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Session: Evidence Synthesis to Derive Model Transition Probabilities (Part II – Quantitative Pooling)

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Dr. Wei Yu: Hi, everyone. My name is Wei Yu, a Health Economist at HERC. Today’s instructor is Dr. Risha Gidwani-Marszowski and Risha is a Health Economist with HERC, and also an investigator with the VA Center for Innovation to Implementation. She is also a consulting Assistant Professor of Medicine at Stanford University. Her expertise is in cost effectiveness analysis, comparative effectiveness research, and quality of care. Risha’s research uses econometric and decision analysis techniques to identify ways to study value, specifically to improve the quality and lower the cost of U.S. healthcare. She has expertise in casual inference from observational data, cost effectiveness analysis, matter analysis and health-related quality of life management. Her content interest include end-of-life care and care for patients with advanced cancer. She received her Doctor of Public Health degree from the UCLA School of Public Health. Today, Risha will discuss the use of meta-analysis for decision modeling. Risha, you can start now.

Dr. Risha Gidwani-Marszowski: Okay, thank you Wei. Good afternoon, good morning everybody. I am going to be talking today about meta-analysis, which is a way to derive transition probabilities for use in a decision model. I hope a lot of the folks on this call attended part I of this lecture. This is part II, of a two part lecture, talking about how to conduct meta-analysis. The first few slides are going to be a review of my last lecture, just to set the stage for those who weren’t able to make the last lecture, or for those people who attended that need a reminder of what we discussed two weeks ago.

You guys have seen these presented slides a few times throughout the course. This is a schematic of a decision model, where we are looking at the relative value of two treatments, drug A versus drug B. And we’re trying to understand our likelihood in successfully treating infection. So, this is what a structured decision model would look like. We populate this decision model with transition probabilities to understand the probability of treatment success under drug A, versus the probability of treatment success under drug B.

There are different ways to derive these transition probabilities, which are your model inputs. The first thing you can do is go to the literature and transform existing data inputs and directly use those in your decision model. And that was the topic of the lecture I gave a few weeks ago. And then the second way that you can create data inputs is to synthesize multiple existing studies, and that’s what we’re going to be speaking about today.

There are different ways of synthesizing available data from the literature. You can do meta-analysis, mixed treatment comparisons, or meta-regression. So the reason we do a meta-analysis, versus just going to a single study and obtaining a transition probability from that single study to use as an input in our decision model, is that we are going to be in a situation where we have multiple studies that have evaluated our question of interest, or multiple studies that we could use to derive a transition probability. And what we want to do is create a single pooled estimate from these multiple studies. And the idea is that when we create a pooled estimate that’s based on these multiple studies, that pooled estimate is going to be higher quality than any estimate that’s provided by a single study. And that’s because single studies may not be well powered enough, or the single studies may have some sort of bias in their sample.

When you do a meta-analysis, you increase the sample size, so you can reduce the effect of random error and therefore, produce a more precise measure of effect. And when you do the meta-analysis, you can also explore variations between studies and assess any factors that might modify treatment response.

We’ve gone over this in the last lecture, but I just want to summarize it briefly because this is our 30,000-foot perspective of what’s actually going on in a meta-analysis. The first thing you do is, when you do meta-analysis, the quantitative portion of it, we calculate a summary statistic for each study. We weight the summary statistic, and you’ll see that I have noted here in parenthesis, conventionally. You don’t have to weight each summary statistic but generally, that’s considered the best practice. And after you weight the summary statistic, you’ll average the individual weighted estimates, from each study, in order to create a single pooled point estimate, and that is the point estimate from your meta-analysis.

Now, of course, each one of these individual point estimates, that were used to create your pooled point estimate, has uncertainty or some measure of variation around those individual point estimates, and we need to incorporate that variation around those individual point estimates into the pooled point estimate. And so, the last step in a meta-analysis is calculating the variance around your pooled point estimate.

So, therefore, meta-analysis is the computation of a weighted mean estimate, along with an estimate of variation around this mean. Now it seems like it’s the mean estimate but that doesn’t mean that the summary statistic itself is a mean. You could have, let’s say dichotomist data, which are oftentimes what we’re interested in for inputs in a decision model. So, you could have a mean odd, a mean odds ratio, a mean relative risk, a mean probability, or you could have continuous data. So, your meta-analysis may be the computation of a weighted mean estimate of mean. And so, just because I say mean estimate, doesn’t mean that the underlying summary statistics are continuous and normally distributed. The underlying summary statistic can be really anything that’s relevant to your decision model but you’re just calculating a mean of that summary statistic, across studies.

Now, remember, you can also run a meta-analysis to synthesize non-comparative data or comparative data. So, non-comparative data would be something like the probability of death from sepsis. Comparative data would be something like the difference in the probability of death from sepsis, from drug A to drug B.

If we have, as our summary statistic from individual studies of relative risk, then the weight in which we would create a pooled estimate is, we would take the relative risk from study A, the relative risk from study B, the relative risk from study C, we would transform all of these things into log relative risks, and then, from there, we would weight each one of these log relative risks and combine them into a weighted pooled estimate, which, in this case, would be the summary log risk ratio. And then, we would un-transform, or exponentiate that log risk ratio, in order to create a risk ratio, or a relative risk that’s in the natural scale.

When we have binary outcomes, as we went over this in the last lecture, but just to remind you, when we have binary outcomes, we work in the logs scale. And, the reason we do this is because the logs scale makes it more likely for study outcomes to be normally distributed, and also, when we log the relative risk, for example, that makes the relative risk of harm the inverse of the relative risk of benefit. And I won’t go too much into this because my last slides detailed this, but if you need a refresher of why that happens, please take a look at the slides from the last lecture.

