Transcript

00:00:06 Speaker 1

If asking your mate down the pub about vaping, here's what they'd probably say.

00:00:13 Speaker 1

No one agrees if it's safer or not, so you might as well smoke anyway.

00:00:19 Speaker 1

Now what your mate needs is a Cochrane review, all the facts have been checked at least twice.

00:00:26 Speaker 1

They find there's a lot that the experts agree on and might give you different advice.

00:00:36 Speaker 2

Hi, I'm Nicola Linson.

00:00:37 Speaker 3

And I'm Jamie Hartman-Boyce.

00:00:39 Speaker 2

We're both researchers based at the University of Oxford, where we work with the Cochrane Tobacco Addiction Group.

00:00:44 Speaker 2

Welcome to this edition of Let's Talk E-Cigarettes.

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This podcast is a companion to a research project being carried out at the University of Oxford, where every month we search the e-cigarette research literature to find new studies.

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We then use these studies to update our Cochrane systematic review of e-cigarettes for smoking cessation.

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This is called a living systematic review.

00:01:05 Speaker 2

In each episode, we start by going through the studies we have found that month and then go into more detail about a particular study or topic related to e-cigarettes.

00:01:14 Speaker 3

This month we searched for new literature on the 1st of October.

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We found two new papers linked to studies already included in our review, one new ongoing study and one new study.

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You'll hear more about the new study and ongoing study in this month's In A Nutshell.

00:01:30 Speaker 4

So the only new included study that we identified in our search was a randomised two-part study conducted by Paul Morris and colleagues who were all employees of Imperial Brands Companies, which is a UK tobacco company.

00:01:42 Speaker 4

The study tested the My Blue e-cigarette product.

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The study recruited 72 adults who were currently smoking.

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Participants were confined to a clinic for the duration of the study, and in the first part, all participants were asked to switch from cigarette use to e-cigarette use for nine days.

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After those nine days, participants were randomised into three groups.

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One group were asked to continue their exclusive e-cigarette use.

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Another were asked to go back to smoking their own cigarettes exclusively.

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and the last group were asked to dual-use cigarettes and e-cigarettes for a further five days.

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The authors reported that in the first nine days of exclusive use, levels of 14 non-nicotine biomarkers of exposure to tobacco cigarettes were substantially reduced.

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These reductions were sustained in people who continued exclusive e-cigarette use in the second stage of the study, but levels returned to those recorded at baseline in those that returned to exclusive cigarette smoking.

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People who dual-used cigarettes and e-cigarettes

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still had reduced levels of exposure compared to baseline, but less than was seen in people who only used e-cigarettes.

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Nicotine levels stayed constant from baseline to follow-up in all groups.

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Thanks, Nicola.

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That sounds, in fact, really consistent with the other studies that we've seen in this area in terms of biomarkers.

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So the one new ongoing study that we found this month is based in the UK, and it's actually led by one of the authors of our Cochrane Review and previous podcast guests.

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Professor Caitlin Notley from the University of East Anglia.

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It's called the COSTED trial, and it's funded by the National Institute for Health Research.

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They're seeking to answer this specific question.

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In people attending the emergency department who smoke, does a brief intervention, including the provision of an e-cigarette and referral to stop smoking services, increase smoking cessation in comparison with usual care?

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And is it cost effective?

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They're aiming to recruit just under 1,000 people and to complete the study in 2023.

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So we look forward to that coming out, but no, we might have to wait a little while.

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So, October has been a pretty exciting month in the e-cigarette world as people in the US have been anxiously awaiting decisions from the Food and Drug Administration, FDA as it's more commonly known, on authorizing nicotine e-cigarettes.

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So Jamie, what does this kind of actually mean in terms of what e-cigarettes will be available in the US?

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Nicola, there's a lot of regulatory jargon that I've been trying to work my way through and understand, but basically, my understanding is the FDA is deciding which nicotine e-cigarettes can remain on the market in the US.

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So far, they've made rulings against quite a few smaller brands, but earlier this month, they authorized three RJ Reynolds Vuse products.

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At the time of recording this, the decision was still outstanding on Juul, and that's something I know a lot of people are waiting for, because that's the market leader for e-cigarettes in the US at the moment.

