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Systematic Review and Meta-Analysis: Applications  (SLIDE 1)

Hello. My name is Susan Ross. Welcome to the ISPOR Distance learning module on applications of systematic review and meta-analysis. This is the second of 2 modules in this series. The first of which was an introduction. I hope that you’ve had a moment to look at that module prior to jumping into the applications. But I will also say that it is not essential. If you haven’t, I think that you will still take home a lot of useful information by investing your time and attention to the following module. So, with no further ado, let’s move ahead and discuss Applications of Systematic Reviews and Meta-Analysis. The applications I’m going to review by the way include those in policymaking as well as in clinical drug development and commercialization.

Learning Objectives  (SLIDE 2)

Our learning objectives in this module are to help you appreciate the pros and cons of using systematic reviews and meta-analyses to inform health care policy and practice decisions regarding efficacy, effectiveness, or safety of health care interventions. I hope you will also learn how systematic reviews and meta-analyses are and will be used for drug development and commercialization activities by industry going forward.

Who uses systematic reviews?  (SLIDE 3)

So, who uses systematic reviews? Policy-makers do for sure, and there are many policy-makers in this country and globally. Two chief ones however, are CMS and NICE. CMS is the Centers for Medicare and Medicaid Services here in the US. It’s the agency which administers Medicare, Medicaid and the State Children’s Health Insurance Program. NICE is the National Institute for Clinical Excellence in the UK. It’s the organization that is responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health.

CMS Follows General Principles of EBM  (SLIDE 4)

Let’s understand how CMS and NICE use evidence to inform their decisions. CMS follows general principals of evidence-based medicine. The CMS assesses evidence regarding how “reasonable and necessary” care may be. The reasonable and necessary is the statute term that guides their decision making. They consider as evidence both published and unpublished studies, expert opinion, technology assessments, assessments from professional societies and recommendations from the Medicare Coverage Advisory Committee. The CMS has a few key areas of focus and these include methodological considerations. That is, they look at study design, how well implemented and analyzed studies were, the relevance of chosen outcomes, preference for patient-reported outcomes, and they look for evidence that is generalizable to the Medicare population. They will also look for qualitative assessments of net risks and benefits based on individual studies.

CMS Example: Bariatric surgery  (SLIDE 5)

Let’s look at a concrete example of CMS in action. In August 2004 through the fall, the Coverage Analysis Group prepared an evidence review and summary of evidence to present to the Medical Coverage Advisory Committee about bariatric surgery. In the following spring, CMS opened a National Coverage Determination (NCD) at the request of several external groups listed here. These were groups which all had a stake in policy decisions regarding bariatric surgery. In February 2006, the CMS had determined that the evidence that they reviewed was adequate to conclude, the certain open and laparoscopic procedures for bariatric surgery were, remember these terms, “reasonable and necessary.” For whom? For Medicare beneficiaries – that is their charge, and for specific beneficiaries who have a
body-mass index (BMI) of at least 35 with one co-morbidity related to obesity, and were previously unsuccessful with medical treatment. That’s a very definite and well-defined population of patients for whom CMS stated that bariatric surgery was reasonable and necessary and therefore would be covered. This is an example over time of the sequence of considerations that went into that decision.

**But..Frequently Unanswered Questions in CMS Decision-making (SLIDE 6)**

There are frequently many unanswered questions in CMS decision making. These questions tend to deal with evidence for cost-effectiveness, adverse events, off-label uses, subgroup results, outcomes for patients or providers who were not present in clinical trials, the comparative effectiveness of the interventions in question relative to something else, questions about outcomes that weren’t measured in trials may be important, the clinical utility of various diagnostic tests, surgery, devices and other technologies that have had limited regulatory review. So, while CMS typically will consider a large body of evidence in its policy decision making – evidence that is assembled ideally in a systematic way and synthesize using meta-analysis, they often are not going to be providing all of the answers to all of the questions that various policy-makers around the world or even in various communities in the United States might still have about particular interventions.

