sometimes it's peripheral blood, although that's less common. Those are autologous products.

There's also **allogeneic** stem cell products where this is, if not from a person and going back into them it's from some other source. A very common category are birth tissue related stem cell products, and here the claim is that these are stem cells purportedly being obtained from umbilical cords, umbilical cord blood derived stem cells, from placentas, from amniotic fluid. So, these are some of the more familiar allogeneic products.

You can even find some businesses that will advertise **xenogeneic** stem cell products. And here the pitch is that it's coming from some other species. I think if *I* saw that my eyebrows would be raised and I'd be rather worried. But there are a number of businesses where that's kind of their pitch for cosmetic applications, for cosmetic purposes.

So, there's a whole range of purported sources and cell types that businesses will advertise, here in the United States and globally as well.

Anne: I notice that you're using terms like "claim" and "advertise," because you're not really sure in many cases whether what's being promised is what's being delivered, is that right?

Leigh: That's true. I mean that's why I'm kind of using these qualifiers. I mean often it's quite clear what businesses are claiming to administer, and maybe in some cases that's true, that actually is the source, but when it comes to just looking at claims on websites, I think we have to be cautious and say well, these are marketing representations. These are claims that are being made and we need to step back and ask 'is this in fact what's being done?' What do I

actually know about these products?

In many instances we may not know very much. As academics looking at the businesses or even patients going to these businesses, we may not know an awful lot about what's actually being put into people. There have been some efforts to look at birth tissue derived products. There one of the interesting findings is that it's clear there are some businesses marketing purported amniotic derived stem cell therapies, and when you actually ask 'well, what's actually being administered to people,' they don't contain any viable stem cells. So, it's not necessarily dangerous or risky, but there's also not much reason to think that there are viable stem cells that are actually going to have some sort of therapeutic value to them.

Anne: In the U.S. and Canada, stem cells are not an approved treatment for autism, but some parents are taking their autistic children to stem cell dealers outside of the U.S. or Canada for what you refer to it as direct-to-consumer stem cells. What does that mean?

Jeremy: So, what we're talking about with **direct-to-consumer stem cells** are going to be businesses that are selling these purported treatments directly to the recipient. So, we're not looking at somebody who is going to their family doctor or specialist and then getting referred to a site within Canada or even abroad for this treatment. Typically, they are not people who are going through insurance, but these are going to be storefront businesses that are selling a product, essentially. You'll see them all the way from kind of strip malls, storefront businesses to larger clinics. There's really a range of different stem cell providers in Canada and abroad that do this, but that's the key element: that they're marketing themselves as selling a product. And even within Canada, sometimes these aren't even approved, and you see this more commonly in the U.S.

There are instances where people will try to get around some of the restrictions as Leigh was referring to…some of these autologous products that are derived from your own tissues, or your own blood, and in these cases there can be some grey zones, or lack of enforcement of what people will offer. So, you certainly don't see that as much in Canada and the U.S. but the direct-to-consumer stem cell business more broadly is pretty common to North America and throughout the world.

Anne: And what are some of the claims that these clinics are making about stem cells as an autism therapy?

Jeremy: Yeah, it really ranges. On one end you will see people who are very, very careful about it….maybe in a legalistic sense or maybe out of a sense of propriety, but you know they will be clear that there's no proven treatment using stem cells for autism, but they'll use words like that it's 'promising' or 'we have hope' that it might do something. In some cases these businesses will not necessarily put anything stronger in their own words, but they'll use patient testimonials where they'll have former customers who have experienced positive results, or what they see as positive results, and they'll make stronger claims then. But 'promising' and

'hopeful' are some of the more common hedges you'll see.

And then on the other end of the spectrum, you will have these business that are making absolute, definitive but completely unsupported claims about what stem cells can do for autism. You will see things like that it 'works', or 'successful', that it's 'scientifically proven'. And in some cases I think are even saying things that I think are going to be fairly offensive to parents of children with autism or people with autism themselves – so you'll see things like they'll 'cure' autism or in some cases I've seen claims that they will 'reverse' autism. It's often sort of marking autism as a disease that needs to be fixed, and 'we have the cure', that these stem cells are going to remove the effects of autism.