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Because of all this kind of conversation around FDA and decisions around authorization and the evidence that FDA might be using, we thought it would be interesting to talk to Nick DeVito this month.

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He's based in the same department as us in Oxford.

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Our research doesn't often overlap, but Nick is undertaking his PhD and he's working with Ben Goldacre and others.

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So you'll hear him refer to Ben sometimes in the interview.

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Earlier this year, Nick and his colleagues had a foray into tobacco control research, and they published a paper in the BMJ journal Tobacco Control, in which they look at Juul's trials and how well they report their data.

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We'll hear more from Nick about what they found in this month's Deep Dive.

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Thank you so much for joining us, Nick.

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Can you tell us a bit about yourself and the kind of research you do?

00:05:12 Speaker 5

Yeah, so my PhD is about trial registration, the benefits trial registration has for transparency and accountability in clinical research.

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And basically, are these systems of trial registration now, which have sort of come into being over the last, really in the last 20 years or so, are they doing their job?

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Are they doing the job we expect them to do?

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Are they helping us have more transparency into the clinical research process?

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Are they helping us

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to ensure that reporting in papers and things like that is correct and free of bias?

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Are we sure that the research that people say they're doing is actually getting published?

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And that's a form of bias called publication bias.

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So that is my research, that's what my thesis is on, and that's the guise under which I undertook the research we're going to talk about today.

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Awesome.

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Just for anyone who's not kind of familiar with the area, can you tell us a little bit about why it matters?

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Like, why does it matter if people are registering their trials or reporting their results?

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And do you have any examples?

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of where things have gone wrong.

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Yeah, yeah.

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So when people ask me about what I do at parties and I talk about publication bias, which is, you know, one, there's lots of reporting biases.

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Another one, which we'll talk about in this paper, which covers publication bias and outcome reporting bias.

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But publication bias is the simpler one, I think, to start with.

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So basically, let's say there's an intervention out there and I want to know if it

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lowers blood pressure, right?

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And it's a drug, and I give it to you.

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And then, so 10 people did trials, 10 different groups did trials to see whether this drug lowers blood pressure.

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And seven of them were negative, and three of them were positive.

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So three of them showed it did reduce it, seven of them showed it didn't.

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But let's

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If we only had the literature, maybe five of those seven never got published.

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So when you bring together all the evidence, you would have three saying it works and two saying it didn't work.

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So it looks like the preponderance of evidence is that it does work, when in fact there's a whole bunch more evidence saying it doesn't work and if you combined everything you knew about together.

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There's a really famous paper by Eric Turner, who used to be an FDA reviewer and is now at, I believe, Oregon Health Sciences Center in the US.

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And he compared antidepressants as sort of a classic case of this, where what the FDA knew about and what was in the literature were not aligned at all, both in terms of the interpretation of what was published and what was published at all.

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So it was in NEJM years ago, the New England Journal of Medicine years ago.

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It's a bit of a 2004, 2007, that study is.

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But that's a really famous example that really articulates what publication bias can look like.

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And then outcome reporting bias, just to

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quickly define that is you're basically changing the rules about what mattered about your trial after the fact.

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So if you say, let's go back to a blood pressure trial, you say we're measuring blood pressure reduction this way.

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Our goal, our definition of success is a, you know, 30 point difference in whatever scale we're using to measure blood pressure.

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And then you do your trial and then you

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report it, but now your definition of success is a 20-point difference or a completely different scale.

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You said you were going to use this way to measure blood pressure, and instead you use this way to measure blood pressure, and you don't say why, and you don't justify.

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So you can make those changes need to happen sometimes for research, but if you don't say why,

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and you don't justify it, and that justification can't sort of be seen by the people assessing the research or the people reading the research and interpreting it, that's a problem.

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Awesome.

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That can lead to bias.

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And I think like in Cochrane, we spend a lot of time trying to chase down unpublished results.

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And sometimes that just happens because the process takes a long time, but other times it's clearly happening because

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their financial interests who don't want those results.

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Yeah, so to get the second part of your question for registration is essentially a way to ensure we can check these things, right?

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So registration is, here's are the details of my trial.

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I've ideally done this before the trial started and enrolled anyone, so I can't cheat.

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And if me or you gets a review request on a clinical trial, we can go in and we can look at their pre-specified outcomes and see if they match what's in the paper.

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Can you tell me what the FDA Amendments Act is?