**NICE (SLIDE 7)**

Let’s switch gears and look at how NICE performs its charge across the pond in the UK. You have to understand that there the situation is not the same as in the US. New medicines are licensed by the Medicines and Healthcare products Regulatory Agencies, The European Medicines Evaluation Agency, EMEA. Once they’re licensed, NICE commissions independent academics to review the published evidence to select new and existing drugs and interventions to study. NICE will issue guidelines on the cost-effectiveness, as well as clinical effectiveness of various interventions for the National Health Service to implement in England and Wales. From there, Primary Care Trusts, that is, the local health bodies will then implement the guidance, by funding treatment for patients when clinicians recommend it. Now, why am I telling you all of this? Because NICE uses systematic reviews to make its determinations.

**NICE Example: Herceptin (SLIDE 8)**

In real terms however, the NICE system has lead to, in some cases, rationing or delayed access to new anticancer drugs. Here is an example in herceptin, where it was approved in 1998 in the US for advanced breast cancer, approved a couple of years later by the EMEA in 2000. But it wasn’t until two years after that, that the NICE guidance was released for HER2+ advanced breast cancer. And even then, patient access to herceptin was spotty due to variable funding decisions from the UK Primary Care Trusts. So all of this is to put out a caveat that even when using best available evidence that has been systematically reviewed and meta-analyzed, policy-makers’ decisions don’t often quickly or directly translate to changes in health care that patients experience. They don’t always answer all of the questions around a new technology or intervention.

**Who uses/needs systematic reviews? (SLIDE 9)**

Let’s move beyond CMS and NICE and consider how payers might use systematic reviews, and by payers, I mean, states, or groups like Blue Cross Blue Shield, or Kaiser Permanente, or the AMCP with regards to formularies.

**States use systematic reviews (SLIDE 10)**
How do states use systematic reviews? Well, here is a nice example out in Oregon where the Health & Science University there, the Center for Evidence-Based Policy produces what are now called DERPs, Drug Effectiveness Review Project.

Oregon DERP (SLIDE 11)
The Oregon DERP compares efficacy of drugs. Now notice, this is quite different from what I just told you CMS and NICE do. Those organizations don’t typically produce formal comparisons of effect. They simply look at interventions in isolation, usually. In distinction, the Oregon DERP is charged with comparing efficacy of drugs and originally they were charged with looking at the 25 most expensive classes of drugs. These 25 classes accounted for over half of all pharma expenditures by States. And as I’ve said, this was originally a partnership between the State of Oregon and the Oregon Health & Science University, the Evidence-Based Practice Center there. But now, there are several EPCs that continue to develop and update the original 25 systematic reviews that Oregon produced. This project will quote, “make available to governments, businesses, non-profits and citizens the best existing synthesis of global research on the relative effectiveness of similar medications. This research will allow these entities to determine for themselves how best to obtain the most value for their pharmaceutical expenditures.” It’s important to know and understand kinds of evidence synthesis that groups like Oregon DERP are using to produce these types of drug comparisons.

Examples from Oregon DERP (SLIDE 12)
Here’s some examples from the Oregon DERP. Several years ago now, they looked at statins. They concluded on the basis of systematically reviewing all of the available evidence on statin efficacy that all 5 statins (then extent) were similar with regard to Cholesterol lowering but only 1 was generic. Some of them had clinical outcomes. The generic was the one that was chosen for the preferred drug lists in Oregon. In 2005, Triptans were reviewed and in this case, 2 states, Oregon and Washington used this review of Triptans to reach interestingly, different conclusions. Oregon accorded priority to the outcome of patients being pain free at 2 hours, and on that basis, the policymakers chose rizatriptan for coverage. Washington however, chose both rizatriptan and sumatriptan after considering a broader array of clinical endpoints. In 2007, 17 states and 2 non-profits were using DERP results for drug coverage policies for their Medicaid programs. So the take home messages from the DERP experience are that increasingly, state policymakers are relying on DERP assessments to make funding decisions about drug coverage. Remember, DEPR assessments typically involve systematic reviews and meta-analyses of the current best evidence. But even that does not guarantee that each state will have a uniform and consistent decision-making policy. Depending on their own relative values and preferences, not to mention resources, drugs that receive coverage decisions will vary based on the same body of evidence.