Anne: You have a recent paper that looks at crowdfunding for an international stem cell clinic that's marketing them directly to the consumer as an autism treatment, and there also is crowdfunding for clinical trials to a U.S.-based university experimenting with stem cells. So, people are crowdfunding 1. The direct-to-consumer clinic, which is a private clinic outside of the U.S. but 2. They're also crowdfunding for a university who's running clinical trials and the parents are seeking funds for one or for both. Can you talk about these two examples of crowdfunding?

[20:04]

Jeremy: Yeah, so a little while back Leigh and I did a study looking at crowdfunding campaigns for neurological conditions more broadly, and one of the things that we saw was that campaigns related to Autism Spectrum Disorder specifically were pretty common, and these were all for purported stem cell treatments. And among those campaigns looking for treatments for Autism Spectrum Disorder, there were a couple places where they were running clinical trials or making stem cells available on an expanded access basis, similar to 'Right to try', it's where these are outside the clinical trials but had approval from the FDA or Health Canada. Duke University and Northwestern were the two most common of those.

We saw among these direct-to-consumer clinics who were selling a product, the Stem Cell Institute in Panama was a very common one as well. And, we saw a lot of overlap between that, so we wanted to take a look and see how different these are, given that they're claiming to provide a very similar product. How are they seen in the minds of people who are trying to raise money to access these purported treatments?

And, you know, we did see a lot of differences between them. It was definitely much more common for people who were seeking to get funds to pay for participation in the clinical trials at Duke, and for these clinical trials generally people did have to pay, not just to relocate, or travel expenses, but to actually take part in the clinical trial. In those cases, you didn't tend to see quite as many of these [claims of] definitive treatments that 'this is going to cure my kid', or 'this is going to end some of the negative effects of autism for my child', but it was a little bit

more measured that 'this is something that's promising or has potential'.

For the campaigns that were for expanded access outside of the clinical trial, and particularly on the direct-to-consumer basis of the Stem Cell Institute, we saw much more that the people were making these definitive claims that 'this will cure my child, that this is going to be successful, that it's absolutely safe' – so much more stronger [statements] when it's something that was seen as a product they were paying for, rather than a clinical trial that they were going to be taking part in.

Anne: But why do you think that is? Is it because of the way that it was pitched to them, do you think, or just because of the different ways that they would be receiving them?

Jeremy: It's hard to say for sure, but my guess would be it's a very different experience when you're taking part in something that's presented as a clinical trial, in some cases there might even be a placebo arm, or, you know, not a guarantee that you're even getting the product that's being studied. And you're being seen as taking part in a research enterprise, so as such that the jury is still out that this is going to be successful.

And in these other cases, you're essentially paying for a product. I think in that case, it's not that you're contributing to research but that you are hoping to get your *money's worth*. That's much more of a market-based exchange and so, that would be my guess that [this] kind of influences how people are likely to react to it.

Anne: Right, but you said with the expanded access program that's also run by Duke, there tended to be more extreme claims made in the GoFundMes as well. Is that because the parents have to pay whatever - $12,000, $15,000 to be in the trial? I mean, it's not a 'trial' to be in the expanded access program. Why do you suppose it's different even though it's the same institution?

Jeremy: You know, that would be my guess as well, and again, we weren't looking at… three, six, smaller numbers in the Duke University compared to the Stem Cell Institute, but I think that would be my best guess, that expanded access is a very similar experience to paying for any kind of treatment. Whereas, the clinical trial…and with expanded access they may be trying to get information about the treatment as well… but again it's money for a treatment, whereas a clinical trial is set up to be a different kind of experience.

Anne: And you discovered that in the GoFundMe campaigns, the parents were discussing research from Duke as motivating or justifying their decision to take their children to stem cell clinics outside of the U.S. Some of the campaigns that you looked at relied on media reports about the Duke studies or may have even been people that were *involved* in the Duke studies, but then Duke has done three trials, and none of them show evidence of benefit, so it seemed like what happened was the media picked up on the initial research hype about Duke's program but never corrected it with the actual results. So, I'm wondering if the hype…has it developed a

life of its own, or how does it impact people's understanding about something like stem cell therapies, which is a very complex topic?

