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Session: Introduction to Effectiveness, Patient Preferences, and Utilities

Presenter: Josephine Jacobs, PhD

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Dr. Josephine Jacobs: So hello everyone. And thank you very much for tuning into to today’s lecture on effectiveness, patient preferences, and utilities which is part of the broader cost-effectiveness analysis course from HERC. My name is Josephine Jacobs and I’m a Health Economist at the Health Economics Resource Center or HERC at the VA Palo Alto. And we also have Jean Yoon on the line who’s a Health Economist at HERC and we’ll be monitoring questions as we go along.

So today I’ll be giving a bird’s eye view of the types of outcomes we often consider in cost-effectiveness analyses. With a particular emphasis on the commonly used outcome measure, the quality-adjusted life year or the QALY. I’ll focus on what exactly a QALY is. How QALYs are generated. And we’ll be concluding with some recommendations and references for more detailed information on selecting outcomes in cost-effectiveness analyses.

So as a brief overview. In cost-effectiveness analyses we are interested in determining the incremental cost-effectiveness ratio or the ICER which is the difference in costs between two treatment options divided by the difference in outcomes. And we’re interested in incremental costs and incremental outcomes because this summarizes the extra amount that we are paying to gain a change, hopefully an improvement in our outcome of interest. Now in previous lectures from this series we’ve explored how to measure the cost of interventions. And today we’ll focus on the denominator in this equation. How to measure outcomes in these analyses. And I’d encourage those who missed our costs lecture to go back to the archives for the February 5th lecture by Libby Dismuke who covered measuring costs.

So the outcome in a cost-effectiveness analyses is defined by the health benefit that’s achieved when a given intervention or with a 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.

Deciding which outcome to use depends on the perspective and the objective of the intervention. So 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 cancer therapies where life extension has been found to account for 90% of total gains of health. This outcome has the added benefit of allowing comparisons across all life-saving therapies because it is a generic outcome. However not all interventions are aimed primarily at extending life and indeed even though that may be, such as chemotherapy, may also involve tradeoffs with respect to quality of life. So using mortality as a primary outcome for these interventions would not capture important potential changes in quality of life.

Other common outcomes used in economic evaluations capture how interventions may impact morbidity. For example rates of heart disease or obesity or self-rated health. Or specific intermediate clinical outcomes such as changes in blood pressure or cholesterol. And 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 economic analyses alongside clinical trials because they require often shorter follow-up periods or smaller sample sizes. However using these outcomes can limit a decision-makers ability to compare cost-effectiveness across different types of interventions. So if a decision-maker in a public system has to consider how to allocate resources, considering a smoking cessation program versus a program aimed at reducing alcohol intake using intermediate clinical outcomes for these interventions they would tell a decision-maker very little when comparing cost-effectiveness across these 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 quantity and quality of life gained due to an intervention. So many international guidelines on conducting cost-effectiveness analyses 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 interventions. And groups such as NICE in the U.K., CADTH in Canada, ISPOR, and the Second Panel on Cost-Effectiveness in Health and Medicine as well as the Institute for Clinical and Economic Research in the U.S. all recommend the use of QALY in their reference case. But there are some notable holdouts like CMS here in the U.S. and Germany as well, being two prominent examples. And we’ll discuss some of the controversies surrounding the use of QALYs towards the end of the presentation.

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 evaluation of their health-related quality of life. Or what we’ll refer to as health utilities. Measuring the length or quantity of life is relatively straightforward. As we’re simply measuring whether the person is alive or not. Measuring health-related quality of life is a bit more complicated and we’ll be discussing this in more detail as we go along.

The scale of QALY weights may contain many points but in the most conventional scale two points that have to be on the scale are perfect or full health and being dead. And these two points are usually selected to be the two reference points for the interval scale of QALY weights. It takes one year of perfect health, a utility score of one to generate one QALY. While a value of zero is assigned to being dead. And one year in a health state valued at 0.5 is equivalent to half a QALY. Now 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 an antibiotic intervention that results in the following QALYs over a year-long period in three-month intervals. So 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?

So to calculate the total QALYs for each intervention we would take the QALYs experienced in each time interval and multiply them by the fraction of the year at each level of health. So in this case it’s one quarter of a year. And then take the sum over the course of the whole year for each intervention. So in the intervention group you can see the arithmetic up on the slide. This would result in total QALYs of 0.675 versus 0.5375 QALYs in the usual care group.