BC/BS uses (and produces) systematic reviews (SLIDE 13)
Switch gears and look at how Blue Cross/Blue Shields uses and produces systematic reviews. I’ve inserted and produced this because they have a Technology Evaluation Center in the Chicago group that is an AHRQ Evidence-Based Practice Center that is jointly managed with Kaiser Permanente. In any event, they use systematic reviews by applying 5 criteria to assess whether technology improves health outcomes: Number 1) a technology that’s under consideration must have final approval from the appropriate governmental regulatory bodies (i.e., FDA in the US); Scientific evidence must permit conclusions concerning the effect on health outcomes, that is, not lab test, such as a hematocrit, but an outcome, such as a quality of life or length of life; The technology must improve the net health outcome, more good than harm per patient; The technology must be as beneficial as any established alternative. In other words, it can’t be worse than the current standard of care. It has to be at least as good; and lastly, the
improvement must be attainable outside of investigational settings, i.e., in routine clinical practice settings is efficacy achievable and thereby called effectiveness.

**Kaiser Permanente uses systematic reviews… (SLIDE 14)**

Kaiser uses systematic reviews as well. It’s the nation’s largest HMO. It’s been around for decades. And Kaiser has, for decade been developing interregional guideline using evidence-based methods and teams who are experts in appraising the literature using systematic review methods. You should know that Kaiser invests a lot of money annually to synthesize knowledge about best approaches to health care. All of this again, is to make the point that you should understand systematic reviews and meta-analyses are the determinants of health care policy decision making in this country and globally.

**AMCP uses systematic reviews… (SLIDE 15)**

In terms of formulary decision making, consider the Academy of Managed Care Pharmacy, which is a very influential group that created a format for formulary submissions almost a decade ago. And this format requires drug manufacturers to provide for any product that they want listed on the formulary: detailed product descriptions and discussions of problems; discussions of actual or anticipated off-label uses; data comparing the drug to other medications; reviews (i.e., systematic reviews) and summaries of key published data as well as unpublished data; and information on costs. Unlike some of the other organizations that review comparative effectiveness or just systematic assessments of safety or effectiveness, AMCP format requires costs information as well. As well as a spreadsheet model to predict the plan-specific outcomes.

**AMCP uses systematic reviews… (SLIDE 16)**

The croaks of information that AMCP considers however, is a systematic review. By 2008, health systems covering approximately 150 (million) Americans have adopted this AMCP format or a similar decision-making process including national and regional managed health systems, Pharmacy Benefits Managers, Department of Defense, hospitals and state Medicaid agencies. This dossier format is now viewed as an industry standard. So please remember, systematic reviews are a key component of the AMCP dossier.

**Patients use systematic reviews  (SLIDE 17)**

Now policy-makers and payers aren’t the only ones using systematic reviews. It’s also informing patients and if you were unaware of this, take a look at Consumer Reports. The one for drugs is called Best Buy Drugs.

**Providers use systematic reviews… (SLIDE 18)**

Providers, I’m happy to say are also using systematic reviews and the reliance on these types of evidence syntheses among clinical care providers is increasing with the spread of personal digital assistance and electronic medical records. Practice guidelines are ideally rooted in systematic reviews and increasingly, these guidelines are also implemented with electronic medical records. Furthermore, clinicians know that they can access sources of systematic reviews such as Cochrane online and these sources are increasingly tapped to inform clinical decision making.

**Providers use systematic reviews… (SLIDE 19)**
There is room for growth however in provider uses of systematic reviews. We know this because there remains important geographic variations in the care and costs and outcomes of clinical care. And to date, still a relatively low level of compliance of evidence-based guidelines. So, translating evidence to practice is now the biggest challenge of evidence-based medicine.

What about Pharma use of systematic reviews? (SLIDE 20)

So, let’s switch gears and spend the rest of this module talking about how the pharmaceutical industry uses systematic reviews. You can think of it in terms of categories of use. There are clinical research and development uses, uses in risks management, uses in commercialization of products, as well as life cycle management of products. I’ve got some examples for each of these categories of use to show you. Because I think an example is worth a thousand words. So let’s just roll through these examples.