When we are working with normally distributed, continuous data, then the summary statistic will be a mean that’s reported from each study. In those situations, you would take the mean estimate from each one of those studies, weight those means individually, in order to create a pooled mean estimate.

This slide- sometimes I think it’s easier to understand how to get to the end goal, when you can see what the end goal is first. And this is the end goal of the meta-analysis, is to produce this figure that looks something like this. So this is an example of a meta-analysis that was published in JAMA in 2012, and it was looking at whether taking Omega-3 fatty acid supplements affect your risk of major cardiovascular disease. And, we have each individual study that’s noted in the row, and you can see here that they actually evaluated three different outcomes. They looked at whether it prevented a mix of outcomes, whether there was secondary prevention of a cardiovascular disease event or, I think this is the risk of getting an implantable cardiac defibrillator device.

And so, here what they’ve done is they’ve reported really specific information from each study. Each study has a control group and a treatment group, and so they tell you the numerator, the number of events that occurred in each arm of the study, as well as the denominator, the number of participants that were randomized to each one of those arms of the study. They also tell you what the specific relative risk was from each study, along with an estimate of variation around that relative risk. And then, that is plotted here, on this figure, which is the final figure of a meta-analysis. For the size of the box, if the box were the point estimate from each study and then the horizontal bars are the constance intervals, or the estimates of variance around the point estimate. And the size of the point estimate, or the size of the boxes reflect their weight and how much importance they contribute to the pooled summary statistic.

Generally, in a meta-analysis, the size of the box is proportional to the inverse variant. Larger studies have a smaller variance and therefore, they get a larger weight. And so, you can see here that studies that have a large sample size generally are getting a larger weight. There is a single pooled estimate for each one of the outcomes, as denoted by these diamonds, and then, an overall pooled estimate across all of the three outcomes. And here you can see that essentially, they’re concluding that there’s no difference in risk of major cardiovascular event, between people who did and did not have Omega-3 fatty acid supplementation. So, this is ultimately what we are trying to get to with the meta-analysis.

You’ve seen this slide before, if you attended my last lecture. These are the steps in a meta-analysis. So, before we can get to producing any sort of quantitative estimates, you have a lot of leg work, that we do. First thing we do is a systematic literature search. From the systematic literature search, we review all of the titles and the abstracts that look like they may be relevant to our study. We discard them if they don’t look like they’re actually answering our research question of interest. For the remaining studies, we do a data extraction and we separate out the observational studies from the randomized, controlled trials. If the summary statistic from each individual study that ended up in our pool of accepted studies, if those summary statistics are different, let’s say one study was reporting an odds ratio, another one was reporting relative risk, we transform all those summary statistics to the same scale. So for example, we may transform everything to a relative risk. Then, we evaluate the heterogeneity of the selected studies, according to outcomes that have been transformed to the same scale. And then, only once all of that work is done, can we actually conduct a meta-analysis.

So, there’s a lot of steps that happen before we get to what we’re about to talk about today, which is the actual conduct of meta-analysis. In the previous lecture, we talked about steps one through six, so if you weren’t able to attend that lecture, please go back and take a look at the slides or the audio, and you’ll be brought up to speed.

So, before we continue, I want to ask a question that actually relates to what I spoke about in my last lecture. But this is a really, really important part of meta-analysis, so I’m curious, from the audience, if you can tell me how do you proceed if you have identified heterogeneity amongst your study? Do you not continue with the meta-analysis? Do you exclude the studies that cause the heterogeneity and then conduct a meta-analysis on the remaining studies? Or do you do something like run a meta-regression?

Heidi: And responses are coming in, we’ll give everyone a few more moments to respond before we close the poll out and go through the results. And it looks like we’ve slowed down here, so I’m going to close it out. And what we’re seeing is 18% of the audience saying do not continue; 21% saying exclude studies that cause heterogeneity; and 62% saying run a meta-regression. Thank you everyone.

Dr. Risha Gidwani-Marszowski: Great, thanks so much. Okay, so the correct answer is really two-fold. There’s one or two options that you can take, if you have identified heterogeneity amongst your studies. The first is, you don’t continue. You feel as though the heterogeneity is sufficiently large, as to prohibit the pooling of these studies into a single pooled estimate. And then you just stop with your systematic literature review, and instead of presenting a quantitative pooled estimate, you present a qualitative review of the entirety of the literature, and that becomes your manuscript. Or, you can run a meta-regression. We’ll talk a little bit more about how you run a meta-regression and some of the pros and cons of that.

The main thing that I want you to take away from this lecture, right now, is that it is not okay to exclude the studies that cause heterogeneity and then just conduct a meta-analysis on those studies that look homogeneous. In that situation, you are cherry-picking your studies and all of the work that you did to create a systematic literature review has now been obliterated because what you’ve included in your meta-analysis is no longer systematic. It’s really biased, I shouldn’t say that it might be systematically biased, so maybe that’s a poor choice of words. But the idea being that your meta-analysis is no longer the result of evaluating the entirety of the studies available in the literature. Your meta-analysis would just be evaluating a subset of the studies in literature, that you’ve selected because they look like each other. Which is empirically not a path that you should be going down.

Okay, so now let’s get into how we actually conduct a meta-analysis. So this is assuming that you’ve gone through those previous steps one through six that we talked about in the last lecture, and you’ve evaluated the heterogeneity of your studies and you feel as though they’re sufficiently homogeneous, as to be able to proceed with a quantitative pooling.

So now what we do, is we’re actually going to do the meta-analysis for the quantitative pooling. And really, this actually ends up being four different steps but they’re each implemented in software, so it’s, sort of, happening behind the scenes, but it’s something I want you to be aware of. What’s going on, in terms of the engine. So, there are two decisions that you, as an investigator, need to make right off the bat, when you conduct your meta-analysis. And the first is whether that you’re going to use fixed versus random effects and the second is how to pool your studies.

