Rob: …turn things over to Todd Wagner. Director Wagner, can I turn things over to you?

Todd Wagner: That sounds great. Thank you, Rob. I am delighted to introduce you all. Doug Owens. Doug has been a professor at Stanford for 30 years, and for many of those years, he was also an active VA clinician and researchers. And in 2007, he received the Under Secretary’s Award for Outstanding Achievement in Health Services Research. He’s been a leader in evidence-based medicine and health policy. He has published cost-effectiveness analysis for HIV, cardiovascular disease, hepatitis C, and most recently, opiate use disorders. He is the current Chair of the Department of Health Policy at Stanford, and he also chairs the U.S. Preventive Services Task Force. He was one of 18 health policy experts who was tapped to serve on the second panel of cost-effectiveness and health and medicine. And today’s talk is entitled Recommendations for the Conduct of Cost-Effectiveness Analysis from that panel. And it’s a great pleasure to introduce you all to Doug and turn it over to Doug.

Doug Owens: Todd, thank you so very much. I’m delighted to be here. I appreciate the opportunity. We do really want to hear from you and questions, so let me just second Rob’s suggestion to use the Q&A. Would love to take questions. We can probably get to many of those as we go. So but thank you very much for that very kind introduction. So I’m going to talk today about the recommendations in the second panel of cost-effectiveness in health and medicine and give a few examples as we go and try to highlight what those of us on the committee felt were some of the important recommendations that came out of this group.   
  
So let me just start, to make sure we’re all on the same page with thinking about, talk about what cost-effectiveness analysis it. So the goal of a cost-effectiveness analysis is to assess the value of health care interventions, as I’m sure you know. And by value we mean do the benefits justify the costs. And cost-effectiveness is used across a whole variety of topics, of course. Some of the ones that we worked on, as Todd mentioned, is HIV screening cost-effective, or implantable defibrillators cost-effective? Is care coordination after admission for heart failure cost-effective? So a very important tool that you can use to address many questions. Let me just page down here.   
  
So cost-effectiveness compares two or more strategies. It’s always comparative. So for example, screening to no screening, and you assess the incremental benefit and the incremental cost of one strategy versus another. And the output of a cost-effectiveness analysis is the incremental cost-effectiveness ratio, and you see it there on the slide. So for example, for a screening, probably would be the cost with screening minus the cost without screening, and the benefits with screening minus the benefits without screening. When you’re accounting for value, let’s think about the universe of outcomes that you could have.   
  
So in this 2 x 2 table, essentially, we have change in costs on the y-axis, if you will, where costs go up as you go up and go down below the zero mark. Gains in effectiveness are on essentially the x-axis where moving to the right past the zero is a positive gain and to the left is a negative gain. And that’s health benefit measured some way, maybe lives saved or cases adverted or something. And so if we look at these four quadrants, there’s four possibilities when you conduct a test or a strategy or provide a treatment, et cetera. You could spend more and get more. In other words, it cost more money, but you get more benefit. That’s the right, top quadrant. Below that, you could spend less and get more. That, of course, would be a great quadrant to be in. It’s unusual. And then on the other side of the 2 x 2 table, at the top left, you can spend more and get less. Something you would never want to do. And then you might spend less and get less, and that’s less common but does sometimes happen.   
  
So let’s think about this right, top quadrant. There we have to ask the question, is it worth it? We’re spending more, and we’re getting more health benefit. But how much do we spend for the health benefit we obtain? And that’s where cost-effectiveness analysis can be a useful tool. So if you look at this this quadrant more closely, when we have change in costs on the y-axis, the gain in health benefit from the x-axis. And here, if you go from the top left down to the right lower, you go from something that’s less cost-effective to more cost-effective. Why? If there’s a large gain in health benefit but only a small increase in costs, then that’s more cost-effective. Conversely, of course, if there is a small gain in health benefit but a big gain in costs, then that’s less cost-effective.   
  
So this is a question I’m not sure, Todd and Rob, if we’re doing anything interactively, but just think about this. I was wondering how many of you’ve done a cost-effectiveness analysis. Oh, there it is right there. And have you read one? And then have you helped conduct a cost-effectiveness analysis? So we’ll give you a minute to do that. And then that’ll hep us think about how much experience everyone has with some of these concepts.

Rob: Thank you, Dr. Owens. I did forget to discuss this before the webinar, but, yes, I made a poll for this question, a poll for the next question on the same slide. And then a poll for the question later on.

Doug Owens: Thank you very much, Rob.

Rob: You’re welcome. It looks like things have slowed down quite a bit. So I’m going to go ahead and close the poll and share the results out, and then I’ll read them to you. What I see here is that 79% answered yes, and only 19% answered no. So would you like me to run the second poll now?

Doug Owens: Yeah, please. Yeah, that’d be great.