Jeremy: Yeah, I think how you put it there that the hype has developed a life of its own, that's really what we saw. It's super common for these direct-to-consumer businesses to try to cloak themselves in scientific legitimacy. If you can draw on an association with a really well-regarded university like Duke or just use the language of research and clinical trials and studies and point people to peer-reviewed journal articles – all of that supports that this is '*something'* that this is real and legitimate and proven to work…and will help them to sell that product.

We saw with these campaigns where they were looking for money to seek treatment in Panama that the website that they were going to for the Stem Cell Institute has links to papers published by the Duke group, and one that we saw very commonly pointed to in the crowdfund campaigns; you saw it on the Stem Cell Institute website, and I've seen it many times on other websites for clinics or direct-to-consumer businesses that are selling stem cell treatments for Autism Spectrum Disorder… it was a particular piece that CNN did.

So, again, you've got the legitimacy of a well-regarded news outlet interviewing the researchers from Duke, and it starts with a vignette of someone who went through the clinical trial and they experienced very 'positive' results. You then get some disclaimer that says, 'well this was an early safety trial, and there was no control' and all the things a scientist would care about. Uh, then sort of sandwiched around that is again anecdotal evidence from the researchers at Duke about the successes with this very small trial, that as you point out hasn't been borne out with some of the larger control trials that they tried to do. In a piece like that, the very cold technical language about 'don't over-hype this, don't over-believe in this, this is all very early days,' gets sandwiched around these emotional, highly compelling stories about people who see themselves as being done very well by these treatments.

And, there is no correction and these stories get shared online; they get shared in the crowdfunding campaigns; they get shared in patient groups. Even if more recent data doesn't support that kind of story, the article is still there. You can look at it today and I think that's hugely problematic.

Anne: Right. And if you have a researcher speaking kind of in one voice to the *media* which is describing anecdotal things – the types of stories that media like to hear, right, or like to put out…the researcher is speaking anecdotally to media, and that gets taken very seriously by many, many viewers. And then the other voice of the institution which is trying to be more objective, but which is only really appearing in dry papers that most people aren't looking at, especially as consumers.

So, what should institutions like Duke do to keep themselves from being leveraged in this kind of hype and marketing by clinics like the Stem Cell Institute for example?

Jeremy: The only thing they can really do is to just be very, very careful about their press releases and how they speak to the news media. Any time I've had a connection with our news media at Simon Fraser University – I think this is a widely shared experience – is that they do want to share feel good stories and they want to share you know the incredible, amazing things that their faculties are doing, and you want to be a part of that. So, it's really easy to get drawn into that, and I think that universities do see it as part of their mission promoting their successes and breakthroughs and all these sorts of things.

But I think it's incumbent on them and their media departments to be very careful about that, because we see concretely in this study that Leigh and I did (and many, many others) that it can be taken out of context and do a lot of damage out there. And I think it's being realistic about how likely media relations departments in universities are to be careful about that. I think researchers have a really big obligation to be careful as well. And, it is difficult. I feel for all these researchers. They want to be part of a feel good story, and they want to trumpet their successes, but you know it's so easy for these things to get misused and I think it's through media training and just being really, really cautious…

I think any researcher working in any of these areas has to be incredibly careful about how they communicate their work. Just one slip up – if that's the pull quote, it's very easy for those things to get misused.

[30:38]

Anne: In your study, you noted that 12 of the crowd-funding campaigns were "equivocating between Duke and the Stem Cell Institute," a couple were noting links between the Stem Cell Institute and a funder of research at Duke [Home Depot co-founder Bernie Marcus, who has solely funded their autism-stem cell clinical trials]. There was a campaign recipient whose child had previously received stem cells at Duke and then there was a campaign that stated the family had been referred to the Stem Cell Institute *by* Duke staff. And that last one really stuck out. Were the parents claiming in their GoFundMe that someone at Duke told them to try the Stem Cell Institute?

Jeremy: (Deep breath) Yeah. That's essentially what they said in the crowdfunding campaign: that it had been recommended to them. And I want to be careful about that, this was only one time where that specifically happened, and you could imagine it being something like they were turned down for participation in the clinical trial or they weren't able to get expanded access, and they still wanted to get a similar treatment, and there being some off-hand remark that there were clinics abroad that were selling this product. But what comes from that is very clear that in people's mind that can be read as a recommendation and that's clearly what was

happening in this campaign.

