Rob Matheis 00:09.822: Hello and welcome to Informed, a podcast series where you'll hear industry experts share their thought-provoking insights and lessons in the field of medical communications. This series is brought to you by ISMPP and is generously sponsored by MedThink SciComm. The opinions shared by the presenters today are their own and don't represent those of their employers. My name is Rob Matheis. I'm president and CEO of ISMPP, and I'm joined today by Laura Happe. Laura, why don't we get started by you giving an introduction to yourself?

Laura Happe 00:35.560: Sure. Thanks for having me today, Rob. I appreciate it. I'm Laura Happe, and I am a professor at the University of Florida College of Pharmacy, I'm also editor-in-chief of the Journal of Managed Care and Specialty Pharmacy.

Rob Matheis 00:49.585: Well, it's great to have you with us, Laura. You know, we were chatting not too long ago about what's been happening across our profession and how there's such a transition from publication professionals becoming more medical communication professionals and doing so much more. But at the same time, we're also noticing that there are a lot of new entrants into our field and people who don't know about some of the rich history of being publication professionals. And I just thought it might be a great idea to put some of the cases in front of some of our listeners, so they have a bit of context and some history. So maybe we could start by chatting through that.

Laura Happe 01:20.593: As you mentioned, Rob, there have been a lot of legal cases over the years that have influenced the profession of medical communications and publications. I've had visibility into that through my work as an editor and my own work over the years, publishing research and working with various companies. What I wanted to share today was a more recent case. So this was interesting. It was a false advertising claims case. This case was settled out of court this past summer. And you might be saying to yourself, how is false advertising relevant to the ISMPP community? And that's a really good question. I'm not here at all to discuss the legal issues of false advertising. I'm not a lawyer. That's not in my scope. But there were certainly several components of this case that I found interesting to the work of publication professionals and medical communication professionals. So we'll kind of dig into that.

The plaintiff here, the entity that filed the suit is a pharmaceutical company, and they filed a suit against another pharmaceutical company or the defendants, again, with those allegations of false advertising. Everything I'm going to talk about today is publicly available on the docket. I am just going to use plaintiff and defendant rather than focusing on the names of the companies because I'm just more interested in the actual content of what's relevant to listeners today, and I don't want to detract from that. But these two companies have two competitor products. And these products are used in patients who are undergoing chemotherapy. And these agents are
intended to prevent febrile neutropenia. Febrile neutropenia is a serious medical event. It's often emergent. And what it often indicates is that there's some severe underlying infection. So we're trying to reduce the incidence of febrile neutropenia by using these drugs.

In the plaintiff's complaint that they filed, they featured some healthcare provider-facing materials that were produced by the defendants as part of their false advertising allegations. There was one particular piece of evidence in this healthcare provider material that I want to talk about that was really interesting. They had a graphic and they showed the incidence of febrile neutropenia with the defendant's drug was 1.3% and the incidence of febrile neutropenia with the plaintiff's drug was 1.7%. And they showed a p-value where the p was equal to 0.01. And so, remember febrile neutropenia is a bad thing. We want to prevent it. So these results favor the defendant's product. And so the plaintiffs and their allegations, they identified several issues with this graphic and this claim of this difference in febrile neutropenia that are relevant to the listeners today.

I want to kind of go through those one by one. The first one was that the source was a real-world evidence study. This is not a head-to-head clinical trial. This is a real-world evidence study. The reference, the study, the reference that supported this 1.3 versus 1.7 was actually in the healthcare provider material, was actually a data on file. So it was, and when you dig into it, you find out that this data on file was a presentation at a conference. So that right there is something that's interesting, right? It makes you think about what is an appropriate reference? Again, this was at a conference, not a peer-reviewed journal. So there are some things to kind of think about and unpack there.

The second issue that they pointed out was the study itself, when they pulled the reference from the conference presentation, in the study they did not control for confounders. And so, people that do real-world evidence studies, you know, and I'm sure many of the listeners today, they know and understand people aren't randomized to their treatments in those studies, unlike clinical trials. So there may be underlying differences in the populations taking the two drugs in the real world. The researchers will typically control for potential confounders using statistical methods. That was not done here, and so that was something that was an issue that the plaintiffs pointed out, a shortcoming of the study. And interestingly, the plaintiffs also found out during discovery in the documents that were produced that the defendants submitted this very same study to two different journals. And even in the journal submissions, they also did not control for confounders. And appropriately, both of the journals rejected the paper. It was never published in a peer-reviewed paper, it was only presented at a conference. And so that's another sort of interesting piece to this.