Rob: Okay, here we go. The question being have you helped conduct a cost-effectiveness analysis. Question. Answer options, yes or no. And as you might expect, Dr. Owens, things are happening quickly. People are making their choices and need to leave it open a few more seconds. Yeah, things have slowed down, so I’m going to go ahead and close the poll. Share the results and read them to you; 42% answered yes and 56% answered no. So pretty consistent across the board there. That’s it, thank you.

Doug Owens: Great. Thank you, Rob. Well, great. So most of you have read a cost-effectiveness analysis, and about half of you have actually conducted one. And so we’ll, I hope, have important messages for both of those groups. So let me jump into the recommendations.   
  
So the original panel on cost-effectiveness and health and medicine was way back in 1996. For those of you who work in the field, you may know it as “The Gold Book”. And it made recommendations about how you should conduct cost-effectiveness analysis. It was very influential. And there was a recommendation for a reference case, a case that all cost-effectiveness analyses would do in a similar way. And the idea behind that was then you could compare one cost-effectiveness analysis results to result from a different analysis. There was an emphasis on assessing cost-effectiveness in terms of cost; per quality adjusted life years, or QALYs; we’ll talk about those. And it became, I think, a standard that many people use—or standard reference that many people used in terms of how to do cost-effectiveness analysis.   
  
So the goal the second panel was to update the recommendations for the conduct of cost-effectiveness analysis and to facilitate cost-effectiveness analyses that are fair and transparent, promote comparability, and use state-of-the-art methods. There’d been a—it was quite a long time between the first and the second, and so there was a fair amount of new methodological work and a lot more experience with cost-effectiveness analysis when the first panel made their recommendations. So this is the folks that were on the panel. It was led by Peter Neumann and Gillian Sanders Schmidler and a group of people who had a lot of experience with cost-effectiveness analysis and related issues. That’s the folks on the panel, I’m sure delivering some important question. It was a great group, and we met over a quite a long time to make our way through all the different topics that we wanted to talk about.   
  
So let me give you an overview of key recommendations, and this is the second book. This is the—so two main products that came out of this. One is the book. The second edition there you see on the right-hand side. The other, if you want a short summary, this *JAMA* paper, I think, does a nice job of summarizing some of the main results of the panel’s deliberations. There’s the table of contents of the book, and I’ll just note that there’s four new chapters. There’s a new chapter on reference cases. I don’t talk about that. There’s a new chapter on modeling, giving recommendations about modeling for cost-effectiveness analysis. And one of the reasons for that is it’s almost all cost-effectiveness analyses includes at least some degree of modeling. There was a new chapter on evidence synthesis that covered some of the more recent methodological advances and how to synthesize evidence. Then importantly, there was a new chapter on ethical considerations in interpreting and conducting cost-effectiveness analyses. I’m not going to spend a lot of time on that, but for those of you who have an interest, it’s an important chapter; I would recommend it to.   
  
So here’s an overview of what I’ll talk about today. So I’m going to first talk about reference cases and impact inventory. Then we’ll talk a little about costs. Then valuing health outcomes. Then some on modeling. Uncertainty analysis or sensitivity analysis. And reporting of cost-effectiveness analyses. So the reference case and the impact inventory, I think this is one of the most important set of recommendations to come out of the new book. The original panel’s recommendation was you have a reference case that used what the panel called the societal perspective. That reference case was to consider all parties that were affected, to address specific decision context as needed. The societal perspective means you count all costs, all benefits, no matter to whom they occur. And really if you did a full societal perspective analysis, you would do it across all sectors, so not just health but other sectors that an intervention might influence, like criminal justice or education, et cetera.   
  
So after the original panel, many, many cost-effectiveness analyses were published; very few of them actually used the societal perspective. It’s challenging to do. And even when people stated—and I would say I’m certainly guilty of this—that we use the societal perspective, there are important elements that were omitted. And so decision-makers are using cost-effectiveness often take a more focused perspective, and most of the time when we’re doing health care, it's the health care sector cost and benefits that are the most salient to the decision-makers. But we’ll talk a bit more about that.   
  
So the second panel’s considerations, there was of course this appeal of the societal perspective because it’s comprehensive. But a question we ask is, is there really a single societal perspective? We also wanted to make sure that if someone followed these recommendations it would promote quality of the analyses and comparability between analyses so that you can make sense of one cost-effectiveness analysis compared to another. And so we had a recommendation for reference cases that was somewhat different than the first panel, and this was probably one of the main new—or the main changes from the first panel.   
  
We recommended that studies represent a reference case analysis based on a health sector perspective and a reference case based on the societal perspective, that is you would have two reference cases. And the health sector perspective, I’ll talk about what goes in that and a societal perspective. We also recommend you measure health effects of QALYs, and, again, this was intended to enhance consistency and comparability. The health sector perspective, we recommended that you summarize your results in an incremental cost-effectiveness ratio. Could use net monetary benefit or net health benefit if you wanted to. And then a range of cost-effectiveness thresholds should be considered.   
  