So, let’s break these down individually. Fixed versus random effects is a major decision and this is really driven about how you think about the studies that you have. So, in your fixed effects meta-analysis, this assumes that the variance that you have amongst studies is due to sampling error. So you really think that there is some fixed, underlying true effect. When the random effects meta-analysis, you assume that there is both that sampling error that’s causing the variance among studies, but also you think that the true effect could actually vary from study to study. And that might be because there were different cohorts that were studied in one analysis versus another or there were different mechanisms of administering intervention. So, the idea being that in a fixed effect analysis, if each study had an infinite sample size, the sampling error would be zero. And in practice, we don’t have an infinite sample size and that’s really why we have variation across studies; it’s just due to the sampling error.

In a random effects analysis, you think that the studies are similar enough to combine but you don’t think that they’re identical. So you don’t think that the true effect is exactly the same in all the studies. Instead, you assume that there is a distribution of effects and a frequent [unintelligible 16:56] approach assumes that this distribution is a normal one. And so, what you’re saying, when there’s this distribution of effects is that there’s both sampling errors that’s happening, as well as this true variation in effects sizes. So, another way to think about that is that in a random effects meta-analysis, we assume that the studies we have represent a random sample of the studies in the universe.

The variance is, therefore, treated differently across fixed versus random effects. In a fixed effect analysis, the only variance that you are propagating through to the meta-analysis estimate, the pooled estimate, is the within-study variation. In a random effects analysis, because you think that the true effects could vary from study to study, you also add tau- squared, which is the between-study variance. So in the random effects analysis, you are incorporating or propagating through both the within-study variance, as well as adding between-study variance, in to the estimate of variation around the pooled meta-analysis estimate.

And therefore, because the random effects analysis is incorporating more forms of variation, or variance, the confidence intervals are wider in a random effects analysis than they are in a fixed effects analysis.

And the inference is also different, because in the fixed analysis, you assume that you are able to identify some fixed true underlying effect, the inference of the fixed effect meta-analysis is the true effect is X. Whereas, in the random effects analysis, your inference is that the mean of the effects is X.

Fixed versus random effects analysis also differ in how they handle small studies. Small studies are generally less precise. They usually have more variation and therefore, in an inverse variance method of weighting studies, in a fixed effects analysis, those small studies are given less weight. In a random effects analysis, those small studies are actually given more weight than in a fixed effects analysis. So, because this fixed effect analysis assumes that the only reason there’s variation amongst studies is due to sampling error, it says that we can largely ignore the information from smaller studies, as we have better information about that same effect size from the larger studies in our analysis.

Conversely, the random effects analysis assumes that we’re estimating the mean of the distribution of effects, and so in the random effects analysis, we can’t discount a small study because it may have information about the effect that no other study has estimated. We also can’t let larger studies have too much of an influence on the final pooled estimate because we don’t want our mean estimate to be overly influenced by these larger studies.

So, this is a major decision, as you can tell because it really effects the estimate of variation around that pooled point estimate. So you need to think carefully about whether you’re going to use fixed versus random effects. Random effects are oftentimes more suitable for a meta-analysis, and that’s because there’s almost always differences between studies. But the thing to keep in mind, is that random effects are not always more conservative. So, if the smaller studies in your analysis are systematically different than the larger studies, then the random effects analysis increases the weight of the smaller studies, and that will bias the pooled treatment effect, relative to if you’d done a fixed effect meta-analysis.

So for example, maybe you have a situation where the smaller studies have a thicker population, and thicker populations are going to demonstrate greater improvement from an intervention. In that situation, if you did a random effects analysis, which gives more weight to smaller studies than a fixed effects analysis does, that random effects analysis will over-estimate the treatment effect. So, you really want to think through what’s going on in your particular group of studies, when you’re trying to think about whether to do a fixed effects or a random effects analysis.

So, in the random effects analysis, we said that we are thinking that we have a sample of studies from a larger universe of studies, and that that sample studies the effects from that follows a normal distribution. And so, the width of that distribution describes the degree of heterogeneity amongst your study. If there is heterogeneity amongst your study; now when I say heterogeneity, I mean that the studies are not so different that you would say, oh we can’t combine them but that there’s almost never going to be a situation in which all the studies are perfectly homogeneous. And so there’s going to be some degree of variation across the studies. You, as an investigator have already decided that the degree of variation, or heterogeneity, across the studies is sufficiently low that you can pool them in a meta-analysis but now you still have to deal with the fact that the heterogeneity low level, as it may be, still exists. And so you’ve decided to do a random effects analysis.

So, if you do have this heterogeneity, your confidence intervals for the random effects meta-analysis, the pooled estimate, is going to be greater than that for the fixed effect pooled estimate and that’s because the random effects pooled estimate derived its confidence intervals from both the within-study, as well as the between-study estimate of variation. Whereas, the fixed effects confidence interval will only be incorporating the within-study variation. So if there is heterogeneity, or there is between-study variation, that’s going to be a non-zero value for tau-squared, and the confidence interval for the random effects pooled estimate will be greater than that for the fixed effects pooled estimate.

One thing to keep in mind, is that if you think that there is heterogeneity across the studies, the pooled estimate from your random effects analysis will only estimate the unbiased average treatment effect, if the biases are symmetrically distributed. If there are, you know, the studies that find a higher than average treatment effect are systematically different than the studies that find a lower than average treatment effect, then you’re going to have a biased effect from your random effect pooled estimate.