Now as a quick aside, we learned about the ICER previously. This could then be plugged into the ICER formula as follows. Assuming a cost difference between the two interventions of say $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 per QALY in this case of around 72,000.

So it may also help to visually outline how QALYs work. We can see here the difference in QALYs between two interventions in a graph like this which compares health-related quality of life on the Y-axis and length of life on the X-axis. In this scenario treatment A provides a consistently greater area under the QALY time curve than treatment B resulting in both greater quantity and quality of life throughout the intervention. And this is similar to the first example that we just worked through.

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

So I’d like to pause for just a second. Give a little pop quiz to make sure we’re all understanding at the basic level how to calculate differences in QALYs across interventions. And in this scenario we have two interventions that generate the following QALYs for one year each. So we’ll keep the arithmetic pretty straightforward. Intervention A results in 0.5 QALYs for the first two years and then 0.75 QALYs for the next two years. Meanwhile intervention B results in a consistent health state 0.5 QALYs across all four years. So I’m going to leave this up for just a bit to make sure everyone can do the arithmetic before moving onto the poll slide which will ask you to calculate the additional QALYs generated by treatment A relative to treatment B.

So maybe we could do a quick poll with everyone, asking what the additional QALYs generated for treatment A were.

Moderator: Okay I’ve got that up on the screen. Just waiting for responses to come in.

Dr. Josephine Jacobs: Great.

Moderator: We’ll give that a few more moments for, to get a few more responses in here then we’ll close it out and go through what we’re seeing. And it looks like that is slowing down. So I’m going to close this out and what we’re seeing is 11% of the audience saying one QALY, 5% two QALYs, 68% 0.5 QALYs, and 16% 0.25 QALYs. Thank you everyone.

Dr. Josephine Jacobs: Okay great. Thanks. So it looks like most people got it. So we’ll just run through that arithmetic quickly. So in this case we can see that treatment A has resulted in 2.5 QALYs and treatment B has resulted in 2 QALYs which means that treatment A generated an additional half of a QALY. So it was 0.5.

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. And measuring utilities has two main components. First you need to define and describe a set of health states that are of interest. And second you need to reflect on the relative value of those health states or in other words measure the strength of preferences for each health state.

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 then there’s off-the-shelf methods where we simply take preference weights from the existing literature. And we’re going to spend a little time now going over each of these methods.

Direct methods involves asking individuals to choose or declare preferences between their current health state and alternative health status 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 or what they’re often referred to as visual analogue scales.

So in a standard gamble approach a researcher assigns a utility value to a health state by asking an individual to choose between two alternatives. One, the first alternative is a health state that is certain. For example a guarantee of 10 years of life with moderate pain issues. The second alternative is a gamble with one better and one worse possible outcome. So in this diagram alternative two represents a health state with certainty, say our 10 years of moderate pain. And alternative one represents the gamble with one better health state, full health and a worse health 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 health state with moderate pain with certainty or going for the risky option. If the individual is indifferent between the moderate pain state and the gamble with an 80% probability of full health but at 20% probability of death than 0.8 represents the utility of the moderate pain health state.

As an example of what a standard gamble exercise or one of the health states might look like in practice. An individual may be asked to imagine a scenario where they experience different levels of difficulty across six health domains so they’re able to see, hear, and speak normally. Require the help of another person and a cane to walk or get around. Are occasionally angry, irritable, anxious, and depressed. Able to learn and remember normally. Able to eat, bathe, dress, and use the toilet normally. And are free of pain or discomfort.

For a given description of a health state the individual will be asked to choose between two treatment options. As we noted one with certainty in the described health state and one with uncertainty but a chance of full health or death.

The respondent will then have to choose the minimum chance of success that would require them to accept the second treatment. So that sort of summarizes the basics of the standard gamble approach.

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 a scenario of again 10 years with moderate pain issues we 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 along the X-axis here we see that the time from zero to t2 is the amount of time in the given health state so of moderate pain while the time from zero to t1 is the amount of time in perfect health. And the difference between the two is from t1 to t2.

If the individual was indifferent between 10 years of life in the described health state with moderate pain and eight years of life in perfect health, so they gave up two years of life with moderate pain issues then the estimated utility for the moderate pain state would be 0.8. So eight years divided by 10. And that sums up the basics of the time trade-off approach.