And then the final piece that was interesting, with respect to the plaintiff's allegations was the graphic itself from the healthcare provider-facing material. And I know we're all audio today and you can't see an example graphic, but just imagine here with me. So remember, we're looking at a difference of 1.7% versus 1.3%. You know, as a journal editor, I'm kind of envisioning in my head a bar graph that shows the two percentages and that point 4% difference, but instead what was included in the healthcare provider material was this giant arrow that had a 31% difference. Well, the 31%, if you do the math, that's the relative difference. So, you know, certainly it was a
healthcare provider-facing material. It wasn't a peer-reviewed journal. I would be surprised if any journal published something like that, but it's a good reminder of the importance of good and bad graphs.

*Rob Matheis 08:14.006:* It's interesting. It's a fascinating case, but what I'm so impressed by is, and I want to ask you a question, was there anything in the case that you would say was wrong? Like, was the data wrong? Was the, you know, the 31%, was it wrong? Or I guess what I'm getting to is - is it an issue of ethics or is it an issue of scientific accuracy for our listeners?

*Laura Happe 08:36.832:* So it's a great question. There's technically nothing wrong with the data. It was accurate to the best of what I reviewed in the case materials in preparation for our discussion. And I think you have two things at issue here - you have what was submitted to the journal and what is the role of the publication professional - and I think that's that in and of itself is an interesting question. So many publication professionals might have said “hey, look this is a comparative effectiveness research study and you did not control for confounders and you probably should have. It's unlikely to get accepted” And so what is the role of the publication professional? Obviously, that's something that I think the researchers should have done in the very first place. But they didn't, and so, the publication professional certainly has the latitude to push back and say, hey, you should do this. That doesn't mean that the authors are going to. So that can be a frustrating situation. At the end of the day, for this particular study, for these two attempts to publish it, the journal made the right decision through the peer review process to not publish a study that didn't control for confounders.

*Rob Matheis 09:49.772:* Right, and that's what's interesting. So, I suppose the peer review process worked the way it's supposed to, and that's a positive. But, you know, in all instances, it doesn't always mean that that's going to happen. And it's really, in my opinion, in a lot of ways, incumbent on the publication professional, and the researchers, of course, and authors, to make sure that even if you have accurate data, that you're being ethical as part of this. And that's really something that we're trying to remind our professionals and listeners about is that there's a big responsibility there to not just have your head in the sand, but to look up and say, this is something that could have impact. So, along those lines, if we stretch this a little bit forward, if you think that this had been published, what might've been some of the implications had this information gone out into public the way it was intended? It's from a patient's point of view, perhaps, right? You know, ultimately clinical decision-making and things like that.

*Laura Happe 10:45.665:* Well, without controlling for confounders, we just simply don't know if this difference was actually due to the drugs themselves or to some underlying differences in the patient populations. So clearly, this would have been a negative thing had it gone out into the public without having the appropriate statistical controls.

*Rob Matheis 11:08.838:* Right, right. So, we were chatting earlier about this case, and you had mentioned a defense mechanism that was used about hands or something along those lines. Can you tell us? It was the first time I heard about it. It was kind of fascinating. Maybe tell us a little bit more about that.
Laura Happe 11:22.587: Sure, I’d be happy to. So we've kind of gone through what the plaintiff said. how the plaintiffs characterize this one particular study and the negatives about it that we've just discussed. So now let's talk about the defense.

The defense comes out with this strategy called “unclean hands”. And the defense says what that means is that the plaintiffs, you cannot bring these allegations against us because your hands are dirty too. You've done bad things. So that was the defense strategy. Again, very interesting. And those are the words they used, “unclean hands”. And so, what does that mean? So the defense found that the plaintiffs had previously published a similar study and it was published in a peer-reviewed journal and it did control for confounders and so you know again the scientific process worked there so that was good but in discovery, they produced the study protocols that preceded the actual publication and what these study protocols demonstrated was in this real-world study, the plaintiffs used three different definitions of febrile neutropenia, but they only published one. And so let me talk about that for just a second.

So in real world evidence, you often use claims data to identify disease states like febrile neutropenia. There is not a specific code for febrile neutropenia. So, researchers have concocted a few different algorithms using the claims data to identify febrile neutropenia. It's actually not uncommon to see these multiple definitions when there's not a specific code. And that's what the protocol said. It showed that they found they used three different definitions. But again, they only published one. And guess which one was statistically significant, Rob?

Rob Matheis 13:12.903: I can take a guess.