So by cost-effectiveness threshold, I mean how much, what is the willingness to pay for a QALY? There’s no agreement about that in the United States, as I’m sure you know, and so looking at a range of cost-effectiveness thresholds make sense so that different decision-makers can bring to the analysis an interpretation analysis, their own views about how much they’re willing to pay for QALY. The second big recommendation that we make was to do what we called an impact inventory for every analysis, and I’ll show you an example what the impact inventory is. We recommended you include an impact inventory table which lists the health and the non-health impacts of the intervention.   
  
The idea behind that is that it would ensure that all the consequences including outside the formal health care sector are considered. It provides a framework for organizing and thinking about and presenting various types of consequences. And I think very importantly, it enables a reader of an analysis to quickly understand what’s included in the analysis and what’s not included in the analysis, to help them interpret the analysis itself. So here’s what we mean by an impact inventory, and I’m going to go through this in some detail, but you see first the columns. So here we have the sector, the health care sector, then the formal health care sector. Then the informal health care sector, which is things like patient-time costs, unpaid caregiver time costs. Then non-health care sectors.   
  
So these are examples of things you might put in the non-health care sectors, so productivity. That would be labor market earnings loss or cost of unpaid lost productivity due to illness. Consumption, which is future consumption unrelated to health. Social services, that may be the cost of social services that are part of an intervention. Legal or criminal justice. So some interventions—and I’ll give you an example in a moment—some health interventions may reduce crime. And so you might want to include that. Education sector, housing sector, and environment. I think you can see from this list of sectors why most people, in point of fact, don’t actually do a full societal perspective because it’s challenging, both analytically and from a standpoint of data.   
  
So these are the things that we just talked about. This is the types of impacts. This is not meant to be a completely comprehensive list, but let’s focus now for a little bit on the formal health care sector. So longevity effects, so does an intervention make someone live little longer or shorter—hopefully not. Health-related quality of life, other health effects, adverse events, transmission. Then medical costs would be cost paid by third-party payers, paid by patients, future related medical costs, and future unrelated medical costs. And so it’s medical cost but unrelated to the intervention. So for example, if I’m looking at HIV screening, when I do a long-term perspective in my analysis, I’m going to count other health care costs, I’m going to include them, that aren’t related to HIV screening or to the treatment of HIV.   
  
The reason for that is that if you have an intervention that makes people live longer, they will incur additional health care costs that aren’t related to the intervention. It’s the health care that we all get. And so you want to consider that as one of the costs that you put in your analysis. So this column is about the types of impacts. So this is a checklist to show what you included and what you didn’t, and you can get a sense here for what the health care sector reference case is and the societal reference case. So the two columns are for the two different reference cases, and so the health care sector reference case as you can see has health outcomes and medical costs. That’s all it has. And for many topics, those are really primarily the major main things to the analysis.   
  
The societal perspective, in contrast, has all of those outcomes, health outcomes, medical costs, but then has informal health care sector costs. It has the cost and benefits, consequences from the other non-health care sectors. And so the idea behind this checklist is that you can check off what you’ve included, what you have not included, and when a reader looks it, they can immediately see, is it a health care sector perspective? If it’s a societal perspective, which sectors did you include? Which sectors did you leave out? So these are just notes about—you can put the sources of evidence to give readers an easy way see where some of the evidence came from.   
  
So the sections of the impact inventory divide consequences across the formal health care sector, as I’ve said, the informal health care sector, and then the non-health care sectors that you might consider. So the checkbox, again, indicates whether you’ve done it. And so you might consider that, let us say, an analysis has longevity effects and health-related quality of life effects and other effects, you would check those off for both health care sector perspective and societal. Here for the informal health care sector, those would go into a societal perspective but not the formal health care sector perspective. And then the other sorts of impacts that we talked about, going through additional sectors.   
  
So let’s do one more question. Rob, if you won’t mind. And so the question is, for which analysis would the societal perspective be most important? Cost-effectiveness of treatment for opioid use disorder, or the cost-effectiveness of use of implantable defibrillator? That’s a device you put in that can prevent sudden cardiac death. So let’s do that and see where people come out on that.

Rob: Sorry, I’m having a little bit of difficulty with this one.

Doug Owens: Okay.

Rob: There we go. Now it’s open.

Doug Owens: Alright so perfect. Question is, which one would the societal perspective be most important?

Rob: Answers are streaming in quite quickly. It’s looks like things have already slowed down, so I’m going to go ahead and close the poll. Issuing out the results. And you’ll see that 89% answered A) Cost effectiveness of treatment for opioid use disorder, and only 9% answered B) Cost effectiveness of use of implantable defibrillators to prevent sudden cardiac death. Back to you, Sir.