Okay, so you, as an investigator, have already decided whether you’re doing a random effects or a fixed effects analysis, and now your next major decision is how you’re actually going to pool your study. So, there’s a number of different ways to do this. What’s oftentimes used is the inverse-variance method. Now this is the main inverse-variance method relates to fixed analysis, so when you use this, if you have binary data and you have the two-by-two tables from your underlying studies, you can also use this if you have continuous data and low heterogeneity across your studies because it’s, of course, fixed effects analysis.

If you’re going to do an inverse variance method, but use a random effect, in order to combine your studies. So that means that each study has a weight that’s inverse to its variance and you’re assuming that the studies that are in your analysis come from a larger universe of possible studies, then you would use an inverse variance random effects method, which is in the literature called the DerSimonian and Laird method.

There’s also other methods of pooling data. The Hartung-Knapp-Sidik-Jonkman approach, the Profile Likelihood approach and you can see the different ways in which you would, when you would, use those types of approaches to pool your studies. So, something to keep in mind is that when you have cells that have a value of zero in them, and you are working in the log scale, that causes really big problems because we can’t take the log of zero. And so, there are specific approaches that you can take, if you have a situation in which you have articles that are reporting an odds ratio and there’s a value of zero, in one of the two-by-two tables that is being used to produce the odds ratio. Okay.

There’s really a lot of information on this slide and really, it’s mainly being presented here for you to use as a reference slide, when you actually go, and you do your meta-analysis. A lot of this isn’t really going to make sense or be applicable, sort of in a theoretical sense. You sort of, can tuck this away as reference material and when you’re actually going to go do your meta-analysis, you can think about which pooling option you want to use, based on the type of data that is reported in the studies that end up making it into your pool of studies.

One thing to keep in mind, though, is that there is a Bayesian approach that you can use to pool studies. Most of these other approaches are frequencies. If, let’s say you were doing a random effects meta-analysis and you don’t think that the distribution of the heterogeneity amongst your studies is normally distributed, which is the underlying assumption in the frequencies approach to a random effects meta-analysis, you can instead use a Bayesian approach to random effects meta-analysis and then you can specify a prior distribution that doesn’t have to be normally distributed.

So, just one last piece of information from this slide. You can see that I have four different approaches to pooling studies, if you assume that you have a random effects meta-analysis, and the difference is, amongst these different approaches, is that they differ in how they handle the between-study variance, or what we call tau-squared. So, for the DerSimonian and Laird method, the tau-squared assumed to have a normal distribution. For this Hartung-Knapp-Sidik-Jonkman approach, it’s based on the t-distribution and anyway. So, there’s just different ways that they handle to distribution of tau-squared.

If you are interested in learning a little bit more about all these different methods, these are some references, I would suggest that you take a look at them, if you are interested in using something that is not the common inverse variance or DerSimonian and Laird method.

Okay, now let’s get into some of the specifics around fixed effects and random effects. And I just want to demonstrate to you how this is actually driving your final estimate. So, let’s say that we are using continuous data in our example. And I’m just discussing this first because it’s more intuitive to understand than binary data. So, let’s just assume that we have a meta-analysis for conducting and our summary statistics from the individual studies are mean estimates. So, the way that the meta-analysis would be conducted in the fixed effects mechanism is that this pooled treatment effect, or T-bar, is a function of the weight of the treatment effect from an individual study, times the weight of that specific study, and then summed. And that’s the numerator. The denominator is the sum of all of the weights of the individual studies. Now here, because this is an inverse variance approach, the weight is calculated as one, over the variance, thus the inverse variance. And so, each study has its own variance and therefore each study has its own specific weight.

There’s a variance of the pooled treatment effect, sorry, let’s just say pooled treatment effect, to be clearer, and the variance of this T-bar estimate is one, over the sum of all of the weights, from all the individual studies. So that is the fixed effect approach.

In a random effects approach, you calculate the pooled treatment effect in the same way as the fixed effect analysis. So, you can see here that this equation for the random effect pooled treatment effect is the exact same as that from the fixed effect, with the exception of the way that the weight is calculated. So, now instead of the weight being one over the variance of that study, which I’m sorry, that’s what this should be. This should be a “v”, not a “w”. The weight is now the sum of the inverse variance, or the same weight that you had in the fixed effects analysis. Plus, this estimate of between-study variance, and that’s just tau-squared.

So, here this is the within-study variance, and I’m sorry that should read “v”, stead of the “w” there. And then the tau-squared is the between-studies variance. So, you can see that there is more variance that’s being propagated in the random effects analysis versus the fixed effects analysis. And then the variance of this pooled treatment effect in the random effects analysis is just, one over the sum of this weight. Which is, again, the within-in study variance and the between-studies variance.

So, one of the things that you can see here is that if the between-studies variance equals zero, and there was no heterogeneity across studies, then the estimate from the random effects analysis would be the exact same as the estimate from the fixed effects analysis.

So, tau-squared is the between-studies variance and that’s what we used in the random effects meta-analysis. It’s the variance of the true effect sizes and we can’t really compute this directly. We estimate it from the observed effects and the reason is because when working with a variance of the true effect sizes, if we had an infinitely large sample of studies and each study itself was infinitely large, it would then give us a true effect for each study. And if we calculated the variance of these effects, we would have tau-squared. Now of course, we don’t have that, so we just have to estimate it [Unintelligible 31:49].

All of the different random effect approaches that I’ve mentioned, so the DerSimonian and Laird, the Knapp-Hartung, the Profile Likelihood, the Bayesian approach, they all differ in how they handle this estimate of tau-squared. And so this, of course, effects confidence intervals and thus tests of significant. So, it is something that you want to think through properly, before you decide how to pool your studies, and which approach you use to do that.

