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Session: Introduction to Effectiveness, Patient Preferences, and Utilities

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Dr. Josephine Jacobs: Hi everyone. Thanks for tuning into today’s lecture on Effectiveness, Patient Preferences, and Utilities. It’s part of the broader Cost Effectiveness Analysis Course at HERC. My name’s Jo Jacobs I’m a Health Economist at HERC in Palo Alto and co-hosting today with Todd Wagner a Health Economist and Director at HERC who will be monitoring questions as we go along.

So today I’ll be giving a birds-eye view of the types of outcomes that we often consider in cost-effectiveness analysis with a particular emphasis on the commonly used outcomes the Quality-Adjusted Life Year. I’ll focus on what exactly a QALY is, how QALYs are generated and conclude with some recommendations and references for more detailed information on selecting outcomes and cost-effectiveness analysis.

As a brief overview in cost-effectiveness analysis we’re interested in determining the incremental cost-effectiveness ratio which is the difference in cost between two treatment options divided by the difference in outcomes. We’re interested in incremental costs and incremental outcomes because this summarizes the extra amount that we’re paying to gain a change, maybe an improvement in our outcome of interest.

So in previous lectures we explored how to measure costs and today we’re focusing on the denominator in this equation, how to measure outcomes in these analyses. Now the outcome in a cost-effective analysis is defined by the health benefit that’s achieved with the given intervention and it’s quantified on a single scale. So that when we calculate the outcome measure for an intervention we use the same measure and scale as the outcome measure for the alternative intervention.

So deciding which outcome to use depends on the perspective and objective of the intervention. One commonly used outcome is mortality or life years gained. And this would be appropriate in evaluating therapies where the primary objective is to extend life such as, some cancer therapies where life extension has been found to account for about 90% of the total being in health. Now this outcome has the added benefit of allowing comparisons across all life-saving therapies because it is a generic outcome.

But not all interventions are aimed primarily at extending life. And, and even those that need be like chemotherapy may also involve tradeoffs with respect to quality of life. So using mortality as a primary outcome for these interventions wouldn’t capture important potential changes in quality of life.

Other common outcomes used in economic evaluations capture how the intervention might impact morbidity. And you can look rates of heart disease, obesity, or self-rated health or specific intermediate clinical outcomes like changes in blood pressure or cholesterol. These outcomes are useful when decision makers are choosing among therapies for the same condition. They can be more practical than mortality or life years gained when you’re conducting economical analysis alongside a clinical trial. Because they require shorter follow up periods and smaller sample sizes. However, using these outcomes can limit a decision maker’s ability to compare cost-effectiveness across different types of intervention. So if a decision maker in a public system has to consider how to allocate resources in deciding between, say a smoking cessation program versus a program aimed at reducing alcohol intake. Using intermediate clinical outcomes for these interventions would tell a decision maker very little when comparing cross, cost-effectiveness across these two interventions.

So given the shortcomings of looking at mortality alone or morbidity alone, ideally, we would have some sort of generic health outcome measure that could capture both the quantity and quality of life gains due to an intervention. So, most international guidelines on conducting cost-effectiveness analysis in health care encourage the use of measures that capture both quantity and quality of life. And the quality-adjusted life year or the QALY is the most commonly used measure that attempts to do this. It provides a generic health measure that facilitates comparisons between health outcomes across different types of intervention.

So what exactly is a QALY? The basic idea behind the QALY is relatively straightforward. It’s a measure of a person’s length of life weighted by a valuation of their health-related quality of life, or what we can refer to as health utilities. Measuring the length or quantity of life is straightforward because we’re simply measuring whether the person’s alive or not. But measuring health related quality of life is a bit more complicated and we’ll be focusing a bit on, on that as we go along in the lecture.

The scale of QALY weights may contain many points. But in the most conventional scales, two points that have to be on the scale are perfect or full health and death. And these two points are usually selected to be the two references points for the interval scale of QALY weight. It takes one year of perfect health, a utility score of one to generate one QALY. While a value of zero is assigned to death. One year in a health state valued at 0.5 is the equivalent to half a QALY. And negative values are possible for states worse than death.

So how would this work in practice? In the context of two interventions, we might have say an antibiotic intervention that results in the following QALYs over a year-long period in three-month intervals that we’re measuring it.