Case 1. Trial Feasibility: (SLIDE 21)

In the clinical R and D realm, it is nice to be able to determine feasibility of a trial before undertaking the trial. And this is an example of a case where my group was challenged to help a pharma company understand whether a planned, multi-center phase 4 trial could succeed in proving that their drug, P, was superior in any way to the first marketed drug Z. The tool that we used was meta-analysis of all the sponsors’ trials of drug P versus all of the trial results that were available through the freedom of information at the FDA under the summary basis of approval for drug Z. To cut to the bottom line, the answer to the question that was posed to our group initially by the sponsor was “No.” It would not be possible for that phase 4 trial to ever win a head-to-head battle with drug Z.

Drug P or Z vs. Placebo: All Outcomes (SLIDE 22)

Here is the kind of data that we presented to make our argument. These results are based upon the meta-analyses that we preformed using the data that I mentioned. Remember I said that drug P and Z were agents for use in asthma and for those of you familiar with this particular clinical area, you know that the usual outcomes in clinical trials of asthma patients are those that I have shown on the left side of this picture. We have FEV1s, we have morning and evening peak expiratory flow rates, and we have beta agonist rescue. And what we did was synthesize, statistically, the effect size of the treatments, versus placebo in the studies that were available for each. And we displayed those effect sizes with the confidence bounds around them, on the same graph to provide a visual aid to help the sponsors see how close in fact the effect sizes of drug Z and drug P were no matter which outcome we used. Furthermore, because the confidence bounds are pretty well overlapping in all cases, we were able to confidently tell the sponsor that it would be almost impossible for any study of any magnitude to separate these point estimates so that their confidence bounds would not overlap. Therefore, it would not be possible to design a clinical trial where drug Z and drug P had statistically significant differences on any of these efficacy outcomes.

Drug P or Z vs. Placebo: All Outcomes, Adults (SLIDE 23)

They countered by asking us to limit our look to only studies of adults hoping maybe that would lead to a different conclusion. Well it didn’t, as you can see on this slide.

Drug P or Z vs. Placebo for FEV-1 By dose (SLIDE 24)
We were asked to look at only FEV1, but by dose. Perhaps there were different doses of drug Z and drug P which would distinguish themselves. Again, no luck.

**Case 2. Replace a 2nd RCT for sNDA  (SLIDE 25)**

Ok. So I’ve shown you a case example of using meta-analyses to assess trial feasibility. Now, let’s consider a different scenario in clinical R and D in industry. And this is based on a case where our group was asked to assess the efficacy of lansoprazole which is a proton-pump inhibitor for healing gastric ulcer. Lansoprazole had been approved at the FDA for use in healing adeno ulcers but not gastric ulcers and so the sponsor wished to extend the indication and they apparently had a lot of unpublished randomized trials but primarily preformed outside of the country and therefore for various reasons not useful for submission of individual patient data to the FDA. There was one state side randomized trial which would be qualifying for one adequate and well-controlled trial, but there wasn’t a second adequate and well controlled trial that had auditable data. And the hope was that performing a meta-Analysis of all of the other extent trials might replace the need for a second randomized trials for supplemental indications. And to cut to the bottom line, the answer is “yes”, we were able to obtain aggregate data on all of the clinical trials that had been performed with gastric ulcer healing as an outcome when Lansoprazole and H2 receptor antagonist were compared. And so doing were able to provide critical piece of evidence for supplemental NDA that was eventually approved at the FDA.

**PPI in gastric ulcer  (SLIDE 26)**

This project was fascinating in that we in the meta-analyses of trials of proton-bump inhibitor versus H2 receptor antagonist for gastric ulcers healing we expressed our results using risk ratios, as well as risk differences, as well as odds ratios. Now you may remember in module 1, I described the difference in those outcomes expressions as well as the differences in the meta-analytic models that could be used: Bayesian approaches, random effects models, or fixed effects models. In this analysis, we did everything. And you can see the results both for 4 week healing and 8 week healing displayed in this table. The take home message is really that the results vary very little regardless of whether you express them as a risk ratio, risk difference or odds ratio and regardless of which meta-analytic model you use to perform your analyses.