Doug Owens: Great, Rob. Thanks very much. Okay, so most of you felt, the vast majority of you felt like opioid use disorder. And use of societal perspective for implantable defibrillators might be useful, but why would it be potentially more of an issue? And for treatment of opioid use disorder, let me just give you an example. This is work that one of our form PhD students did along with many of us at the VA and colleagues at Stanford, and it was on the cost-effectiveness of treatments for opioid use disorder. And this is just a little snippet from the methods section, and if you look in this red boxes, it said we used a health care sector perspective for costs and QALYs, as well as a limited societal perspective that additionally included criminal justice costs and discounted all values to present at 3% annually. So that’s our method section where we say which perspective, which reference cases we’re going to include.   
  
And so this is the impact inventory that we included within our analysis. And so if you look at the top part, you can see that for the formal health care sector, we included the longevity, health-related quality of life costs, as you would imagine. So those were applicable both to the health care sector perspective reference case and the societal reference case. And then for the limited—and you might say it’s very limited—societal perspective, if you look down the column, you’ll see really the only thing that we included in terms of other sectors was on cost of crimes related to the intervention or cost of—reduction in crime potentially from the intervention.   
  
Let me just show you, so, again, the point is for readers to be able to tell what we put in, what did we not put in. And let me just show you some results. Let’s look at the first panel on the left side. And so the details of this are not important, I just want to make a couple of points. So on the left panel, these are a bunch of different treatments for opioid use disorder. On the x-axis, we have costs; and on the y-axis, we have QALYs. And so those of you have done or familiar with cost-effectiveness, this is the cost-effectiveness frontier, the line that’s shown. I just want to make a point. If you see the open triangle that’s circled in red, that is essentially the do-nothing strategy. And all of these treatments in panel A, many of them are cost-effective, very cost-effective, but you can see that they’re all—they’re better in terms of QALYs. But they also cost more. So many opioid use disorder treatments from the health care sector perspective are cost-effective.   
  
But now if you look at panel B, this includes a health sector and criminal justice cost. And now take a look at the open triangle, the red, circled triangle. It’s the same; it’s do nothing. And now what you see is that when we include the savings associated from the criminal justice system, most of the strategies are now cost saving, not just cost effective. They are more effective, and they actually reduce costs. And so we would suggest that it’s important to consider these. Now health care sector decision-maker isn’t going to see those savings, but from the broader more societal perspective, we would. The society at large would. And so this is an example. So for those of you who answered that the societal perspective would be helpful here, exactly so. You see quite a difference in the results that you get when you include other sectors. And so I just wanted to show that as a potential example, both of how we hope people might use an impact inventory and why for some analyses the two reference cases will give you different answers. And that may be an important insight from the analysis.   
  
So let me switch gears now and talk about quantifying and valued non-health components in the impact inventory. And so our recommendations say analysts should attempt to quantifying value non-health consequences, unless those consequences are likely to have a negligible effect on the analysis. And I mean, I’ll talk about measures used, and we suggested that analysts present items listed in them impact inventory in the form to disaggregated consequences across different sectors. So in other words, break it out so people can understand and see what the different outcomes and how they’re being affected by an intervention. And we also suggested people use one or more summary measures such as incremental cost effectiveness ratio, net monetary benefit or net health benefit that includes some.   
  
The issue is that when you calculate an incremental cost effectiveness ratio, depending on intervention and the complexity and the perspective you’re using, all the costs and benefits might not get wrapped up in that incremental cost effectiveness ratio. And the impact inventory can help you identify consequences. And then note whether or not they are included in the analysis.   
  
Alright, let’s talk for a moment about valuing costs. So again, our suggestion for the two different reference cases, the health care sector reference case includes medical costs, current and future; related and unrelated. So you’ll sometimes see that people put only the costs associated with medical intervention, and we recommend both for the reasons that I just mentioned to you previously. This would include costs that are associated, that are borne by patients, paid for out-of-pocket by patients, and of course by third-party payers. Those are the main costs associated with the health care sector reference case.   
  
The societal reference case would also include time costs of patients in seeking and receiving care, time costs of informal unpaid caregivers. I’m sure you can imagine there would be some topics were that might be very important, like care of dementia where much of the care is sometimes given by family members. They are not paid, but those are certainly costs, at least for them. Transportation costs. And then what’s not included that often but effects on future productivity and consumption, and other costs and effects outside the health care sector. In the societal perspective, you wouldn’t potentially include effects or consequences such as loss of income if people aren’t able to work. Or if they’re ability to work is restored by an intervention, those gains and productivity. So that’s the idea behind the broader set of societal outcomes and consequences.   
  
So now let’s talk about valuing health outcomes. So we recommended that health consequences should be aggregated in a single measure using QALYs. That’s the same recommendations as the first panel made. There’s been a debate, for those you who follow this, about whether when you assess quality of life, whether you should assess quality of life from patients or from members of the community. And the first panel came down on that by suggesting that we use community preferences because cost-effectiveness analysis is being used, in theory, to allocate societal resources. And so society’s preferences, the community members’ preference should be included. What I would say to you is that’s sometime not available, and you sometimes might wonder whether community preference adequately represents or people understand the outcomes associate with particular clinical conditions, et cetera.   
  