In the top row we have the new treatment and in the bottom row we have usual care. How would we go about determining the total QALYs over the course of this year for the treatment group versus the usual care group? For the calculate the total QALYs for each intervention, we take the QALY experience at each time interval and multiply it by the fraction of the year at each level of health. So in this case since we have three-month intervals, that’s one quarter of a year, so 0.25. We then take the sum over the course of the whole year for each intervention. So in the intervention group this results in a QALY of 0.675 versus 0.5375 QALYs in the usual care group.

We can then plug this into the ICER formula as follows, assuming just a cost difference between the two interventions of $10,000. We would simply take this cost difference and divide it by the difference in QALYs between the two interventions to arrive at a cost for QALYs, in this case of 72,000.

So it may also help to visually outline how QALYs work. And we can see here that the difference in QALYs between two interventions in a graph like this. In which we compare health-related quality of life on the Y-axis, [clears throat 8:54] excuse me, with length of life on the X-axis. And in this scenario, treatment A provides a consistently greater area under the quality time curve. In treatment B, resulting in both greater quantity and quality of life throughout the intervention. And this is similar to the first example that we worked through.

But, one can also imagine a scenario that’s less straightforward. Where an intervention for disease with a poor prognosis initially leads to a gain in quality of life compared to no intervention. Adverse effects, they soon lead to a diminished quality of life but an overall increase in the length of life at a lower quality. So in these cases, it becomes more complicated as one considers longer length of life with lower quality of life versus a shorter length of life with higher health-related quality of life.

So now I’d like to pause to give a little pop quiz to make sure we’re understanding at a basic level of how to calculate differences in QALYs across interventions. In this scenario, we have two interventions that generate the following QALYs for each year. Intervention A results in 0.5 QALYs in the first two years and then 0.75 QALYs for the next two years. Meanwhile, intervention B results in a consistent health state of 0.4, 5 QALYs across all four years. So I’m going to leave this up for a second to make sure you can do the arithmetic. But the question for the poll will ultimately ask, which, uh yeah. The, what are the additional QALYs generated by treatment A? Okay. [Pause from 11:00 to 11:07] So.

Heidi: Do we have that poll up? Responses are coming in we’ll give everyone a few more moments to respond and then will go through the results here.

Dr. Josephine Jacobs: Okay.

[Pause from 11:22 to 11:32]

Heidi: And it looks like we’re slowing down. So I’m going to close this out. And what we are seeing is 5% of the audience think, 5% of the audience saying 1 QALY, 13% percent saying 2 QALYs, 73% saying .5 QALYs and 10% saying .25 QALYs. Thank you, everyone.

Dr. Josephine Jacobs: Great. So I think most people got it, 0.5 QALYs. So, in this case, we can see that treatment A has resulted in 2.5 QALYs and treatment B has resulted in 2.0 QALYs. Which means that treatment A generated an additional half of a QALY.

So now that we see how QALYs can be used, it’s important to understand how they’re derived. As we noted, generating a QALY involves generating quality of life valuations referred to as health utilities. Measuring utilities has two main components. First, you need to define and describe a set of health states of interest. And second, you need to reflect on the relative value of those health states. So you need to measure the strength of preference for each of the health states.

We can derive preferences in a few ways. There are direct measurement methods, where individuals are asked to rate the desirability of various health states. There are indirect measurement methods where utility algorithms are applied to generic or disease-specific preference based questionnaires. And there’s off-the-shelf methods where we simply take preference weights from the existing literature. And we’ll spend a little time now going over each of these methods.

Direct methods involve asking individuals to choose or declare preferences between their current health state and alternative health state scenarios. There are a number of options for which valuation methods to apply. But the three most commonly used are standard gamble, time trade-off and rating scales, which are often visual analogue scales.

In the standard gamble approach, a researcher assigns a utility value to a health state by asking an individual to choose between two alternatives. The first alternative is the health state that is certain. For example, a guarantee of 10 years of life with mobility issues. The second alternative is a gamble with one better and one worse outcome possible. So in this diagram alternative two represents a health state with certainty. And alternative one represents the gamble, with one better state full health and one worse state, death.

Respondents are asked, what probability of the better outcome, so full health in this example, would make them indifferent between remaining in the described, say mobility impaired health state with certainty or going for the risky option? If the individual is indifferent between the mobility impaired state and a gamble with an 80% probability of full health but a 20% probability of death, then 0.8 represents the utility of the mobility impaired health state.