**PPI vs. H2RA Healing at 4 Weeks  (SLIDE 27)**

Here is a graphic display of the studies that were available to us. The comparisons that were available, that is, the PPI versus H2RA comparisons using intent to treat denominators and healing rates. You can see individual studies showed a nice consistency of benefit of PPI versus H2RA in the sense that the direction of effect was pretty much the same in all of the studies. But the magnitude of effect was quite different. And in some of the studies, it did not reach the statistical significance and in others, it did.

**Risk Ratios: PPI versus H2RA Healing at 4 Weeks  (SLIDE 28)**

When we produced a forest plot of these results with the outcome of risk ratio, you can see that some of the results reached statistical significance and that is that the point estimate and confidence bound does not touch the unity line. But in many cases, the confidence bound does cross the unity line suggesting that that treatment effect did not reach statistical significance by itself. However, when the results of all of those studies are pulled in a meta-analysis, the result clearly favors lansoprazole
Case 3. Cumulative meta-analyses for safety monitoring  (SLIDE 29)

Ok, let’s consider a different kind of use of systematic reviews and meta-analyses in industry. And this is a case that demonstrates cumulative meta-analyses for safety monitoring in particular. This is a case of the COX-II inhibitors and the risk of myocardial infarction. I’m sure you are aware that there’s been a link established between that class of drugs and the risk of MI and this has been quite recent and led to the removal from market of a couple of the COX-IIs. And the question that has been posed and not by us but by some authors for a journal article that I will cite for you was, “could the safety problems with COX-IIs have been detected earlier than they were?” The tool that was used to answer the question was a cumulative meta-analysis and that is pulling results of all published and unpublished trials as they finished. The answer was “yes”. The safety problems might well have been detected earlier if cumulative meta-analyses had been performed.

Cumulative Meta-Analysis (post hoc): Vioxx & RR of MI  (SLIDE 30)

The article is from the Lancet a few years ago now, and their conclusion from their meta-analysis was the findings indicate that rofecoxib should have been withdrawn several earlier. Now, why did they say that? Because they looked at studies of Vioxx and looked at the risk of MI in each individual study going back to 1997 and you can see that there’s really no significant risk detected until 19… well looks like in the 2000 the study by the time 44 events had cumulated in 14,000 plus patients had accumulated. At that point, if you’ve been cumulating the results of all the prior studies as each one finished, at that point in time, it became clear that something was going on here, in terms of risk. And I invite you to read the article to get a better sense of it. Now there are legitimate critiques of this article as well, and one you may spot just eyeballing these data are that in the year 2000 we have a jump of accumulated patients from 5,000 up to 13,000. And it’s with that sudden jump, and very likely the addition of a study or two, that for whatever reason, which should be explored further, had a sudden change in direction and magnitude of effect with regard to MI. That would make you take a closer look to see what was going on in those studies.

Cumulative Meta-Analysis (chronologically ordered RCTs)  (SLIDE 31)

Be that as it may, I wanted you to understand that cumulative meta-analysis has a critical role to play in clinical R and D. Cumulative meta-analysis was touched upon in my first module, the Introduction to Systematic Reviews and Meta-Analyses. But I wanted to reiterate here, what it is in case you have forgotten or haven’t seen the first module. So, cumulative meta-analysis allows you to perform a new statistical pooling every time a new trial becomes available. The impact of each study on the pooled estimate is assessed and will reveal a temporal trend. Temporal trend, that’s the key towards superiority, frankly, or inferiority of a treatment or control, or indifference. It’s performed retrospectively; the year when a treatment could have been found to be effective can be identified. That’s the example I just gave you. If however you perform this prospectively, real time, effective treatments may be identified at the earliest possible moment. I think this is the great promise of cumulative meta-analysis in clinical R and D.