And so what we do if we really have both community preference and patient-based preferences, we often use both and see if it makes a difference. Sometimes it won’t make any difference, but if it does, that’s something that’s notable. We recommended the use of generic preference-based measures, things like EQ-5D, Health Utilities Index. We do not recommend a specific one. And again, you may have other measures of utility, such as standard gambles, et cetera. And again, one of our approaches is to simply see if you have different measurements and from different instruments, if that makes a difference in terms of the answer you get. And we would note that for transparency if it does.   
  
So the potential limitations of generic preference-based measures, so they may not be sensitive in terms of specific conditions, et cetera. So again, situations in which you may think about other kinds of instruments, situations with the generic preference-based measures are known to lack responsiveness to a particular condition. There are important spillovers from the interventions such as effect on the health of caregivers or other members of the family. Or it’s difficult for those who have not experienced the health state to understand what it means to provide meaningful scores. So those are the circumstances I said where you might consider supplementing with other kinds of instruments that measure quality of life.   
  
So how do you calculate QALYs? I’m just going to give you a simple example. And the idea behind calculating QALYs is that you have some quality of life here from a scale from 0 to 1. That’s on the y-axis. And then on the x-axis is we have time. And so for example for this person, first, their quality of life is perfect is 1.0 in the greenish blue, and they stay like that for two years. Then they have a 1-1/2 years with a quality of life of 0.7 in about a year. With quality of life, it’s much reduced, 0.3, and then they get better. And they have 2-1/2 years with a quality of life of 0.9. So the life years, you would just add those up, and it’s seven years. But the QALYs, you multiply the quality of life rating, the utility, require life assessment, times the period of time you spend with that quality of life. So the calculation is shown on the bottom, so it’s two years with quality of life of 1 plus 1.5 quality of life 0.7, et cetera, or 5.6 QALY adjusted life years.   
  
The QALY has a couple of very important characteristics. One is that it accounts for both mortality and morbidity, so it gives you a single measure. And the second reasons that it’s important to use QALYs is that it allows you to compare across analyses. So if you have the effective intervention measuring qualities, you can compare cost-effectiveness of HIV screening to the cost-effectiveness of treatment for cancer to the cost-effectiveness of coronary bypass graph surgery. So it provides a common metric that enables you to compare one intervention to another. So when you do a mathematical model, it estimates QALYs. It does something like this. So here again on the y-axis, we have quality of life. On the x-axis, we have years of life. And so this lines represents someone’s quality life over time. And the QALYs are the area under this curve. And you can see that they go along, then they have a big drop. And then they get better, and then eventually they die.   
  
And intervention then can change both someone’s quality of life and how long they live. And so the red line shows the quality of life and length of life with treatment, and the QALYs gained is the area between these curves. And so when you’re doing a cost-effectiveness analysis and your estimating QALYs, that’s what you’re trying to estimate is this difference in length and quality of life. So that’s all I was going to say about valuing health outcomes.   
  
Now a bit on our recommendations on conducting and implementing CEAs, we recommended the use of a protocol. Now you’re probably used to hearing something like that for randomized-controlled trials. I was just on a call about a systematic review where they registered the protocols. I think that’s more familiar, but really it’s unusual for people to register a protocol for a cost-effectiveness analysis. We suggested it so that people can see what you intended to do, and then see how what you did compared to what you said you were going to do. And so the idea behind the listing of the protocol, you would include the objectives, the perspective, the interventions, the comparators, population, time horizon, sources of data and key assumptions.   
  
Now for those of you who’ve done cost-effectiveness analysis, you know that this often changes as you go along, and you encounter problems with data or new information. So a protocol could be updated, as you know, but it still would allow people more transparency about the intention. I’d have to say I don’t think this has been widely used, but it’s something we felt might be useful in terms of transparency and making sure that a cost-effectiveness analysis abreast what the investigators really set out to do.   
  
So for the vast majority of cost-effectiveness analyses, you’re going to need to do modeling. And the reason is that the cost-effectiveness analysis should include all costs and all benefits caused by the intervention no matter when they occur. And for most of the analyses that we do, that extends for very long period of time. So screening for HIV, for example, you’re screening somebody, but then you treat them for life. And so the time horizon on an HIV screening analysis would be a lifetime. Treating somebody for opioid use disorder, they’re going to be on treatment for many, many years potentially, and so the time horizon would be years. It’s very uncommon that you have empiric data that extends over the entire time horizon that you need to use for a cost-effectiveness analysis; therefore, for most cost-effective analyses, you will need to use a decision model. And here are the reasons.   
  