Okay, something else that you need to think about, when you are pooling your studies, is publication bias. So, it is possible that the studies in your analysis are systematically different from all the studies that should have been included in an ideal world. And that is oftentimes, the difference is oftentimes the result of publication bias. So, most of you are, no doubt, aware that studies with significant results are more likely to be published. So the studies that don’t have significant results are less likely to be published and you don’t pull them in to your meta-analysis because you didn’t find them- they weren’t published- then the meta-analysis will actually overestimate the treatment effect. We also see that larger studies are more likely to be published and the results of larger studies are systematically different than the results of smaller studies, then we’re going to have problems, if we used a random effects meta-analysis, which gives greater weight to smaller studies, compared to the fixed effects analysis.

So, all of the prep work that you did to get to the point where you could even do a meta-analysis, the systematic literature review, the data extraction, these steps of heterogeneity; you did that so that you could get all of the studies that exist or are relevant to your search question. Unfortunately, even really well-conducted systematic literature reviews cannot obviate concerns about publication bias because you don’t know what is not published in the literature, right? You don’t know what isn’t available to you. And so, you have to do some due diligence to assess whether publication bias actually exists in your analysis. And there’s ways that you can do this.

One of the ways that you can do this is by plotting your data in a funnel plot. And essentially the short conclusion is that asymmetry in the funnel plot is problematic. Symmetry doesn’t mean that there’s a lack of a problem, but asymmetry is a problem. So, what do I mean by this? This is an example of funnel plots. So this is a great article, I’d highly recommend reading it. It’s called Recommendations for Examining and Interpreting Funnel Plot Asymmetry in Meta-analyses of Randomized Control Trials. And these are some real heavy hitters in the field of meta-analysis, that are often from this study.

So, here you can see that there’s this inverse funnel, right here. It’s noted by the dotted lines and the middle of the funnel represents the mean pooled treatment effect and you can see that studies in this plot on the left, are generally equally distributed on either side of this midline of the pooled treatment effect across the study. However, in this funnel plot on the right, here we have this pooled treatment effect as this dotted line. But you can see that there’s a lot more studies on the left-hand slide of this dotted line than there are on the right-hand side of this dotted line. So that indicates that there’s asymmetry in this particular meta-analysis, which means that there’s a problem here. That you have some degree of publication bias in the plot on the right.

So, a couple of things that you do need to think about when you’re evaluating the asymmetry or symmetry of a funnel plot. If you have an asymmetric funnel plot, you just want to be careful and make sure that this isn’t due to something else. So, it’s possible for funnel plots to be skewed by things, other than publication bias. If, let’s say, the quality of the studies varies with their size, it may look like there’s publication bias, but there’s not. So, do your due diligence and delve a little bit more into this.

If you have a plot that looks something like we have on the left, a symmetric funnel plot, we may think, “great, I have no publication bias because my funnel plot is symmetric.” Unfortunately, it’s just not that easy to come to that conclusion. Just because a funnel plot is symmetric, doesn’t mean that there is not publication bias. So, like many of the tests that we have in meta-analysis, if you see a problem, most likely that problem exists. But, oftentimes, we have low power to detect problems in meta-analysis and just because there appears to be a lack of a problem, doesn’t mean that the problem doesn’t exist. So just because something looks symmetric, doesn’t necessarily mean that there is no publication bias. I wish there were something I could tell you that was, kind of, a more conclusive statement that we could make about publication bias, but unfortunately that just doesn’t seem to exist right now, in the field.

Okay, so if you are looking at your funnel plot and you’re thinking about asymmetry, you want to evaluate whether the quality of the study varies with size, and when you evaluate that funnel plot, you want to evaluate it in the context of the other information you have about the study. And so, you look at the quality of the study or look at the heterogeneity of the intervention. If the funnel plot is going to be useful to you, it needs to have studies with various sizes. So, you really want to make sure that it’s not just large studies that you’re including in your meta-analysis.

So if the true effect’s size is small, then small studies with a small effect won’t be significant and are less likely to be published, but small studies with a large effect are more likely to be published because it is statistical significant. Or, if you have large studies with non-significant results that are less likely to be published, then you’re going to see some asymmetry in your funnel plot. So, you kind of, want to think about that.

Okay, and then failure to find asymmetry doesn’t mean that there isn’t a publication bias that you’ve done. So, if you do have publication bias that you suspect is happening, and you have an asymmetric funnel plot, you are going to need to do something about that publication bias. So, there is a number of different things that you can do, in order to deal with that type of publication bias. And unfortunately, given the length of this seminar, we don’t really have an opportunity to go into each one of these in detail but I would recommend reading the book that’s denoted at the bottom of your screen, because it will give you more information about how to do this.

Just a little bit information about some of these approaches, if you’re doing a cumulative meta-analysis, you order them by the precision of the study and you run the meta-analysis with one study, and then you add another study to that meta-analysis and produce a pooled estimate. And then you add a third study to that meta-analysis, produce a pooled estimate and so you’re adding a study to the meta-analysis, in order of how precise they are. So, the more precise studies get added first. If the pooled point estimate has stabilized and isn’t affected by the inclusive of the less precise studies, then there is no reason to assume that including smaller studies has injected a bias.

Another approach is a trim-and-fill approach, and what that does is it uses an iterative procedure to remove the most extreme small studies from the positive side of the funnel plot. And then you recompute the effect size that each iteration until you have a funnel plot that’s symmetric around the new effect side. There’s a problem with this trimming approach. It reduces the size of the variance and therefore, it can yield too narrow a confidence interval and therefore, what this algorithm does is, it adds this fill to the trimming. It fills in the original study back into the analysis and then shoots a mirror image for each. And so, this has no impact on the point estimate because it’s a mirror image, but it does correct for the variance.

So, there’s a number of different things that you can do, in order to deal with a publication bias. Definitely recommend that you read the chapter on publication bias, in this book, on those pages to get a better sense of what you would prefer to do with your meta-analysis, in dealing with publication bias.