You do have people who were participants in the clinical trials at Duke [who] then went straight on to Stem Cell Institute when they wanted to have additional rounds of treatment that weren't being offered.

And so, you see two things. One being that it's clear you know, no matter the intentions of the folks at Duke, it's very clear that in the minds of a decent part of the public, these are very similar institutions, selling very similar products, and the Stem Cell Institute gets to wrap itself up in the legitimacy of Duke University. And at the same time by putting out there 'this is hopeful, a possible new treatment for autism using stem cells,' that folks who for whatever reason can't participate in a clinical trial there, or can't get the treatment or the purported treatment within Duke University, or based on the hype or based on the promise of the stem cell treatment, they're going to go and look elsewhere for it and find somebody who is willing to sell this product to them, and to make claims that it's going to work for them.

Anne: Right. And there's so much feedback as well when you take into account things like Facebook where parents have groups--and I've been lurking in these groups for a book that I'm writing--they [parents] share information with each other and build up hype within this echo-chamber that they have on the stem cell and autism cure chat groups, right? So, they're also sharing with each other and cross-promoting to each other through the Facebook groups.

Jeremy: In that one example that you gave where the person said that they were referred by Duke to the Stem Cell Institute, because the nature of this is social media, sixty-odd people donate[d] to this campaign and then it got shared hundreds of times online on Facebook, so it does reach a very wide audience.

Anne: One thing that is confusing to a lot of people is that there are all these scientific papers online. They're in a lot of different types of journals that may or may not scientifically reviewing the content that they accept.

I see a few approaches that someone selling a product uses. One, they can create their own publication that looks academic and vetted and they publish the work there, which is essentially almost like blogging, but it looks like a scientific journal. Another thing someone who's trying to sell product might do would be publishing in a journal that either doesn't scientifically vet papers or that's just an outright pseudoscience journal, but it has a really science-y sounding name, and looks scientific. And then the third thing is they can [write] a paper with weak evidence or other issues (for example if they don't disclose conflicts of interest), and they can end up getting into a more mainstream publication and it takes on a life of its own – and I'm thinking of Andrew Wakefield as like the prime example of that.

You've recently written about a paper from 2019 that was published in a peer reviewed publication about stem cells and autism therapy. I'm wondering if you could explain some of the issues with that paper?

Leigh: Sure, I can respond and provide a bit of an overview. I think you've done a nice job of providing an overview of some of the various tactics that businesses marketing purported stem cell therapies use. There's the white paper approach – just kind of putting up some information on a website, for example. There's a whole marketplace of what's described as predatory journals when you kind of just pay a fee, $800, sometimes more, sometimes less, and you get your manuscript in there and that can be used to justify a company's practices. So those are a couple of strategies.

What we got interested in was an example of this sort of approach where a company involved in marketing purported stem cell treatments claimed they did a study and then ended up publishing it, not just sort of a home brew thing on their own website, or a predatory journal, but got a study into what I would characterize as a reputable, credible stem cell journal. I think many prospective clients could look at information like this from a company website and really find this quite persuasive and quite compelling.

There's literature that looks at these businesses and discusses the tokens of legitimacy that they use to make what they're doing seem scientific; to make it seem credible. They want to make what they're doing look scientific… make it look like it's safe, make it look like it's efficacious and it's important to distinguish that from coming across as being engaged in quackery of some kind or participating in pseudoscience.

Anne: Mm-hmm.

Leigh: So this is really an understandable move, certainly for marketing purposes. In this case, it was the study that stood out. It raised these really troubling questions and I think what was especially interesting to us was it was a study that *looked* like any other study. It involved twenty research participants, they were all minors around 10 years of age, so all children.

And you could read through this study and it looked quite typical like anything else in the literature, but it was what *wasn't* said in the article that I think was quite fascinating. There were two crucial details that we tried to focus on in our piece -- this was one Jeremy and I had written together. One, it's clear from publicly available evidence that each individual who was in this study (the parents or a guardian) they were paying $7,200 per child to enrol their children into this study. That was an actual inclusion criteria to participate in the study.