One of the main ones is you have to go behind the time horizon of clinical trials. You also sometimes have to extrapolate from intermediate or surrogate outcomes to long-term outcomes. You may want to assess the cost-effectiveness and intervention and population subgroups that were not observed. You might want to look at long-term outcomes associated with diagnostic test strategies. And then you, of course, may want to be comparing strategies that have never been studied empirically in head-to-head comparison. That’s a very common problem. So for all these reasons, the vast majority of cost-effectiveness analyses, we’re going to need modeling, and that’s one of the reasons we included a chapter in this book.   
  
So let me just illustrate the time horizon issue, and that is that the—this shows the incremental cost-effectiveness ratio over time. And the idea is that different time horizons, you get a very different cost-effectiveness ratio. I’m not going to go back to that now, but that’s the main point. And if your time horizon is short, you may either overestimate or underestimate the cost-effectiveness ratio. So some of our key modeling recommendations for the initial conceptualization of the model should be independent of the data identification phase. That is to say you should build a model that encompasses the important considerations, not just a model based on what you have data for. The documentation and justification of structural assumption should be provided, and validation of the model should occur throughout the conduct of a CEA. For those of you who do this, you’ll know that the validation may be one of the most intensive areas of effort in building a decision model.   
  
Let me now talk about uncertainty analysis. Many of you would know this is sensitivity analysis, and I think back in the day, we used to do one-way sensitivity analyses and two-way sensitivity analyses. The idea is that you want to understand how important uncertainty is in your analysis. And so the propagation of \_\_\_\_\_ [00:39:55] informs the decision uncertainty. The field has progresses, as most of you probably know now, to doing much more sophisticated uncertainty analyses, an idea being that you should look at uncertainty over all the parameters that you have in a model simultaneously, in addition to doing that kind of traditional sensitivity analyses that we would often do. To do that, you sometimes have to consider correlations among parameters, and this ends up with what we call probabilistic sensitivity analysis where you get an understanding of how all the uncertainty in the model affects the conclusions that you’re going to make. And you’ll often see this in a reported paper as probabilistic sensitivity analysis, 80% of the time such and such strategy was cost-effective. Or something like that.   
  
Finally, we talked about structural uncertainties, and that has to do with how your model is structured. And again for those who’ve done this, there are often many choices that you have to make in terms of how to structure a model, what to model, what to include, what not to include. And it’s important when you can do that, to try to explore the implications of the assumptions that you built into the structure. And so structural uncertainty should be explored if possible. So in terms of structural certainty, one question of course is how to model the effects of intervention beyond the time horizon of your data, the trials. Another would be how different states of health and pathways of care are characterized in a model. Another would be how disease progression is modeled over time or extrapolated. And then judgments about the relativist and appropriateness of different sources of evidence.   
  
As Todd mentioned, I was on the United States Preventive Services Task Force, which creates national prevention guidelines. On some of our important cancer screening topics, we commissioned models, and we often have what we call collaborative model where there are two or three or four models. And the investigators work together, but the models usually have a different structure, some different assumptions, et cetera. And so that’s one approach to understanding structural uncertainty. You have essentially different models that are built in different ways, and that can often provide a lot of confidence if they agree about the results of an analysis.   
  
Sensitivity analysis. Examining the model outputs. As we talked about, one-way multi-way sensitivity analyses and threshold analyses are standard. And again, they can be used as a measure of understanding the importance of the uncertainty and the importance of heterogeneity. You may have situations in which the effects of a treatment or the cost of treatment center are varied, and you can examine that heterogeneity with sensitivity analyses.   
  
So let me now turn to reporting of cost-effectiveness analyses, and we had a few recommendations. Again, primarily meant to improve transparency completeness and comparability. Those of you, 80% of you’ve read a cost-effectiveness analysis, and you know in doing that that sometimes it is challenging to understand exactly what people did, what assumptions were built in, how exactly data was used, et cetera. So the idea was to try to improve upon that situation. So the key is that we had were to use a structured abstract; the impact inventory, which we’ve talked about; being explicit about intermediate outcomes; and reporting disaggregated results.   
  
So the structured abstract format, these might not be relevant to every analysis, but these are the main categories we thought that an investigator should consider reporting. I won’t read them all; you can see them there, but these cover the main design features of a cost-effectiveness analysis. So elements to include in the standard abstract, so standard abstract format, the object, the methods with the items you see there. The results of the base case analysis, the results of uncertainty analysis and limitations. And then conclusions. This is reporting checklist. You’ve seen these kinds of checklists for randomized trials and systematic reviews and meta-analyses, et cetera. This was just one that we did, not meant to be the only one that people might use, but it was just to give people help in thinking about what are the important elements to include in their report of a cost-effectiveness analysis. And these are some of the other factors in terms of the results and discussion.   
  