And a third commonly used direct measure is the rating scale often in the form of a visual analogue scale where the anchors are the best possible health state and the worst possible health state. Individuals are asked to place the described health state on this scale and a value is then just assigned to that health state. So it’s the most straightforward of the approaches.

So I’d like to stop to do a quick poll relating 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? Is it standard gamble, time trade-off, or visual analogue scale?

Moderator: And responses are coming in. We’ll give everyone a few more moments to respond before we close the poll out and go through the results.

Dr. Josephine Jacobs: Great.

Moderator: Waiting for things to slow down a little bit.

Dr. Josephine Jacobs: Okay.

Moderator: Okay so I’m going to close this out. And what we’re seeing is 83% of the audience saying standard gamble, 17% of the audience saying time trade-off, and zero saying visual analogue scale. Thank you everyone.

Dr. Josephine Jacobs: Great. And yeah I think most people got it there. Standard gamble. And standard gamble tends to be preferred in economics or by some economists at least because it measures preferences under conditions of uncertainty. And the utilities that are generated from it are dependent on risk behavior of the individual. In general since people tend to be risk-averse they will tend to shy away from the gamble. Especially when the gamble involves risk of death. Therefore it produces, tends to produce higher utilities for health states. So some argue that standard gamble measure is not only preference but also risk attitude, so it’s risk sensitive. In the time trade-off method 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 preference. Choices are made under conditions of certainty and when choices are made under conditions of certainty and people’s risk-averse nature isn’t accounted for then the utility will tend to be lower. And visual analogue scale is the most simplistic approach and does not involve either choice or conditions of uncertainty. So some economists argue that there are some validity issues with this approach without a sort of forced choice between alternatives. It’s not really compatible with some economic evaluation principles and it’s often used as a warm-up to a time trade-off or a standard gamble exercise. But this is not always the case.

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

And one final important issue to consider with direct measures is who should researchers be asking to provide these valuations? It can be argued that preferences of patients who actually experience the impact of these disease and treatment should be of the highest importance. It’s very likely that patients with the health condition are better informed about the burden of the disease and the experience of undergoing treatment. There may be practical issues though with recruiting sufficient patients with a given condition to account for the high degree of variation within a given population. And alongside these practical considerations, studies have found that individuals experiencing illness and in particular chronic illnesses, adapt to their circumstances and often end up valuing these health states much higher than the general population. In general sort of community preferences tend to be favored particularly in public health systems where it’s argued and viewed that the general public is the population bearing the cost for specific treatments that they have the potential to use.

So next we’re going to consider indirect methods for valuing health states. With indirect measurement methods which are most commonly generic instruments, generic utility instruments use a set of non-disease specific health states that cover multiple domains of health are outlined. And 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.

These take on a number of forms but to get a sense of how these measures work we can focus for a minute on the EuroQol-5D, the EQ-5D which is one of the more commonly used instruments. The EQ-5D looks at the following health dimensions, mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. And under the five-level version there’s also a three-level version. Individuals are asked to identify whether they have no problems, slight problems, moderate problems, severe problems, or extreme problems with each of these health domains. Based on their responses a health profile is then constructed for the respondent ranging from no problem with any states so 11111 to extreme problems with all states so 55555. And this profile is then converted into health utilities by applying weights obtained for that health state from a community sample.

There’s a growing number of commonly used instruments. And here are just some of the more widely used ones which include the EuroQol-5D like I mentioned. The Health Utility Index, the 15D, the EQ-5D like I said and the SF-6D, and the Quality of Well-Being Scale.

Each of these instruments differs with respect to the health dimensions that are used, the size and nationality of the population used to establish the weights attached to each health state. And the health states defined by the survey. And as well the method of valuation that’s applied. For instance, to assign weights to health states EQ-5D has been valued with time trade-off. While SF-6D and the Health Utility Index have been assigned using, valued using standard gamble. All measures however have weights based on a large general public sample.