So, now let’s bring this back to our cost effectiveness analyses. This is a cost effectiveness analysis cybercourse, the reason that we’re talking about meta-analysis is that meta-analysis is a mechanism that you could use to produce point estimates that you use as inputs in your cost effectiveness analysis. So, if you have done your meta-analysis correctly and you this forest plot, this is your end graphical result for your meta-analysis, you can then use the results from this, as inputs into your cost effectiveness analysis.

So this is just a meta-analysis that was published in the Annals of Internal Medicine. It was looking at the accuracy of testing for albuminuria. And you can see that there were only five studies included in the meta-analysis. This is not uncommon to have this level of studies that ends up making it to the final round. And then, there’s this combined estimate. So, this combined estimate of .96, that’s your point estimate and that’s your input in your base piece cost effectiveness analysis. But, of course, this combined estimate, this pooled estimate has its own estimate of variation around it. And so, you use that 95% confidence interval around the combined point estimate. You use that in your cost effectiveness analysis, in order to run the sensitivity analyses in your cost effectiveness analysis. So, this is how we link the results of the meta-analysis and use them to be the inputs in our cost effectiveness analysis.

So there’s a number of different software programs that you can use, in order to conduct meta-analyses. Oftentimes people use RevMan, which is what the Cochrane Collaboration recommends. But you can really do them in a number of different software approaches. The one thing I will caution is just to be careful with plug-and-chug software. If it’s ridiculously easy to do a meta-analysis, that means that a lot of the decisions about pooling and weighting studies are happening behind the scenes, and that’s problematic. You, as the investigator are the one that knows the most about your research question and knows the most about the research studies that you’re using to conduct your meta-analysis and so, you should really be making the decisions about the fixed versus random effects analysis. And you should be making the decisions about how to pool the studies and how to deal with publication bias, rather than ceding all of that control to, like a plug-and-chug software, because what their default specifications are may not be the right mechanism to operationalize your specific meta-analysis.

If you wanted to do a meta-analysis in a Bayesian framework, so you wanted to not have that normal distribution assumed for tau-squared, you could do something Bayesian and you can use OpenBugs or WinBugs, in order to do this.

Okay, so now in the remainder of the time that we have, I want to briefly cover some advanced topics. As you can probably tell, meta-analysis is relatively complex and it’s hard to convey everything that one needs to do in a one-hour, even two-hour lecture. So, this is absolutely not going to be comprehensive. This was just more to give you a sense of what these topics actually are, so that if you’re interested, you can investigate them further, on your own.

So, in individual-patient level of meta-analysis is one of the things we’re going to be talking about and it has a lot more data points than a regular meta-analysis. So, the regular meta-analysis that we’ve been talking about uses a summary statistic from each study. That could be the odds ratio or that relative risk, or a mean from each study. So, if you had eight studies in your meta-analysis, that means that you have eight data inputs into your meta-analysis. If you are doing an individual-patient data meta-analysis, you are using individual-patient data from each study.

And so, if those eight studies each had 50 patients, your individual-patient data meta-analysis has 400 data inputs, instead of the eight data inputs the regular meta-analysis. So, obviously that’s much richer data and you can do a lot of interesting things with that, like subgroup analyses but it does require that the authors of those eight studies give you underlying data for each one of their patients. And that can be a challenging thing to actually obtain. So, if you’ve got individual-patient data meta-analysis, kudos to you. Most people, in reality, are not going to be able to do this because they won’t be able to get the right data inputs.

If you do have these data inputs, you can do some nice things like evaluate potentially different follow-up times. You can, of course, calculate different summary statistics, you can do a time-to-event analysis, you could impute missing data. And this missing data piece actually can be sort of, this double-edged sword. If you are doing an individual-patient data meta-analysis versus a regular conventional meta-analysis, you could actually produce different results because of differences in the handling of missing data. So maybe one study didn’t impute missing data. Another study did impute missing data and a third study did a mean imputation of missing data. Those are all different ways to handle missing data and that could, depending on the frequency of the missingness [sic] of your data, could affect what you get in your pooled estimate and in your variation around your pooled estimate.

All righty, if you are not one of these lucky few people to get individual-patient level data for a meta-analysis, but you have heterogeneity of studies, you could do a meta-regression-what we talked about in our poll question. In a regression analysis, where you guys, I’m sure, are all familiar with, we’re adjusting for differences at the unit of analysis, which is oftentimes the patient level. In a meta-regression, you’re adjusting for differences but you’re adjusting for differences at a study level. That’s what makes it meta. So, in a regular regression, you’re adjusting for covariates that might be imbalanced amongst groups. In the meta-regression, you’re adjusting for covariates that might be invalid amongst studies. And so, obviously you’re not going to be able to do as well in adjusting for covariates when you’re doing it at a study level, versus the patient level.

So, be careful with this and don’t consider this a tangency. Understand that these limitations exist, specifically ecological fallacies. So, an ecological fallacy from epidemiology, you guys might recall, is when a relationship exists at the group level that may not exist at the individual level. So an example of that would be the group level we know at a population level that’s smoking causes lung cancer, but that doesn’t mean that at an individual level, all individuals who smoke will develop lung cancer. And so, just because something is happening at a group level, doesn’t mean that that same relationship applies at an individual level. So, just because you’re adjusting for things at a group level, or a study level in a meta-regression, doesn’t mean that you’re actually able to make that proper adjustment at the individual level.

So, the meta-regression can help get you to rectify some of the imbalances and covariates across studies but really, adjustment is stopping at the study level and not at the individual level and really, that adjustment at the individual level is what we want to see, in order to truly make unbiased comparisons.