So in summary, we continue to emphasize transparency. Enough details should be allowed to provide for replication, so the elements that we thought would help that would be the structured abstract, reporting checklist, impact inventory, the intermediate outcomes and disaggregated results, and a technical appendix. I’d say those of you that haven’t done it, it’s really standard I think in most cases to include a technical appendix. For example, the cost-effectiveness analysis that we showed you of opioid use disorder has a technical appendix that goes into enormous detail about the assumptions data, structure, et cetera. That’s pretty much standard fare these days, and the hope is that if somebody really wanted to replicate your study, there would be enough transparency and information available to them that they could come close at least to doing that.   
  
Guidance on conflict of interest. Of course, we think as with all research, conflict of interest should be transparently reported. I think some of the challenges and issues going forward are whether you share models and data, or whether that’s required. One of the things that we talked about is whether there should be an expectation that people would make their model available to people to look at or to use. We’ve done that in our research on some occasions. Honestly, I don’t think people have ever really used our models that much, but there’s also issues of intellectual property, et cetera, in these. So there’s no real recommendation from us on this, but, again, areas that I think that the field has continue to look at.   
  
So valuing health outcomes. Just to summarize, health consequences should be aggregated into QALYs, community preferences for the reference case, but we didn’t recommend a particular measure as I mentioned. So I’m going to wrap up here, and if there are people, if there are any questions, of course I’d be happy to take them. Two references cases instead of one, a health care sector and societal. The use of the impact inventory. And then there are new recommendations on modeling, ethical considerations and reporting.   
  
And again, here’s the *JAMA* paper as a short summary that I think would be a more accessible way than diving into the entire book, but the book is available for those of you who want to go deeper into the topic. And with that, I’m going to stop here, and I think you all. And, Todd, if there were any questions or anything we should address, please let me know.

Todd Wagner: That sounds great. Thank you, Doug. That was a great presentation. I appreciate your input. We’re going to start with one question that gets back to the costs that you’re using in these models. Could you comment on how medical costs are calculated in these analyses? My understanding from the economic literature is that included cost should represent the true marginal cost production for the care delivered, since any excess payment is just a cash transfer. How are medical costs typically estimated in cost-effectiveness analysis given how much reimbursement rates vary across payers?

Doug Owens: Great question and be loathed to answer that question with Todd on the line because he’s the one I always call to ask how we should estimate cost. But, Todd, so I’ll hope you’ll jump in here. Yes, you’re trying to estimate economic costs in practice. That’s rarely possible to do. So I’ll just tell you, to the person who asked, what’s typically done. It’s often—so you surely have to make a distinction between charges and costs. What the charge for a service or item or device or a drug has often nothing to do with how much it actually costs.   
  
So we do not use charges, per se, but we do sometimes use, for example, for people which it’s relevant, what does Medicare pay for something because that is a governmental or societal cost of something. So we would often use Medicare payment, depending. We would sometimes use third-party payments, or sometimes you actually try to do micro costing and build up from the utilization that occurs in the provision of some service to what the cost would be. That’s very labor-intensive. Sometimes it’s hard to do. So it’s really a variety of approaches that people use.   
  
I would say it’s an area that can be challenging. Drug costs are challenging. Again, I turn to Todd to ask about how you do that, and there are different approaches to it. And costs are highly variable, so one of the things that I do try to mention when I talk to people about it is there’s not a single cost because for most things, the costs depend in some way on the context, on the system that you’re in, et cetera. And so there’s enormous variability. We try to account for that when we do an analysis through sensitivity analyses or uncertainty analysis. Todd, please jump in here and add what you’d like to. You’re actually the expert on this, not me.

Todd Wagner: Thanks, Doug. I think you hit on a lot of the key points which is we don’t really know the true marginal cost, and so the data that we have or the methods that we’re going to use, we’re all trying to estimate that. So you’re going to get some sort of mean estimate or central tendency that gives you information on that, and then you’re going to vary that off of sensitivity analysis to make sure you’re feeling pretty confident that small variations in that aren’t going to drastically change your analysis.   
  
There is—for some of you, if you’re working with VA data, you’re probably good to see these data sets that we have, like the managerial cost accounting data sets that are really trying to estimate the cost of producing care. And you’ll notice that they vary considerably across facilities, and some of those relate to just input prices vary. So you have to be a little bit careful that wages here in Palo Alto are very different than wages in Kansas City, and you need to take that into account. But even still, there’s different decisions that are made here Palo Alto than Kansas City that could affect that on building space and staffing and so forth. So again, we’re still trying to get that estimate, and we often make assumptions that make our life much easier. But great point, Doug.

Doug Owens: Thanks very much, Todd.

Todd Wagner: Let’s see, there’s another question. Thank you for the great presentation. Can safety be measured in a cost-benefit analysis, and how is it determined?

Doug Owens: Safety and how—okay.

Todd Wagner: And they us an ADRs of a drug, so a drug related—I think that’s a drug effect.