So as an example of what a standard gamble exercise might look like in practice. An individual will, may be asked to imagine a scenario where they experience different levels of difficulty across six health domains. Where they may be able to see, hear and speak normally but require the help of another person to walk or get around. They’re occasionally angry, irritable, anxious and depressed but able to learn and remember normally, function normally with respect to ADLs and are free of pain and discomfort.

 For a given description of the health state the individual will be asked to troose [sic 16:33], choose between two treatment options. Treatment A allows them to live 10 years in that described health state. And treatment B gives them a chance of returning to full health but also a chance of death. And the respondent will then have to choose the minimum chance of success they would require to accept the second treatment.

The time trade-off approach is a second commonly used valuation method. With this approach, we ask people to consider the relative amount of time, for example, life years that they would be willing to sacrifice to avoid a certain poorer health state. Assuming for instance again, the scenario of 10 years with mobility issues. You would ask the number of years at which the respondent would be indifferent between this state and a shorter length of life in full health. So if the individual was indifferent between 10 years of life in the described health state, so with reduced mobility and eight years of life in perfect health. So they gave us two years of life with mobility issues, then the estimated utility for the mobility issue state would 0.8 or 8 divided by 10.

And a third commonly used direct measure is the rating scale. It’s often in the form of a visual analogue scale like the one shown on the slide. Where the anchors are the best possible health state and the worst imaginable health state. Individuals are simply asked to place the described health state on this scale and a value is assigned based on where they put it on the scale.

So I’d like to stop again to do a quick poll related to the direct valuation methods that we’ve discussed so far. And I’d like to ask with which valuation method would a respondent’s utility be affected by their willingness to take on risk?

Heidi: And the options here are standard gamble, time trade-off, or visual analogue scale. And again we’ll give everyone a few moments to respond and we’ll go through the results. [Pause from 19:20 to 19:28] And it looks like we’re slowing down here so I’m going to close this out. And what we’re seeing is 77% of the audience thinks standard gamble, 21% saying time trade-off, and 2% saying visual analogue scale. Thank you, everyone.

Great. So most people got it. It, it is standard gamble. And standard gamble tends to be preferred in economics because it measures preferences under conditions of uncertainty. The utilities that are generated from it are dependant on the risk behavior of the individual. In general, since people are risk-averse people will tend to shy away from the gamble. Especially when the gamble involves risk of death. And as a result, it tends to produce higher utilities for health states than time trade-off and visual analogue. So it measures not only preference but also risk attitude making it risk sensitive.

In time trade-off methods the participants are asked the amount of time they’d be willing to give up to achieve a better health state. So time trade-off is risk insensitive and measures only preferences. So, because the choices are made under conditions of certainty it, they, utilites assigned under this method tend to be lower than under standard gamble.

And visual analogue scale is sort of the most simplistic approach. And it doesn’t involve either choice or conditions of uncertainty. So there are some validity issues with the approach and it’s often used as a warm up to time trade-off and standard gamble exercises.

So overall, as you might imagine, these approaches can be very time consuming and they can be complicated for respondents. They might be necessary if the effects of the intervention are complex and involve multiple health domains that are not easily captured by methods that are more restrictive in the health domains that they consider.

One final important issue to consider with direct methods, is who should researchers be asking to provide these valuations? So it can be argued that preferences of patients who actually experience the impact of the disease and the treatment should be the highest priority. It’s very likely that patients with the health condition are better informed about the burdens of the disease and the experience of undergoing treatment. There are issues however, practical issues with recruiting sufficient patients with the given conditions to account for the high degree of variation within a given patient population. But alongside practical issues, studies have also found that individuals experiencing illness and in particular chronic illness adapt to their circumstances and often end up valuing these health states much higher than a general population. So in general community preferences tend to be favored, particularly in public health care systems. Where the general public is viewed as the population that will be bearing the cost for a specific treatment that they have the ultimate potential to be using.

So next we’re going to consider indirect methods for valuing health states. With indirect measurement methods, most commonly generic utility instruments, a set of nondisease specific health states that cover multiple domains of health are outlined. A composite state is then constructed based on the individual's responses. And that composite state is linked to weights that are generated from a public sample of individuals.