Laura Happe 13:15.405: The one that they published was statistically significant and the other ones were not. So, you have some very clear cherry-picking here. And it was also another thing that was really interesting that I think will be interesting to the listeners is there was the study sponsor and then there was an external vendor that they were using, a third-party health economics outcomes research firm. The communications between those entities were produced in the case, and you could see a very clear change. The initial versions of the manuscript had all three definitions in them. And there was a lot of communication going back and forth. And then at some point in time, that communication clearly went offline. It went to phone calls and the comments and the drafts of the paper really disappeared. And the two non-statistically significant findings disappeared. So, it seemed that there was a very intentional decision to take that data out and not to have clear written documentation about that.

Rob Matheis 14:20.157: I hope these are scenarios that now in today's day and age sound very unfamiliar to our listeners. But, you know, the reality is there's the potential for these types of things to happen behind the scenes. And I'm glad that we're talking about them openly so that those who are listening to this can be aware of and try to really have their eyes and ears open for potential things that could impact the data at the end of the day. So very, very helpful. You know, when we talk about RWE more broadly and we talk about cherry-picking and selective
reporting, that certainly is an area where there is a lot of concern that gets brought up. Do you have any suggestions about how that can be prevented for our listeners?

Laura Happe 14:55.249: Yes, it can best be prevented by registration of study protocols on external sites. We do that in clinical trials on clinicaltrials.gov. And there is a movement and a press towards that happening more and more frequently with real world evidence studies. And so that's really the best way to prohibit or to prevent cherry picking.

Rob Matheis 15:19.726: So similar to the RCT process, making sure that there is accountability. And in this case, there was so much that happened, all the potential areas where, again, data maybe wasn't inaccurate, but could have been swayed or presented in a way that could change clinical decision-making. You know, I'm thinking back to the fact that even some of the data that was based on poster presentations early on. Right. So, some of the claims being made, are there standards different there or, should the standards for posters versus publications be different? What are your thoughts there?

Laura Happe 15:50.789: Yeah, I think it's a great question and I can share my opinion. I'm not sure if it's the right one and I would be interested in the listeners' opinion as well, but I've always viewed research poster presentations as an opportunity to present some preliminary data and preliminary work. and to get feedback from the audience. And then that can help to inform the next steps of the research, which would often ultimately be what goes into a peer-reviewed publication. But when you review a case like this and you see what I view as preliminary results being then promoted to prescribing physicians or shared with prescribing physicians, it does make you really kind of think about what is the appropriate standard.

Rob Matheis 16:37.246: All right, so Laura, we've talked a lot about different elements of this case, and it's been really interesting. I do have one other question for you. I can't imagine that there weren't other people or other organizations involved in all of this and not just the companies themselves. Was there a role of a third-party vendor in all of this, and what role did they play?

Laura Happe 16:55.909: Sure. There was a third-party vendor that was involved with the publication that was submitted. As I had kind of described, it seemed like from what was produced in the case that there were iterations of the manuscript that included all three definitions of febrile neutropenia, and then there were two that were taken out. And it seems pretty clear that the communications intentionally sort of went offline at that point. I think it just raises this question of, or maybe just emphasizes the importance of, the vendor in their consulting capacity and advising the client, their client, on what the right and ethical thing to do is. I would like to hope that the vendor in this situation encouraged the client to include all three definitions as that would have been the right thing to report the entirety of the evidence. But at the end of the day, the vendor may have, but the company likely, you know, made the decision and went forth with their path. So it's definitely a tricky situation for both parties.
Rob Matheis 18:14.294: Yeah, I agree. And I imagine there, there might've been some dialogue, but these do get to be sticky situations and certainly ones where there's a level of accountability that happens there, but I can say, and as our time is coming to an end, what I've taken away from this podcast is definitely a sense of awareness building for our listeners, right? So that they're aware that these things can potentially happen and to make sure that they're vigilant about being proactive and making sure that at the end of the day, the right data is presented in an ethical and transparent manner. So, Laura, before we officially bring the podcast to a close, I want to give you an opportunity to talk about our exciting partnership between our organizations.

Laura Happe 18:51.456: Yes, the University of Florida College of Pharmacy Online Degree Program in Pharmaceutical Outcomes and Policy and ISMPP have a partnership. ISMPP members who enroll in our program can get a 50% discount on their first and last class in our program. We have a great curriculum, and we talk about a lot of the things that we covered today that are important for publication professionals.

Rob Matheis 19:18.640: I want to thank you for joining us today, and thanks to everyone for listening to Informed Medical Communications. Please take a minute to subscribe to the show on your favorite podcast app, inform your colleagues, and rate our show highly if you liked what you heard today. Also, you might join ISMPP today to become part of our community, to participate in our webinars, and to also, you might join ISMPP today to become a part of our community, to participate in our webinars, and to receive instant access to exclusive tools and resources. If you're interested, just go to ismap.org, that's I-S-M-P-P.org, to learn more. I'm Rob Matheis.