Doug Owens: Yep, yep. Adverse drug reactions, yep. So well what we include in a cost-effectiveness analysis, what you should include, there’s both medical benefits and medical harms. And so for example, if there are significant harms associate with a therapy, you would include that, both. And there would be two elements of that. One is the effect, the health outcomes. Obviously could be fatal effects if you would count changes in mortality. That might be quality of life effects, let’s say if you have some adverse reaction. And so if they seem like to the analyst that those are significant, then you would include those as harms. You would also include the cost of those harms. So let’s say it’s a surgical procedure, and there’s leg complications. That would be a harm, and it would also entail a cost. Or it could be a drug that causes—for example, it could be a chemotherapeutic agent that, in fact, causes subsequent cancers in the long-term. So you would try to estimate all the harms as well as the benefits and capture both the effect on length and quality of life and any effects, if there are any, on costs.

Todd Wagner: Great. And question for you, Doug, to riff on that, those would be known harms. In our current debate about vaccines, would you ever include perceived harms?

Doug Owens: Well, there are two ways to think about that, Todd. Really interesting question. One would be if there are quality of life effects. Sometimes there are psychological effects of an intervention. You would include those potentially. You could, if you have uncertainty about harms, you could include harms that you think could occur but you don’t know that occurs or sensitivity analysis to see if they would change the main conclusions of an analysis. So you could do scenario analyses or hypothetical analyses where you include harms that you think could happen, but you don’t know. And then try to understand the implications of conclusion.   
  
I would distinguish that from including that people say are harms that aren’t harms. That I would not do in an analysis. The [garbled audio] be based on your best medical evidence and with a potential hypothetical if there’s some kind of harm that you think is possible, but you don’t have enough evidence for. You could assess how important it might be.

Todd Wagner: Great, one more question. This might be the last question depending on timing. So if you go back to thinking about how you measure outcomes and QALYs, increasingly we are seeing people who are measuring outcomes using a disease-specific measure, like a disease-specific quality of life scale. And then they develop a crosswalk that links that to an indirect utility measure. Let us just say it’s the EQ-5D. This method introduces two sets of possible errors. One is the error in the EQ-5D itself, and then the second one is in this crosswalk. Did the panel take a position on this?

Doug Owens: Well, I don’t recall specifically that topic. There’s an entire chapter on value, and it may well be covered to some degree. But for the person who asked, it does introduce two sets of potential errors. And I would just say first we look for direct quality of life evidence if it’s available, but it’s often not. And so the question is premised on that. And a disease specific sometimes might be more sensitive to or responsive to conditions, so there may be reasons to use one. I would kind of fall back on the sensitivity analysis and uncertainty analysis. If differences in the quality of life estimates are important in a sensitivity analysis if it changes materially, cost-effectiveness or decision you’d make, then I’d be very transparent about that.   
  
And if you’re—the more indirect your quality of life assessments are, the more uncertainty you would have about them. We do this always pretty much to—even if we have direct evidence on quality of life impacts because even with direct evidence, they’re measured with uncertainty, and none of the instruments are perfect. They measure different things, and so our standard approach is to do careful sensitivity analyses on the quality of life estimates and see if they matter. If they do, we report them. We report that.   
  
And depending on—and then mention as a limitation if you think there are issues with the way the quality of life information is obtained or the indirectness of it, then I would call that out for the reads to understand. We sometimes also just report life years if we think there’s no quality of life information at all or it’s just so uncertain. Sometimes we also report life years. So again, I would fall back on trying to understand the impact of variations in the quality of life and then be transparent about that.

Todd Wagner: Great answer. Thank you, Doug.

Rob: Can we get one in through the chat? You may have answered it in the presentation, but I don’t think in the Q&A. This person asked is there a published guideline for the conduct of cost-effectiveness analysis, and, if so, could you please provide related reference?

Doug Owens: Is there a guideline for doing cost-effectiveness analyses? That is what the—if that was the question, that’s the book is, and that is what the paper and *JAMA,* they provide guidelines for the conduct and how you would do a cost-effectiveness analysis.

Todd Wagner: And I put a link to the *JAMA* paper in the Q&A, so you could grab that link if you want.

Doug Owens: Thank you, Todd.

Todd Wagner: Well, thank you, Doug. This has been fantastic. I appreciate your time and a great presentation.

Doug Owens: My pleasure. And if people have questions, they can certainly feel free to email me, and there’s my email address. Thank you all so much. Really appreciate the opportunity to be here.

Todd Wagner: And thanks, Rob and Heidi, for all your help behind the scenes with the organizations. So thanks.

Doug Owens: Let me second that. Thank you, Rob. Thank you, Heidi.

Rob: Thank you, Sir. Attendees, when I close the webinar momentarily, a short survey will pop up. Please take a few moments to provide those answers to those questions. Thanks, everybody.