Basic Method of Cumulative Meta-Analysis  (SLIDE 32)

Here is a pictorial diagram of what I’m talking about. As studies on the left are finished, they’re pooled so that you have a running and building estimate of effect size.

Intravenous Streptokinase Therapy for Acute MI  (SLIDE 33)

This example may look familiar to you. It’s the example from Tom Chalmers and Joe Lau’s article in New England Journal of Medicine on streptokinase therapy and acute MI. It, on the right, has been analyzed using cumulative meta-
analytic techniques and there you can see, very early on, the point estimates and confidence bounds pulled away from the unity line. We’re talking about early 1970s when it was clear that streptokinase therapy prevents acute MI in a statistically significant way, yet that drug wasn’t approved for that indication until the 1980s. It could have been known and acted upon way earlier and acted upon not just by pharmaceutical sponsors who were spending money on R and D for the drug but also, by patients, by providers, policymakers, payers. Evidence like this would be extremely persuasive, I would think, for any of those constituencies.

**Thrombolytic Therapy for Acute Myocardial Infarction (SLIDE 34)**

Here is another way of looking at the results of cumulative meta-analysis to make the point that what is being recommended in traditional narrative reviews, in textbooks is often lagging years behind what the evidence tells you. So take a look at the cumulated results through the mid 70s in the forest plot on your left, you can see it’s clear that streptokinase prevents MI. Yet, if we look to the right, we see the results of what experts were recommending at the same time point. Basically, they were saying that streptokinase was either experimental or they didn’t mention it at all. That’s in the 70s. Only in the mid to late 80s and then into the 90s did the experts finally start to clue in to what the data could have told them years earlier. If you want to read more about this particular example, check out the Chalmers and Lau companion paper to the New England Journal article I mentioned which was in JAMA in 1992. These two papers have rightly been called seminal publications of the century.

**Case 4: Indirect Comparisons (SLIDE 35)**

Ok, let’s continue on in our examples of pharmaceutical industry using systematic reviews and meta-analyses. Often, it behooves industry, as well as others, to want to compare treatments A and B when there no direct comparisons have yet been performed. Is it possible to do this? The answer is “yes”, using meta-analysis. It’s a way of establishing the relationship between A and B in this case, when all we have established are relationships between A and C and B and C. It’s like an old algebra equation. If you drop out C from both sides, you get the relationship of A and B that is left.

**Indirect comparisons (SLIDE 36)**

Let’s look at some examples. First example I have was from a meta-analysis our group performed of published randomized trials of GPIIb/IIIa inhibitors in patients undergoing PCI. We looked at many things in this project but one of the outcomes we assessed were through incidence of death or non-fatal MI for each of 2 inhibitors that were in our study at 30 day time point.

**Results: 30 day Death/MI = OR 1.4 (advantage abciximab) (normal (SLIDE 37)**

Here is what we saw. 30 day death or MI of 60 mab versus placebo studies, compared with tirofiban versus placebo studies was yielded an odds ratio of about 1.4 suggesting an advantage for 60 mab compared to tirofiban. You can kind of eyeball that and see the treatment effects size for 60 mab is somewhat larger than for tirofiban.

**Indirect comparison validation (SLIDE 38)**

And subsequently this indirect meta-analytic comparison was validated by the publication of a randomized control trial of those two agents in a head-to-head comparison where the odds ratio for 30 day death or MI was 1.3. Our result was pretty close. The advantage again was at 60 mab.
Beyond pair-wise indirect comparisons… (SLIDE 39)

Beyond pair-wise indirect comparisons, it is also possible to compare several treatments to each other at the same time. This is now being called network meta-analysis, also called mixed treatment comparisons or umbrella reviews, particularly by the Cochrane group. So the answer is, is it possible to do this? Yes it is, using network meta-analysis.