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Yeah, the FDA Amendments Act is, just really quickly, it is U.S.

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legislation that covers...

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broadly, like the way drugs are approved and applied for in the US.

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But a part of that was they, clinicaltrials.gov is a US registry, biggest in the world by far.

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So they had it.

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wasn't, there were some requirement to do stuff there, but they were obtuse and nobody was keeping an eye on them.

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The FDA Amendment Act comes along and they say, if you are doing a trial on a drug or a device or vaccine, biological, whatever,

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of these set of interventions that you hope to one day get approved, that you are actively approving, or that is already approved.

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You have to register it.

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And this is anyone.

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This is industry or if you know, independent, academic, anybody's doing studies on these drugs.

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And it falls under the regulatory purview of the FDA, the US.

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So mainly that means if it has a trial location in the US.

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But there's other ways trials can be covered under the law as well.

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You need to register your trial on clinicaltrials.gov within 21 days of its starting, which is unfortunate that it's not prospective registration, but regardless.

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And at the end of the trial, you have a primary completion date, which is the last date you collect data for your primary outcome.

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Within a year of that, you have to put results on clinicaltrials.gov.

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In early 2000, e-cigarettes were obviously in the news a bunch because the FDA ban had on the flavors had just happened and happened to notice that Juul.

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was a sponsor covered that we saw had covered trials under the FDA Amendments Act.

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And they were 0 for five in reporting their trials.

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And I'm like, oh, that's really interesting at this exact point in time.

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So I was like, oh, this might be a good candidate to like do a deeper dive into.

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So are they published, are these trials published elsewhere?

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Why haven't they reported under the FDA Amendments Act?

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Why isn't the FDA more interested in them having that reported?

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And why, and you know, what's the quality of the reporting?

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I can do a deep dive because there's such a small amount.

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trials.

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So that was the motivation.

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So we did searches, we did detailed outcome assessments, comparing the registrations to what we found, and yeah, that was the project.

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Awesome.

00:11:34 Speaker 3

So you're going through, basically, you're finding the studies that Juul has said it's doing of its products, you're looking at what Juul said they were going to do, and checking to see if they actually report the results of what they said they were going to do.

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What did you find?

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The 5 trials we included, which were the five that

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looked like they were covered by the FDA Amendments Act.

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There's more registered JUUL trials, but they didn't look like they were covered for some reason, which was sort of an odd discrepancy because a lot of them were very similar.

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That's based on our algorithm we had developed to identify trials that are covered for the trials tracker.

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And so they had all completed, I believe, yeah, they were all completed sometime in 2018.

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They were, I think, all of them were done in very, like,

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They weren't like real world studies.

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They were like contract research organization studies where people like went and lived in a lab for a week and smoked various things and had measurements taken.

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And so it didn't seem unreasonable to me that results should have been available by mid-2020, especially that controlled, like your data is right there.

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There's no sort of, yeah, you shouldn't have a whole lot of difficulty getting your results out there into the world in those conditions.

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I mean, global standards, ethical standards are like, they should be somewhere, ideally a registry within a year.

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That's like the WHO's line on the map.

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And in a journal, ideally within two years.

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Makes sense?

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The one year being a fallback in case you like can't get it published, right, or something like that, for whatever reason.

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So were they there?

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Yeah, so one of the five was in the literature.

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Nicotine and Tobacco Research is the journal, I believe.

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And then that one and three others had posters.

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So they had posters from conferences.

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And then one was, we couldn't find anything.

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So then we said, okay, now everything we have, what does their outcome reporting look like?

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And let me remind myself of the numbers here.

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So there were primary outcomes.

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There were 23 pre-specified across all five studies, and they reported 15 of them with no problems, no issues.

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And most of the problems, I believe, are confined to one, the one trial that was unreported, which was like 4 primary outcomes or something like that.

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And then of the secondary outcomes, it was 13 of 38 were sort of unambiguously reported with no issues.

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So a lot missing.

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That's not totally unexpected based on what we found.

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Conference Abstracts

00:13:56 Speaker 5

Obviously, you have some space limitations, you have limitations.

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But I mean, we found some weird stuff too, like for the study that had a paper, they had these measures of nicotine that they were going to measure.

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They had some measures they were going to look at in urine and some in blood.