There are a number of forms that these can take. But to get a general sense of how these methods work we can focus for a minute on the EQ-5D which is one of the most commonly used instruments. The EQ-5D looks at the following health I mentioned, mobility, self-care, usual activities, pain discomfort and anxiety or depression. And under the three-level version, individuals are asked to identify whether they have no problems, some problems or extreme problems with each of these health domains. And based on their responses a health profile is constructed for their respondent and converted into health utilites by applying weights that were obtained for that health state from a community sample. There’s a growing number of commonly used instruments. And some of the most widely used ones include the Health Utility Index EQ-5D, SF-6D and the Quality of Well-Being, so.

Each of these instruments differs as with respect to the health dimensions that are used, the size and nationality of the populations used to establish the weights that are attached to each health state, and the health states that are defined by the survey. As well as the method of valuation applied. So for instance, to assign weights to health states EQ-5D has been valued with Time trade-off methods. While SF-6D and the Health Utility Index have been valued using Standard Gamble. All the measures though have weights based on large general public samples.

So these general utility instruments address some practical difficulties of conducting direct Time trade-off or Standard Gamble exercises. They provide standardized off-the-shelf questionnaires that describe generic health states and can be completed in a limited time period by patients in trials. They allow researchers to generate QALYs that can be used for comparisons across different types of interventions. There are some limitations though. The measures can lack sensitivity in specific disease context. So one recent review in Pharmacoeconomics looked at the ability of EQ-5D to detect meaningful health changes across 56 conditions. And they found that it performed well for about 45% of conditions reviewed, mixed results for about 48% of conditions. And for the remaining four conditions which were alcohol dependency, schizophrenia, limb reconstruction and hearing impairment it wasn’t responsive at all. So it’s important to weigh these pros and cons when choosing an instrument.

And I’d just like to provide a brief overview of some of the more commonly used instruments. We’ve talked a bit about EQ-5D before which has five questions or five health domains and looks at a total of 245 health states. And the basis of its domain weights originally were a British community sample, though there’s also U.S. weights available now.

The Health Utility Index has 41 questions though many of these can be skipped. And there are eight domains of health with 972,000 possible health states. It focuses on vision, hearing, speech, ambulation, dexterity, emotion, cognition and pain. And the basis of the domain weights was a Canadian community sample.

And the SF-6D converts the SF for Short Form 36 and Short Form 12 scores into utilites. And when it’s based on the SF-36 it uses 10 items, when it’s based on the SF-12 it uses seven items. And it considers six health domains which include physical functioning, role limitations, social functioning, pain, mental health and vitality. Overall it defines about 18,000 health states and the basis of it’s original domain weights was a British community sample.

So as we noted previously, despite the large number of health states covered by these tools they will still lack sensitivity with respect to some health outcomes. And in response to some of these sensitivity shortcomings, disease-specific utility measures are also being generated now. These measures can be difficult to establish values for. Especially when working with community respondents who don’t necessarily understand the disease. I won’t go into too much detail here, but at the end, I do provide a link to some publicly available disease-specific measures that are being generated in partnership with NIH such as the Neuro-Qol, which focuses on health outcomes for individuals with neurological disorders.

Finally, if neither direct nor indirect measures are possible to collect for a study, you can also consider using off-the-shelf preference weights. This implies sort of digging into the literature and applying qualities from other studies to your population of interest. But it should be noted that the values generated in the literature can be greatly influenced by the elicit patient procedures used for that specific study. So combing utility weights from several studies isn’t always recommended. And, this method though, is very useful in decision modeling. And in upcoming seminars we’ll be discussing that in later HERC lectures.

So when you’re considering which method to use in your own study you have to consider the trade-offs between the sensitivity of the measure and the burden of collecting that data. It’s useful to start off with a literature search for the condition of interest in your population of interest and for the outcome of interest.

The easiest methods to apply will be to simply use what you find in your literature search, if you happen to find highly relevant results. If you don’t sort of hit the jackpot there, indirect measures are the next easiest way to determine health-related quality of life. Disease-specific surveys can also be used alongside these indirect measures if you have some concerns about sensitivity. Finally, if you are able, direct measures like standard gamble and time trade-off will give you the most precise measures but at a high time cost for both the researchers and respondents. And I’ll also note for standard gamble and time trade-off these methods require an ability to understand sort of basic probability and mathematical concepts. Which as researchers dive more, and more into this they find that even highly educated individuals can have difficulties with these concepts. So some studies involving standard gamble and time trade-off seem to point to patients values being inaccurately represented by some of these methods as a result of this issues with numeracy.