Okay so these general utility instruments address some practical difficulties of conducting direct time trade-off or standard gamble exercises. They provide a standardized off-the-shelf questionnaire that describes 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 comparison across interventions but there are some limitations. These measures can lack sensitivity in specific disease context. And one review by Payakachat, Ali, and Tilford, which I’ll link to at the end, looked at the ability of EQ-5D to detect meaningful health changes across 56 conditions. And they found that it performed well for 45% of conditions reviewed. They found mixed evidence for 48% of conditions. And found that for the remaining conditions alcohol dependency, schizophrenia, limb reconstruction, and hearing impairment EQ-5D was not 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. As I noted before EQ-5D has five questions and five health domains looking at a total of 3,125 health states. The basis of its domain weights were initially a British community sample. Though there are now U.S. weights as well. And Pickard et al. a 2019 article which I have included in the references section, walks the reader through how the U.S. weights were determined. Including how time trade-off versus discreet choice experiment methods were selected. How the functional form of the regressions used to determine the weights were selected. And how something called lead time, time trade-off methods were used to elicit worse than death values. These are all beyond the scope of this lecture and it is a bit technical, the article, but it does walk the reader through the steps required to assign weights to health states. So I recommend checking that out if you have any interest in some more details on that front.

The Health Utility Index has 41 questions though many of the items can be skipped. There are eight domains of health, 972,000 health states and it focuses on vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. And the basis of the domain weights were originally a Canadian community sample.

The SF-6D, I think this might be the most commonly used in the states, converts the SF-36 or SF-12 scores into utilities. And when based on the SF-36 it uses 10 items. When based on the SF-12 it uses seven items. And there are six health domains which include physical functioning, role limitations, social functioning, pain, mental health, and vitality. Overall it defines 18,000 health states. And the basis of the domain weights were originally a British community sample. So similar to the Pickard article you could check out Craig et al. which I’ll link to at the end which also walks the reader through how the U.S. sample weights were determined.

And finally one of the more comprehensive measures is the 15D which has 15 health states. I won’t name them all, they’re up on the screen. And it was developed in Finland so the basis of the original domain weights was a Finnish community sample. I would recommend looking this one up or checking out their website because they do have some nice graphics outlining how the instrument works and it provides a little more for those of you who enjoy sort of pictorial representations.

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 outcomes. So in response to some of these sensitivity shortcomings disease-specific utility measures are also being generated now. These are often used in studies in addition to the more generic measures that we discussed already. The measures can be difficult to establish values for especially when you’re working with a community respondent who doesn’t necessarily understand the disease. I won’t go into too much detail with these but at the end I will 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.

And finally if neither direct nor indirect measures are possible to collect for a study you can also consider using off-the-shelf preference weights. So this implies digging into the literature and applying QALYs 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 elicitation procedures used in a specific study. So combining utility weights from several different studies isn’t necessarily recommended. This method is very useful in decision modeling though and we’ve discussed decision modeling in a previous HERC cost-effectiveness analysis lecture which you can look up as the March 4th lecture by Jeremy Goldhaber-Fiebert.

So when considering which methods to use in your own study you have to consider the trade-off between sensitivity of the method and the burden of collecting the data. So it’s useful to start off with a literature search for the condition of interest, in the population of interest, and for the outcomes 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 hit the jackpot there indirect measures are the next best way to determine or next easiest way to determine health-related quality of life. Disease-specific surveys can also be used alongside indirect measures if you have concerns about sensitivity. Finally if you are able, direct measures like standard gamble and time trade-off will often give you the most precise measures. But at a very high time cost for both researchers and respondents. And I’ll also note for standard gamble and time trade-off these methods require an ability to understand basic probability and mathematical concepts, which studies have found that even highly educated individuals have difficulty with. So some studies involving standard gamble and time trade-off seem to point to patients’ values being inaccurately represented by these methods as a result of this.

So some final considerations when using QALYs is that they are not without debate. As we noted there can be a lack of sensitivity. For instance when comparing the efficacy of two competing but very 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 difficult to quantify using a QALY. There are also criticisms that QALYs attach inadequate weight to emotional or mental health problems. And completely overlook important non-health outcomes or the impact of health problems on caregivers or other family members to the extent that these aren’t incorporated into a patient’s own assessment of their health state. There’s a growing literature devoted to measures that attempt to capture broader concepts related to people’s capabilities to live a life that they value. Such as the ICECAP it’s called, I-C-E-C-A-P. And these focus more on stability, attachment, autonomy, achievement, and enjoyment. And the argument is that these can be used beyond the health sector. And also related to policies in justice, education, or social care. And finally there is a large debate in the literature on whether all QALYs should be weighted equally. QALYs consider overall efficiency gains but not necessarily the distribution of those health gains. And there are arguments for weighting QALYs of some members of the population at higher rates whether to reflect 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 to QALYs and there’s a good article that discusses this that I’m happy to provide a reference for if anybody is interested.