Meta-regression is also not recommended when the number of studies is small. So this is, I will say, somewhat contested. In regression, there is a rule of thumb, not data-based but just sort of, a general rule of thumb that statisticians often follow that you need to have at least 10 events occurring per covariate that you’ve included. So, you need to have 10 “yeses” per right-hand side variable. In meta-regression, there is no established rule. It’s just the number of studies you need in order to conduct a meta-regression but when you have a small number of studies, you’re not really going to be able to adjust for many differences across the studies.

Okay, so if you are doing a meta-regression, you still need to figure out whether you want to do something that’s fixed effects versus random effects. And the interpretation of a fixed effect meta-regression is that you’re saying that when the fixed effects, the study-level effects are fixed, that all variations between the studies outcomes can be accounted for by covariates in the regression model. And you’re saying that studies that have the same values for all of your covariates share the same population level effect.

If you are doing a random effects meta-regression, this assumes that your covariates explain part of the variation between your studies’ outcomes and that studies that have the same values for all covariates share a distribution of effects. Or, you’re saying that the mean effect size is the same for all values of the covariate.

Okay, meta-regression really works well when you have all of your studies evaluating the same intervention. So, if you’re really interested in the effects of drug A versus placebo and all of your studies are evaluating drug A versus placebo, great. But, generally, when you’re doing your cost effectiveness analysis, you’re interested in the effect of one active intervention versus another active intervention. And oftentimes, randomized controlled trials has not directly evaluated these interventions. So generally, what we see in the literature is that some studies have evaluated drug A versus placebo and other studies have evaluated drug B versus placebo. But what you’re interested in, for your cost effectiveness analysis, is which treatment is the highest value, which active treatment is the highest value. And thus, you’re really interested in the comparison of drug A versus drug B.

So, what do you do, in this situation? There is a relatively new method called mixed treatment comparisons. Some people also call it network meta-analysis and what this does is it actually allows you to estimate the relative treatment effect of interest by using a network of evidence. So, you have this situation where you have some studies that are comparing treatment A to placebo and from there, you’ll get an estimate of theta A to placebo, or the difference in treatment effect between, or the difference in outcome between treatment A and placebo.

Then you have another group of studies that is evaluating the effect of treatment B versus placebo. And from there, you get from a meta-analysis, your estimate of theta B versus placebo. But what you really want is the difference in effect between treatment A and treatment B.

So what you can do is utilize the fact that both treatment A and treatment B are connected in a network of evidence by having a common node of placebo. And from using this common node of placebo, we can actually estimate the effect of theta AB. So, the way that we do that is theta AB is the difference between theta A and placebo, minus the difference of theta B to placebo. And so, what you’re essentially doing is you’re leveraging the fact that there’s a common comparator and assuming that the studies are homogeneous enough. The ones who studied treatment A versus placebo are homogeneous enough relative to the ones who studied treatment B versus placebo, that you could pull out from this network of evidence, the relative treatment effect, the good trip.

Now you do pay for this, you sort of, pay for using a network of evidence rather than directly measuring, or directly examining the difference between treatment A and B. You pay for that, in terms of your variance. And what you do is, in order to create the variance around your estimate of theta AB, what you do is you sum up the variance that occurred in B’s studies and you sum up the variance that occurs in the study that estimates this effect. And that’s where you get your estimate of variation around your indirectly measured effect of theta A versus B.

So, this mixed treatment comparisons relies on a connected network of evidence. So, this is an example of a figure of a mixed treatment comparisons analysis, I conducted, where we were looking at a bunch of randomized controlled trials that were going to treat heavy menstrual bleeding or HMB. And then we were looking at different interventions that would affect menstrual blood loss or MBL. And so here, you can see that we have a number of different interventions that we studied. We have eight different interventions and the reason we could study all these eight interventions is that they were all connected by a network of evidence. So, even though Ablation and Danazol were not directly evaluated, what we could do was we could leverage the fact that Ablation was connected to LNG-IUS, and that was connected to COC and COC was connected to Danazol, in order to get the indirect estimate of the difference between Ablation and Danazol, in treating heavy menstrual bleeding.

And the nodes represent the different treatment interventions and the lines between the nodes, and the numbers on those lines represent the number of studies that connect these two, that study these two interventions in a head-to-head randomized controlled trial.

So, one thing to kind in mind when you’re doing a network meta-analysis, or a mixed treatment comparisons, is that you have to have a complete network. You can’t have any islands. So, if for example, this line between Ablation and LNG-IUS no longer existed, because there was no study that actually directly compared these two interventions, then we would not be able to compare Ablation to any one of the different interventions because it wasn’t connected in the network of evidence.

Mixed treatment comparisons have been around for a few years and are really gaining a lot of popularity, especially amongst people in Europe, that are doing a lot of cost effectiveness analyses. And so, there has been now, in the recent past few years, a number of articles that have come out about how to conduct mixed treatment comparisons, or network meta-analyses. People do call them different things. Again, some people say network meta-analyses, some people say mixed treatment comparisons. They are the same thing but just keep that in mind when you’re doing any literature searches about this method. And this is an example of a paper that gives you standards for reporting how to do a network meta-analyses, and I find that these types of articles are generally quite useful. They’re telling you what you should report but from that, you could glean the types of processes that you should be conducting, in order to have a gold standard network meta-analysis.

Okay, so we’ve gone over a lot of things and just in our last couple of minutes, I want to summarize briefly, what we’ve talked about. When we do a meta-analysis, we are creating a single pooled estimate, and then estimate of variation around that pooled estimate. The way that we, generally, get that pooled estimate in variance, is from weighting and combining individual effects from multiple studies. The weighting part is optional, but it is generally the way that good pooled standard meta-analyses are conducted.