Some final considerations when using QALYs is that they are not without debate. As noted there can be a lack of sensitivity for instance when comparing the efficacy of two competing but similar drugs in the treatment of less severe health issues. They can also be difficult to apply to chronic diseases or preventive measures. In the latter case the impact on health outcomes may not occur for many years, and it might be difficult to quantify using a QALY. There are also criticisms of QALYs that they attached inadequate weight to emotional or mental health problems. And can overlook important non-health outcomes for the impact of health problems on caregivers or family members to the extent that there not incorporated in the patients QALYs. There is also a growing literature devoted to measures that attempt to capture, to capture broader concepts related to peoples capability to live a life that they value such as the ICECAP. And these focus more on stability attachment, autonomy, achievement and enjoyment. And the argument is that, these can be used beyond evaluation in the health sector but also can be used in policies related to justice education or social care. And finally, there is a large debate as to whether all QALYs should be weighted equally. So QALYs consider overall efficiency gains, but not necessarily the distribution of the health gains. So there are arguments for weighting qualities of some members of the population at higher rates. Whether to reflect the equity preferences of the general population productivity maximization or other moral or ethical arguments. And some countries like the Netherlands suggest in their guidelines to effectively apply what amounts to severity weights the QALYs.

And on a final note, I’d like to provide a reference to a study that provides a pretty clear outline of how they generate the QALYs in their cost-effectiveness analysis. A lot of studies don’t outline the steps very clearly. But this one does talk about collecting EQ-5D data at various time points, generating index scores, and calculating QALY gains for both the intervention and control groups.

And I will end with some references for other examples of cost-effectiveness studies. Tufts Center for Evaluation of Value and Risk in Health provides a lot of resources on utilities and cost-effectiveness analysis. And the National Institute for Health Research and NICE in the UK has been sort of trailblazer in developing QALYs and more so incorporating them into public policy decisions in the UK. I also provide some links for some helpful overviews for patients based outcome measures in general. And some links to the Tufts Cost-Effectiveness Analysis Registry. The PROMIS measures I discussed earlier from NIH which are related to disease-specific quality of life measures such as the EuroQol. And finally a link to HERC’s Guide Book on preference measurements.

And also please note that there are some upcoming HERC lectures. We have Risha Gidwani-Marszowski, Estimating Transition Probabilities for Models on February 28th. And on March 7th, we have Medical Decision Making and Decision Analysis. So, thanks very much for your time. Do you have any questions or comments?

Gary: Thanks, Jo. That was wonderful. So for those of you who want to ask questions, please type in your questions in the chat bar. The one question that I think was raised, was you mentioned a paper on the EQ-5D in responsiveness to change in or view paper.

Dr. Josephine Jacobs: Yes.

Gary: A couple of us searching, it looks like it’s the December 2017 Special Issue. Is that what you were referring to Jo?

Dr. Josephine Jacobs: I can give you, actually the exact, so yeah, it’s called “Can The EQ-5D Detect Meaningful Change?” It’s a systematic review in, it was a 2015. It was by Nalin Payakachat, Ali and Tilford and it’s in November. So, 33 (11) is the issue.

Gary: Great.

Dr. Josephine Jacobs: \_And, yeah.

Gary: Thank you. So if folks can’t find it, then we are more than happy to respond to you and send you that citation if you can’t find it.

Dr. Josephine Jacobs: Right.

Gary: Well, we have, I have a compliment. One was, clear, concise and useful. Thanks. So that, that’s good to know. And there’s, just another one came in. For evaluing health utility none of the measures include patient cost utility. How much would you pay for X? Are these often not used in measuring QALYs?

Dr. Josephine Jacobs: So like, willingness to pay? Is that what a\_

Gary: I’ve, that’s my interpretation of the question. Which is the, your right a contingent valuation. How much would you be willing to pay for X?

Dr. Josephine Jacobs: Right. So, so these are also often used. I think not in conjunction with QALYs but as another measure for, I, I haven’t used willingness to pay that much. Are, Gary are you familiar with\_

 Gary: So we have used willingness to pay in studies. It is typically asked as a survey question in the contingent valuation realm done frequently in environmental economics. But sometimes in health as well, where you ask somebody, what are they willing to pay for? And it could be a service or to avoid a risk. There is no standard format. There’s been a lot of discussion about the response options and the best way to answer this. As you can imagine, it’s very dependent on the kind of framing you have for the question. So we can provide more details on that if you want to connect us or contact us.