This is what's known as a **pay-to-participate** stem cell study: the other detail that wasn't disclosed in the published article itself. And I think that's really important information for readers, whether they're academics or parents or other individuals. They ought to know that

people are being *charged* to participate in this study. And we can talk about why that information is worth knowing.

The other detail that wasn't disclosed is that this is a business that (at the time of our article, at the time of their publication [and] today) continues to advertise purported stem cell therapies for a wide range of indications – cerebral palsy, autism spectrum disorders, spinal cord injuries, and the list goes on. And I think it's important when someone is publishing what they're representing as a clinical study, if they're also advertising that they use stem cells to treat a litany of diseases and injuries and they call it a stem cell therapy or a stem cell treatment. If they're packaging this as a stem cell therapy, what's going on here… there's this early stage clinical study taking place, where there's actually these basic questions about safety and efficacy. So, there's this disjunction between marketing representations and what's actually going on in the article itself.

Why does this matter? Why might [it be important to have] information that this is a business that markets purported stem cell treatments and charges people for that, and that it costs money to participate in the study? Why might knowing that affect individuals' perception of what's going on in the study? Well, I can give a couple of examples. There's a section here where they go through various adverse events that have occurred in the study, just like many other articles. There was actually a high number of adverse events…. There were 133 adverse events out of 296 infusions. That's actually quite a high number of adverse events – getting close to 50 percent.

Anne: Yeah.

[39:54]

Leigh: But, when they say well, which ones were attributable to the stem cells, it drops down to only 58 instances, which is a rate of less than 20 percent. One move that takes place here is to make it seem like there's quite a low rate, a comparative low rate of adverse events associated with stem cells, but there's not any real detailed account of how were they making distinctions between adverse events that were caused by the stem cell infusion that was being done and adverse events that weren't connected in any kind of way. That's something where you're kind of relying on the judgement of the investigators, and when you're not given this detailed kind of story, it's very difficult to know how adverse events are being classified.

And one of the questions that we had was basically 'are individuals who are connected to a business that is operating in this direct-to-consumer way perhaps discounting – unintentionally maybe – but are they perhaps discounting some adverse events in a way that is advantageous for their business but isn't necessarily a full accounting of what's taking place?'

That would be one kind of practical example where you really want people disclosing conflicts of interest, and being forthright about it, as opposed to having individuals kind of look elsewhere to piece together what exactly is taking place.

Anne: Right…but I also wonder if someone reading that paper who isn't familiar with the concept of a conflict of interest, *even if it were disclosed*, would understand what that means?

Leigh: Not necessarily. I mean, it's possible that the undisclosed conflict of interests that are a real concern to us and prompted us to write our article – you know that's an interesting point, that perhaps they could have had a C.O.I. section (I mean they do have one, they just don't mention these conflicts of interest) but it's possible they could have just plopped it into their manuscript and it might not have really impact at all on the average reader. They might not think about how these financial conflicts of interests matter? Or how might they affect the article itself?

But, I think there are some ways where even if many readers might not be aware of it, I think there are some ways in which these financial conflicts of interest could play out affecting the results that are reported in the study and certainly I think potentially affecting the way in which any of us reading the article might interpret the study results.

I'll give you one practical example. One of the real challenges when it comes to conducting not just studies in which stem cells are being administered to individuals, but other kinds of investigational interventions as well when it comes to autism spectrum disorder is there's always this possibility that what's being identified as a result of the investigational intervention is basically a **placebo response.** And so one way of trying to evaluate that is that you have a placebo arm or you have a sham surgical procedure of some kind when you try to figure out [is it] basically just a placebo response or are you getting something else. In this case, there was no placebo arm, but there were parents who were completely, basically doing self-assessments of their children's symptoms…

Anne: Right.

Leigh: And doing quality of life – filling out forms in a way where it's the parents themselves who are providing these evaluations, but if the parents are the ones who are paying for their child to participate in the study, one possibility is that you have parents who think what's going on is they're basically *paying to enable* their child to obtain access to a stem cell treatment or a stem cell therapy.