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And

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the paper references that they looked at the stuff in blood, but then we couldn't find the blood outcomes anywhere.

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It wasn't even like in the paper, we looked, combed through the supplementary material and couldn't find it anywhere.

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So very odd.

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And then, you know, sometimes they declared, so like three of the outcomes, I believe, I forget which ones off the top of my head, but three of the outcomes, they said, these specific outcomes we plan to report in a later paper.

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So that we considered, you've at least articulated what's going on.

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That considered like,

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properly reported, right?

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I think so that knocks it up a bit of those numbers I shared.

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And then some, they did some weird things like they had a scale, they might, they have these scales, and they might be like a master scale that has subscales, and they said in the registration they would use the whole scale, but they only report in what they published like two of the scales or one of the scales.

00:15:07 Speaker 5

So that, you can see how that can lead to bias, right?

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if it didn't perform so well on the other scales, why are you the only report the one it performed well on?

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I mean, maybe their pre-specification was bad, too.

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Maybe they only planned to use that one scale overall.

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And that's sort of a plea for better pre-registration.

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Make sure you're being as detailed as possible about these things.

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And it sounds to me like there are quite a few holes, as it were, in terms of the reporting.

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How does that compare to other areas?

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Like, is this worse for e-cigarettes?

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Is it better?

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for e-cigarettes.

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I kind of, I like to imagine that, for example, the pharmaceutical industry, which has now helped, I'd hope fairly strict standards, would report better, but I know from our reviews they don't always.

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So I'm just wondering, is Juul an outlier or is it kind of part of the norm?

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Yeah, I don't think Juul's an outlier.

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I think they're probably pretty par for the course.

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You know, I don't have an individual sponsor's data off the top of my head to sort of compare them to.

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But I mean, the fact that

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four out of five of their things were out there in some way.

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It's actually like, that's probably pretty par for the course as it is.

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And actually, I should add that Jewel, after we did our analysis, two more of them ended up in papers.

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So to their credit, 100%, they should be, it was a little delayed for my liking, but ultimately, like they got out there and they're in there.

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So, one could update the analysis and see what that looks like with these new papers.

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But so, I'd say that actually in that regard,

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are like might be good.

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The outcome reporting bias, that is another layer though that I think gets even less attention than publication bias.

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And they're not potentially so great in that.

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I don't think Julie is like that unfortunately acting that unusually compared to how clinical research is generally reported these days.

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The world of clinical medical research gets more difficult

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I'm going to cut Juul some slack and then take that slack, pull back that slack very quickly here, I think, because like they're entering this space, they're doing clinical trials for the first time.

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It's a jungle of regulations and the way we do these things, right?

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And maybe they're not so quite so familiar with that.

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But on the other hand, Juul is like owned by Altria, part owned by Altria, right?

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Which is like

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That's old Philip Morris, right?

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Yeah.

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That's a huge company that's been around the block and has probably done their share of, funded their share of research over the years.

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They should know how things work.

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Like it's a little bit of inexcusable to like have that connection and not, you know, do this right.

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And when you're, especially when you're at Juul and you're making a product, I think that's like controversial and you're entering this space, like you should dot your I's and cross your T's and make sure your reporting is sort of like up to a level.

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And I mean, that goes for being involved, not just the e-cigarettes, but the tobacco, the reputation of industry-sponsored tobacco research, shall we say, is not great, like, overall.

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That's really interesting.

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Thank you.

00:18:01 Speaker 3

So I'm probably about to date this podcast because at the time of recording, this is the case, but it might change.

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We still don't have a decision from the FDA at the moment around regulating JUUL.

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And we're waiting on that any moment.

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Do you have any comments on that?

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And do you think reporting efforts, the sort of things you've flagged up, are those going to hamper FDA's efforts when it comes to assessing Juul?

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Should that hamper FDA's efforts when assessing Juul?

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Yeah, so I don't think so, because...

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So I should add, when we published this paper, Jewel put out, they commented on it through the BMJ rapid response system, and on PubPeer, actually, same comment.

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And they made some points, like they pointed out the two additional articles that have been published since we did the analysis, which was fine.

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But they also said, oh, the FDA has all this data.

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Like we've given the FDA everything, which is the way it works for drugs.

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So that doesn't surprise me.