And then there’s a, a question that came in. It’s actually not a question, but clarification for you. I would change death to dead in earlier slides. And it\_

Dr. Josephine Jacobs: \_Yeah, okay.

Gary: Patient-centered, assessment resources rather than PROMIS. PROMIS and Neuro-Qol are part of the PCAR funded by NCI. Just for clarification.

Dr. Josephine Jacobs: Oh, thank you. Great.

Gary: Yes. Thank you for that clarification. And then another question for you. Jo can you suggest any other references to off-the-shelf EQ-5D scores for congestive heart failure or sources of ES-5D scores that might include congestive heart failure CHS?

Dr. Josephine Jacobs: Off the top of my head I can’t. But that’s something we can definitely look into if you reach out over email. I, I haven’t had experience with congestive heart failure. But we can definitely look into some of the databases we’ve provided and, and see if there’s anything. If you want to reach out over email.

Gary: That’s right. We also have, we work a lot with Paul Heidenreich here at Stanford and the VA who does a lot on heart failure. And he might be very familiar with these types of methods. In the incontinence worlds that I know a little bit better, they’ve been using a lot of methods to try to crosswalk sort of all of Brazier algorithms from disease-specific, quality of life measures, to generic quality of life measures. I, I have to admit that I’m a little bit skeptical of that approach just because it puts a lot of faith on the algorithm. But I’d be interested to see more research on that.

And then, can, there’s another question that comes in. What is the ICER value for deciding whether or not an intervention is good value?

Dr. Josephine Jacobs: Yeah, that’s a great question. I don’t know if we cover it in later lectures. But the sort of rule of thumb in a lot of countries or at least here in and in Canada tends to be around 50,000. But there is a lot of debates and some thought about it being fairly arbitrary. I think in the U.K. it’s between 40 and 60,000 pounds. And it, it’s huge ranges in terms of, and a lot of debate in the literature about this just sort of being an arbitrary number. But 50,000 seems to be a rule of thumb that is often turn around.

Gary: Yeah. So I’ve also note, heard twice the GDP as a way of normalizing it across countries. But as you point out, correctly, it’s rather arbitrary. And I think what a lot of people do when they start developing these cost effectiveness curves and what Jeremy will talk about in a future slide, is sort of your cost-effectiveness accessibility curve. And it traces out across sort of different thresholds what your cost-effectiveness might be. So you don’t have to sort of say, is it cost effective based on just 50,000 or not? That’s very helpful.

Any other questions? I think that’s it for right now that I’m seeing. We’ll give it a moment to see if, see if any other ones come in.\_

Dr. Josephine Jacobs: \_If there are other questions we can always be reached by email directly or if you, or HERC help desk as well.

Gary: And Heidi, just out of curiosity. So I gave the last lecture and perhaps some of those folks are on the phone now. I don’t, and maybe it’s just my email box overflow with, with a, with email and love. But I never remember seeing the normal follow-up where the questions were raised so that I could follow-up on those. And I do want to follow-up on those.

Heidi: What do you mean the normal follow-up?

Gary: So there, a number of people raise questions that we did not have time to address in the, in the talk. And I just want to make sure\_

Heidi: \_Okay.

Gary: That I get back to people on those.

Heidi: Okay. I will double check to make sure that I sent those to you.

Gary: Got it. Thank you. And I apologize if it’s my end. But I’m still, that’s the only questions I’m seeing so far, Jo. So I think you’ve done such a clear job. You’ve answered all the questions. And thanks again for the folks who provided clarification during the talk.

Dr. Josephine Jacobs: Yes, thank you very much. We’ll be sure to change those in the future slides.

Heidi: Wonderful [unintelligible 44:46]\_

Gary: \_[Unintelligible 44:46] I think it’s back to you. Yeah.

Heidi: It’s back to me. If we don’t have any other questions coming in we can probably wrap things up for today. We are taking next week off from the Cost Effective Analysis Course but we will back in two weeks. I know most of you are registered for that session already. If not registration information will be sent out next week. Thank you everyone for joining us today. And we look forward to seeing you at a future HSR&D Cyber Seminar. Thank you, everyone.

[END OF AUDIO 45:23]