When you do a meta-analysis, you have a lot of different steps that you need to complete successfully before you actually get to the conduct of the meta-analysis and the quantitative pooling. When you are doing your quantitative pooling, you need to decide whether or not you’re going to used fixed versus random effects in your meta-analysis. If you have fixed effects, you assume that you have the universe of studies and that what you are inferring from your fixed effects analysis is the true effect size.

If you are doing a random effects meta-analysis, you assume you have a sample of studies from the universe of studies and thus the inference that you have from your random effects analysis is that you are estimating the mean of the true effects size.

You need to also think about how to pool the studies in your meta-analysis. If you have binary data, like an odds ratio or relative risk, you can oftentimes use the Mantel-Haenszel or the Peto method, for pooling studies. If you have continuous data, you can use a number of different methods to pool studies, often inverse variance, or DerSimonian and Laird are most frequently used.

If you are trying to do some more advanced meta-analyses, those could take the form of individual-patient data meta-analyses, mixed treatment comparisons or meta-regression. If you do an individual-patient data meta-analysis, when you have all the studies that have evaluated your interventions of interest and you have the individual-patient data underlying all those studies. You conduct a mixed treatment comparison when the interventions of your interests have not been evaluated in a head-to-head trial and you can do a meta-regression, either with a meta-analysis or with a mixed treatment comparisons analysis. What you’re doing with the meta-regression is you’re adjusting for covariates at the study level.

Something to keep in mind, is that meta-analyses and mixed treatment comparisons themselves, are observational studies. Even if those meta-analyses and mixed treatment comparisons analyses are conducted from randomized controlled trials, the summary statistic is considered to be an observational summary statistic because patients are not randomly assigned to studies. They’re randomly assigned to treatments, within studies.

I strongly recommend all of these pieces of literature, if you’re interested in conducting meta-analysis. The Borenstein book, especially, is very easy to read. Actually, they’re all pretty easy to read. None of them are very technical and these are really informative documents. So, with that, I know we don’t have a lot of time, but I’ll open it up to questions and you guys are also free to email me. My VA email is noted there. I will say I’m having email problems this week and seem to be locked out of email so it might take me a day or two to get back in and get back to you. With that, any questions, please let me know.

Dr. Wei Yu: Okay, Risha, I think we have one question. I believe that question is related to the question raised in the poll. That is the when there is heterogeneity in studies, what should we do? And there were two correct answers, one is do not continue and the other one is do a meta-regression. Now, the question raised by [Unintelligible 59:27] is that if things randomly effect allow for different effects across studies, I mean, is that allowed for heterogeneity studies making it possible to do meta-regression under most, or all conditions?

Dr. Risha Gidwani-Marszowski: Well, I mean it’s a great question and this sort of harkens back to you have to make this decision yourself, as a principle investigator, as to how much heterogeneity sinks a ship. There’s not really any hard, or fast rules that say, “ok this much heterogeneity means you shouldn’t continue, versus a certain degree of heterogeneity means continue and just conduct a random effects meta-analysis”. I would say that if you have really systematic differences, then you need to be really careful about whether or not you want to continue.

And the nature of the differences matter, as well. So, let’s say that you have an intervention and one study is looking at a six-month follow-up time and the other study is looking at a two-year follow-up time. And there may be heterogeneity in response because maybe this intervention takes a while in order to see an effect. Maybe like a diabetes management program. Six-months isn’t enough, and you really need that two-year outcome, in order to see an effect. Well, in that situation, you couldn’t just do a random effects analysis, or a meta-regression because you wouldn’t have information on the other follow-up time that you could use to adjust for how the effect might vary, with respect to follow-up time.

So, I think the type of heterogeneity you have, make a difference and it’s a fantastic point and maybe one that I should spend a little bit more time on, in the next lectures. But I will say you know, if I spent more time in the next lectures, it would really be my opinion that I would be giving you, as to when you should proceed and when you should stop because there really isn’t any guidance in the field, as to thresholds for heterogeneity that would result in needing to do a random effects analysis, a meta-regression or just abandoning the idea of a pooled estimate altogether.

Dr. Wei Yu: Okay, there’s another question maybe you can cover. When you talk about the mixed treatment comparison, and the question is, is there a limit to the length of separation, when doing this mixed treatment comparison?

Dr. Risha Gidwani-Marszowski: I assume that means the number of nodes that one has to go to, in order to link two treatments and the answer is no, there isn’t. But remember that you pay for the number of nodes that you go through. So, let me go back to this. Okay, so the variation around your estimate, that you’re indirectly estimating through this network of evidence, is the sum of the variation of the length it took you to get there. So, let’s say in my example of looking of Ablation to Danazol, I now have one, two, three lengths. Four nodes, or three lengths that I’m using, in order to connect Ablation and Danazol, I would add the variation from this length, the variation from this length, the variation to the third length, in order to get my estimate of variation of the indirect treatment effect of Ablation and Danazol.

And so, theoretically there isn’t a limit but you’re going to end up with a really wide confidence interval, around your indirectly estimated treatment effects, the more nodes you have to go through, and therefore the wider your confidence interval, the less likely it is that your going to find that one treatment is statistically different than another. [inaudible 1:03:15] decision, of course, in the indirect treatment effect that you’re estimating and the less precise the estimate is, the less useful it is, as well.

Dr. Wei Yu: I think that’s it, maybe you should close today’s seminar.

Dr. Risha Gidwani-Marszowski: Okay, great. Well, thanks all for your attention and I guess, Heidi, we’ll turn it back over to you.

Heidi: Great, thank you so much Risha. For the audience, I’m going to close the meeting out in just a moment. When I do, you will be prompted with a feedback form. We really do appreciate if you take a few moments to fill that out. Thank you everyone for joining us for today’s HSR&D Cyberseminar and we look forward to seeing you at a future session. Thank you.

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