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But like,

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What you choose to make public gives context to what the FDA decides ultimately, right?

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So if the FDA just approves Juul through the pre-market tobacco application system for whatever they're applying for approval for, if all the public that, you know, as far as I know, they're not going to make that information public, or at least not easily public.

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Someone would have to go through a lot of trouble to make that information public that Juul gave the FDA.

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So

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By only selectively or like choosing to report only certain things, the public context for the FDA's decision is less, right?

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We are unable to understand how the FDA arrived at their decision.

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So if they approve it, we can't sort of understand whether that's acceptable or not.

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And if they reject it, we can't know why for like future context and understanding.

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All right, so what kind of after doing this study, what would you like to see change as a result of this study or what future research do you think should be done in this area?

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Yeah, I haven't had time as I have to do all my other thesis stuff, but I think doing a quick reanalysis of our paper with those two additional studies and seeing how that might have impacted the outcome reporting

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I assume it went up when they had more room.

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I can only assume that.

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I would like to give Joel the benefit of the doubt there.

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But there is also interesting, right?

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So if they never publish that 4th paper or they only make that fifth one available in an abstract, right?

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That's a form of bias too.

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To only, like, to choose what you want to put in full text and choose what you want to put into conference abstract, that's a choice.

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And that could lead to bias.

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If they just put all their outcome, all their pre-registered outcomes in full on clinicaltrials.gov, that would be it.

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Then they could go publish, and that's on the journals and the reviewers to make sure they're publishing them correctly.

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And that's on whether they choose to publish certain common abstracts in the literature or not.

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It's irrelevant because it's there.

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It's out there.

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I mean, it lacks that step of like peer review, but they're also not, you don't provide interpretation in a clinicaltrials.gov results report.

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It's just the numbers.

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So for someone like yourself who's trying to synthesize this evidence, that might be really helpful.

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Yeah, absolutely.

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I mean, in our Cochrane Review at the moment, we have certain trials where we only have data from clinicaltrials.gov, but we have that, and that means they can be in our analyses, and otherwise they wouldn't be.

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So that's amazing.

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And you know, another perception we wanted to sort of preempt in the paper, which we did, you know, briefly touched upon, but I think you might get some people who hand wave this away and say, oh,

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tobacco industry research, it's all useless.

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Like, it's all too biased to even care about.

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And that's like one thing we didn't do here as well, I think, which someone more in your position or probably more positioned to do is...

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We didn't look at the quality of these studies at all.

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We didn't actually look at how well they might be designed or answer the questions they set out to answer and provide useful data, right?

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We were just looking at very binary assessments.

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And we think that if the trial was done, the evidence should be out there.

00:22:05 Speaker 5

And that lead, like you said, that people like you who are synthesizing this evidence are the ones who should make the determinations as to how well the studies were done and how externally or invalid they or internally valid they are and how they

00:22:17 Speaker 5

fit into the larger evidence base, but you have to be able to do that.

00:22:21 Speaker 5

Like, it's not, it's silly to just throw it all away and say, because some of it might be useful.

00:22:27 Speaker 5

Like, it might be fine.

00:22:28 Speaker 5

Maybe they didn't, like, they did a useful study, right?

00:22:31 Speaker 5

You know, there's no reason they couldn't have.

00:22:33 Speaker 5

And if it is so biased to be useless or so poorly designed as to be useless, like,

00:22:40 Speaker 5

We'd rather be able to publicly make those determinations than have it just like not be published, like and contribute to publication.

00:22:47 Speaker 5

I'd love to see Jewel make the decision to voluntarily report.

00:22:51 Speaker 5

I'd love to see clearer interpretation from the FDA on this matter.

00:22:55 Speaker 3

Is there anything else that you'd wanted to cover that we didn't cover?

00:22:59 Speaker 3

cover.

00:23:00 Speaker 3

I think you've covered a lot.

00:23:01 Speaker 3

I understand a lot more now, which is great.

00:23:03 Speaker 5

Yeah, no, I don't know that I cover anything else.

00:23:05 Speaker 5

People like it's like the idea of publication bias and reporting biases and things like these are like fascinating to you and you like to learn more.

00:23:13 Speaker 5

You know, we have our trials tracker projects.

00:23:15 Speaker 5

It's trials tracker.net has links to like all the work we've done in that area.