There's something known as **placebo amplification,** for example, where the act of paying money, the act of paying a substantial amount of money for something can actually amplify the placebo response. And so this is something else, right? I think it's important to know that parents are being charged and that they're paying in excess of $7,000 and it does raise some questions about the study findings that are being presented in this article. It's as you said, the

mere presence of a C.O.I. disclosure might not allow people to piece that together and understand it, but as we step back from the article and start to think about some of the findings, I think these are questions that are worth asking: *Is it possible that the fees people were charged, the payments that they made might that actually interweave with their responses to the instruments that were used in the study…[whether] the results are in fact bound up with the payments they were making?*

Anne: Right, I mean, because after paying the $7,000 or $15,000 in some cases for a treatment, especially involving friends, family and their whole community in fundraising for it, how likely is it going to be that a parent's going to come home from this and say 'Meh, it didn't really work.' Like, that's a really hard thing to say after sinking all that money into it, and obviously you've mentioned that it's clearly a phenomenon where people are suggestible to the idea that something worked because they've invested so much in it and they'll report positive results using the study's own metrics.

And in autism research this is a constant conundrum. I don't know what it's like in other areas of research, but in autism research it's not like there's like a blood test…it's not like…a tumour, like if they go in and take out a tumour then they take and MRI and there's no more tumour and you know that it worked, right? [Ed: I made this comparison to make a point that autism has literally nothing in common with cancer, even though some marketers try to compare cancer and autism to make money. In my view, we need to abandon the medical model of autism and embrace the social model, as discussed in other episodes]. But with something like autism where there's no definitive test for autism and you're tracking something like child development where children develop over time… If you do a study and then two years later you ask the parents to fill out a form and say how much their child has developed, how much are you going to be able to attribute that to what was done in the study versus *two years of child development*? It's impossible to say.

So, it's really kind of subjective, a lot of the measures that they use. And they tend to be also relying on parents to report them. Parents who like you said might be having this placebo effect.

Leigh: That's all true, and you kind of covered a lot of territory in the points that you made. To go back to the first point that you made, I think that the individuals who engaged in crowdfunding, for example, have gone to friends and family members and strangers and offered a narrative about why they're seeking something. If they then go to a clinic and spend you know $5,000 or $25,000 and it doesn't seem to affect in any way, it doesn't help them in any way…I think for many individuals this is awkward, uncomfortable, sometimes even embarrassing to have to acknowledge that. I know some individuals who've gone to these businesses and have come to the conclusion that they've been basically scammed – taken advantage of, and it's a very awkward and difficult thing to acknowledge that. I think there are these instances when people really feel quite embarrassed that they've made these decisions.

Another way of responding to it might be, uh, you know, kind of along the lines you were mentioning is that people may end up spending money and be so invested in their decision making that they, you know kind of see significant changes taking place and it's understandable that they're reacting that way. But I think we have to take those kinds of reactions with a grain of salt, that maybe they're deeply invested in whatever it is that they've paid for and maybe they're perhaps reading a little bit into what's taking place. I think using tools that assess parents' responses to symptoms – I don't mean to suggest that these should be completely dismissed or that these are useless tools. I don't think that at all. I think they're important tools to use, but I also think that if people are paying and if they think that something is a stem cell treatment, we need to take that knowledge and think critically and carefully about whatever kinds of responses they're providing.

I certainly think that's information that ought to be provided to readers of journal articles. So those kinds of failures to disclose I think can really affect the presentation and interpretation of results.

Anne: Exactly--by researchers and by everybody, really.

Leigh: That's true. And part of what you want from academic journals is to have editorial teams and peer reviewers asking these questions right at the peer review stage, so that this information all comes out during the peer review process. In this case, it made it to the peer reviewed literature without all these kinds of issues surfacing. That in part prompted our response to try and look at this article and ask some questions about how people were thinking about what they were paying for and how those kinds of payments might affect the findings that were reported in this article.

Anne: There's really a lot to think about there. I guess as we wind this up, I wanted to ask both of you, Leigh and Jeremy, this: So we have commerce and research coming together. We have the stem cell researchers who might try to be careful with their claims but then we have companies selling stem cells – they're private companies and they can be looser with their claims. There's also a number of different interests involved as well. So, my question is where does it become the responsibility of the university or of regulators to put some controls on those business relationships and the claims by those businesses?