Network Meta-analysis: First-Line Antihypertensive Drug Rx and (SLIDE 40)

Here is an example of what it looks like taken from Bruce Psaty’s paper in JAMA a few years ago. This example is looking at many first line antihypertensive drugs that are used in health care in the US. You can see we’ve got virtually every category of drug and the lines connecting those boxed categories show the numbers of studies that were available with that particular comparison. So for instance, for low dose diuretics compared to beta blockers there was one study and the reference is provided. For low dose diuretics compared to calcium channel blockers, there were 8 studies available with that comparison. These authors were able to demonstrate that there is a hierarchy of effect among those classes of agents. And I invite you to take a closer look at the article to see the results.

Case 5. Efficient portfolio management (SLIDE 41)

Lastly, they use systematic reviews and meta-analyses in the pharmaceutical industry is, I think, very well designed for portfolio management. The question that pharmaceutical sponsors in particular should be asking is can I monitor real time, the results of all relevant studies that is randomized as well as non randomized trials as soon as they are available and can I make course corrections if needed based on that quantitative objective synthesis of cumulating results. Using prospective cumulative meta-analysis, the answer is “yes”, you should be doing that.

Planning a Prospective Cumulative Meta-Analysis (SLIDE 42)

There is a way to do it. It’s been published. I refer you to this citation for an example of how it’s happening in the academic setting. Prospective cumulative meta-analyses are happening. And if you wanted to do one, these are the components of the plan that you would have to write up front. You should state your objectives; state the eligibility criteria of the trials and patients within the trials; state the outcomes definitions; any subgroup analyses that you intend to do, and so on.

Cumulative Meta-analyses (SLIDE 43)

Examples of cumulative prospectively planned meta-analyses that have already been published are in the field of cholesterol reduction, Prospective Pravastatin Pooling Project, or the Cholesterol Treatment Trialists’ project. In the area of injury prevention, look at the FICSIT analysis. This was prospective cumulative meta-analysis of cooperative studies of interventions techniques to reduce falls and frailty in elderly patients. Or take a look at the SPORTIF III and V projects where atrial fibrillation antithrombotic prophylaxis strategies were assessed. There are increasingly examples of these types of meta-analyses being published primarily by academic investigators but it’s my contention that the sooner pharmaceutical companies climb on board this approach, the better off everyone will be.

Summary: Applications of Systematic reviews in decision-making (SLIDE 44)
So in closing, let me summarize – applications of systematic reviews in decision making – there are many pros. Systematic reviews and meta-analyses really do provide the best available evidence that one can get your hands on. These are providing evidence-bases that are transparent, comprehensive and current. They do improve the process of decision making. They can improve decisions. And I think the jury is still out as to whether outcomes of patients are improved. But there’s a building consensus of studies that have demonstrated outcomes are improved.

**Summary: Applications of Systematic reviews in decision-making**  (SLIDE 45)

There are some negatives as well to using systematic reviews in decision making. Be aware that the application and interpretation of results may not be consistent across stakeholders or it may not be transparent. Why? Because local resources, values, and preferences differ. There is a potential for misapplication of results to support cost-containment strategies. It is easy to use these kinds of analyses to mislead non-sophisticated audiences and that is to hide behind the shield of evidence-based medicine. So if one’s intentions are not always on the up side, it is easy to subvert systematic reviews. They’re also only as good as the raw material. And unfortunately, most medical practice is still not supported by published literature, it’s ‘grandfathered’. Safety and information from the literature is poor, still. Off-label use information from the literature is variable. And studies of comparative effectiveness are rare. Although, now that we have meta-analytic methods for indirect comparisons, maybe that problem is circumvented. They are indeed labor intensive to do and to update. And they’re frequently only good for “first-order” effects, in other words, if you are working with aggregated data, it’s very difficult to come to any conclusions about subgroups, for instance, or time to event phenomena that are really necessary to study using individual patient data. And often there are no costs or utilization information available. But be that as it may, systematic reviews and meta-analysis are still providing us with the best available evidence.

**Systematic review & Meta-analysis: Applications**  (SLIDE 46)

So, on that note, I will close. Thank you for your attention. If you have any issues with anything I’ve said or a question or comments, please don’t hesitate to get in touch. Following this last slide are a series of slides to give you further reading should you be interested. I’ll scroll through those before the slide module finishes.