00:23:19 Speaker 5

Like I said, definitely go check out the compare trials project as well, which is, you know, Ben's all their work.

00:23:24 Speaker 5

And then

00:23:25 Speaker 5

Yeah, we have papers published in good journals about all this stuff that you can check out as well.

00:23:31 Speaker 5

But yeah, I don't know if I'll be doing more stuff in the tobacco space.

00:23:35 Speaker 5

You know, I was sort of, like I said, I was sort of a visitor in the space because I found it a compelling sort of moment to do that research.

00:23:42 Speaker 5

And I didn't need to be an expert in tobacco research to make sense of what I was studying.

00:23:46 Speaker 5

So it helped.

00:23:47 Speaker 5

But I certainly got a crash course in the regulation of these tobacco products, which was interesting and exciting.

00:23:51 Speaker 5

And as a policy wonk myself, it was probably more enjoyable than it would

00:23:55 Speaker 5

for a lot of people.

00:23:57 Speaker 5

But no, I think that's it.

00:23:59 Speaker 3

Awesome.

00:23:59 Speaker 3

Well, thank you for visiting the tobacco space and thanks for coming to the podcast.

00:24:03 Speaker 5

Yeah, no problem.

00:24:03 Speaker 5

Thanks for having me.

00:24:04 Speaker 3

Thanks, Nick.

00:24:05 Speaker 4

Well, so that was really interesting and something quite different for us and really interesting to get that just that deep insight into that particular area of trial registration and it's regulatory issues around e-cigarettes.

00:24:20 Speaker 3

Absolutely.

00:24:20 Speaker 3

It's

00:24:21 Speaker 3

I think very tempting to see bad reporting in these trials and think, oh, it's something specific to e-cigarettes.

00:24:29 Speaker 3

But we have to remember that it is happening across the board.

00:24:32 Speaker 3

And we also have to remember, I think, with every piece of medical research, but I'd argue particularly with e-cigarettes, where we know we have real issues with public understanding in terms of the evidence we have so far on e-cigarettes, that more than ever, transparency is key.

00:24:46 Speaker 3

So like Nick, I really would be a big fan of all the evidence that could be

00:24:51 Speaker 3

being made available, being made available so we can use it in our review.

00:24:55 Speaker 3

And also other people can look at it and make their own decisions about that evidence.

00:25:00 Speaker 4

Definitely.

00:25:01 Speaker 4

One thing that I think our listeners might be interested to hear, Jamie, is whether those studies that Nick was talking about that Joule have conducted, whether they're actually included in our review, because he spoke about the fact that they obviously didn't do a quality assessment on them.

00:25:16 Speaker 4

We do do quality assessments in our review, but I believe these studies aren't included.

00:25:22 Speaker 3

Yeah, for the most part, they're not included, and that's because most of them, as Nick mentioned, are kind of really controlled, short-term laboratory studies, and we're interested in

00:25:31 Speaker 3

in longer-term outcomes in our review, and we really want to see more longer-term studies of JUUL as well as other e-cigarette devices.

00:25:40 Speaker 3

So that's it from us this month.

00:25:42 Speaker 3

Thanks so much for listening and to Nick for the fascinating discussion.

00:25:46 Speaker 3

We look forward to catching up with you all next month.

00:25:49 Speaker 3

Please subscribe on iTunes or Spotify and stay tuned for our next episode.

00:25:53 Speaker 1

Vaping is safer than smoking may help you quit in the end.

00:25:58 Speaker 1

But remember to mention the findings we have, can't tell us what'll happen long term.

00:26:05 Speaker 1

Even though we know vaping is safer than smoking, we may still find cause for concern.

00:26:12 Speaker 1

If you're thinking of switching to vaping, do it! That's what the experts agree.

00:26:19 Speaker 1

Smoking's so bad for you, they all concur that vaping's burning, but there's much to learn of a bad long term.

00:26:28 Speaker 3

Yet to be seen.

00:26:28 Speaker 3

Jonathan Livingston-Banks for running searches, to Ailsa Butler for producing this podcast, and to all of you for tuning in.

00:26:34 Speaker 3

Music is written with Jonny Berliner and I and performed by Jonny.

00:26:38 Speaker 3

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00:26:42 Speaker 3

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00:26:48 Speaker 3

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