(Silence)

[49:13]

Leigh: Sure, I can comment. I mean ideally what we want is we want to have businesses themselves being very cautious in any kind of claims that they're making, providing evidence backing whatever representations they're making and not engaging in hyperbole, spin, using promissory rhetoric that takes advantage of people's hopes and aspirations. But, we know that there are some businesses that are really kind of going far beyond available evidence and this is where it's important to have regulators providing oversight.

I think national regulators like Health Canada and the Food and Drug Administration in the United States play important roles in this marketplace. Organizations like the Federal Trade Commission in the United States, State Medical Boards, or Colleges of Physicians and Surgeons, but there's also another kind of entity that you mentioned--universities and medical centres. I think they have an important role to play as well. Not in terms of regulating business that have no relationship to themselves, but I think they can play a role in encouraging their scientists, their researchers to be careful in their messaging, be responsible in terms of any kind of science communication exercises.

I also think there are some important distinctions to be made in terms of when you start charging individuals for access to investigational stem cell products, and I think that's a question that academic institutions need to be very careful with in terms of how they're handling it--and I think it can sometimes be mishandled. It's important. Many individuals will gain access to investigational products in the context of investigational trials, and they're not going to be charged when they are research participants in the clinical trials.

But, there is this other category of Expanded Access, and Duke is one example of a number of examples where people, parents in the case of children, are being charged for their children to obtain access to stem cells on an expanded access basis. There's a cord blood bank in the United States that is now basically going to open up a clinic and provide access to investigational stem cell products for children with autism spectrum disorder. You do it on an Expanded Access basis and I think this is where we need to start to ask ourselves some really troubling questions, like, for example, if we don't have stem cell products that are known to be safe and efficacious and approved by the FDA and yet [they are] charging people.

If it's going to be done on this routine kind of commercialized wide spread basis…have we basically just moved the goal post for FDA approval?

Anne: Right.

Leigh: Instead of having umbilical blood cord products that are FDA approved, we've now got this expanded access category where people can be charged. That seems like a dramatic shift in terms of the amount of safely and efficacy that you need to start charging people. So I worry that expanded access is going to become the new way of bringing products to market, and I think this is something that academic medical centres --whether it's my own or Duke or other institutions-- need to be very cautious and reflective and careful in terms of what they're doing, because many individuals may be paying thinking that they're getting a stem cell therapy when at the end of the day, it's an investigational stem cell product. Even if there's reasonable evidence about safety, with something like autism there's not…compelling, convincing evidence of safety, and so I think it's important to tread carefully in a space like this.

Jeremy: I agree with that 100 percent. I would just add that in some instances there are places for universities to provide oversight on some of the activities of faculty. For example, I serve on our research ethics board here at Simon Fraser and you know when people are proposing to do research, we can take a look at their consent documents and what they're going to be telling people who might want to enrol in these, and we might take a close look at a trial that wanted people to pay for access to it. I think that's one place where universities can be careful about this.

But to Leigh's point when we're looking at where universities are part of being with different individuals and faculty members and researchers to provide these on expanded access basis and to turn these into businesses, there's much less oversight and I think that might be a place where universities need to look to provide more of that. Specifically, I'm thinking of faculty here.

It's one of those situations where if there can be wider reputational harms that if a university or a group of people get a reputation for being being dishonest or disreputable with some of the practices that they're engaging in that can hurt the wider community and it can go against the mission of the university as a public actor.

Anne: Right. It can really undermine the university in some ways.

Jeremy: Yeah, absolutely.

Anne: Thank you very much for coming on the show. I really appreciate you having taken the time and talking about these issues. They're complicated issues and they're so important. Thank you very much for being on the show, Jeremy Snyder and Leigh Turner.

Jeremy: Thanks for having us on.

Leigh: Thank you very much; really appreciate it. Good talking with you.

(Theme song – soft piano music)

Anne: You've been listening to Noncompliant. I'm your host Anne Borden King. Noncompliant is usually recorded at MCS Recording Studios and engineered by Nathan Greavette and TJ Liebgott. The Noncompliant podcast is transcribed by Julie-Ann Lee. Thanks to everyone involved and thanks for listening.