And on a final note I’d like to provide a reference to a study that provides a very clear outline of how they generated 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 the EQ-5D data at various time points, generating the index scores, and calculating the QALY gains for both interventions and control groups.

And I will end with some references for other examples of cost-effectiveness studies. Tufts provides a lot of resources on cost-effectiveness studies as does ISPOR, the International Society for Pharmacoeconomics and Outcomes Research, and NICE in the U.K. has been a trailblazer in the development of QALYs and their incorporation into policy decisions in the U.K.

For a much deeper dive I’d also recommend checking out these two textbooks. The first is by Brazier and provides an up-to-date deep dive into a lot of the topics that we discussed today. The second is the basis of the Second Panel on Cost-Effectiveness in Health and Medicine which we had a seminar on in January by Doug Owens who was on the panel. And they can give you the latest recommendations for patient outcome measurements by the panel.

Also by Brazier these are some articles that provide an overview of the best practices for economics evaluations in the form of a checklist that covers outcome measures, that’s the first reference. As well as a study that looks at the development and testing of a number of condition-specific measures.

And here is a link to the Tuft CEA Registry which is a database of over 8,000 cost-utility analyses and covering a wide variety of diseases and treatments published from 1976 onwards. This is a great place to start for off-the-shelf measures. And there’s also a link here to the Person-Centered Assessment Resource which has developed, as I mentioned earlier, some disease-specific measures like the Neuro-QoL. And finally I have a link here to HERC’s Guidebook on Preference Measurement, it’s an oldie but still a goodie.

And the references I talked about throughout the lecture can be found on this slide.

And finally please note these upcoming HERC lectures from the cost-effectiveness series on conducting a Cost-Effectiveness Analysis Alongside a Clinical Trial by Todd Wagner on March 25th. And Budget Impact Analysis again by Todd Wagner on April 8th. And next week we have a HERC Cyberseminar, it’s a group effort from HERC and Ci2i here at VA Palo Alto looking at a study on the Causes and Consequences of Inappropriate MRI of the Lumbar Spine.

So I’m happy to take any questions or comments you have or please feel free to also follow-up over email directly with me. My email’s on the slide or else with HERC which the email is also on the slide.

Dr. Jean Yoon: Okay, there is one question currently in the queue. If you have any questions for Jo please go over to the Q&A panel and type your question in so that I can read it off for her. The first question asks, do you have any guidance for using off-the-shelf utility values when it is not possible to conduct an EQ-5D?

Dr. Josephine Jacobs: I think as I mentioned the most important thing might be to be careful when you’re, I assume you’re referring to sort of taking values from literature reviews and using those and plugging them into a decision model. If you’re not then please let me know. But I think the biggest piece of guidance we’d have is to be careful when using those values across different studies. And also as a great place to start like I mentioned, you might want to check out the CEA Registry at Tufts which will have a huge database of possible values for whatever sort of disease area that you’re interested in.

Dr. Jean Yoon: Okay. The question, I guess how sensitive are some of these instruments to picking up differences in health status. So for example at HERC some of us have been involved in clinical trials where we’ll compare different treatments and we often don’t find any differences in like EQ-5D or these other instruments in quality of life.

Dr. Josephine Jacobs: Yeah, so that’s a really good question and I think it’s often the case with specific diseases or like we mentioned when there’s maybe a very small difference between two very similar drugs. It’ll be very hard to pick up any of those differences. So in those cases a lot of the times people alongside EQ-5D will also use condition-specific measures that will be more sensitive to whatever disease area you’re focusing on. And also I think there are some sort of indirect measures like the 15D, I think that is the one I’ve seen with the most sort of health dimensions covered. They have 15 of them. So it’s a little more burdensome than say the EQ-5D but it does cover a lot more of the health measures that might be impacted by whatever the intervention is. So I’d say either go to more dimensions or else use disease-specific measures.

Dr. Jean Yoon: Okay, great. Thank you for that. So that was it for the questions from the audience. Do you have any final words before we wrap up?

Dr. Josephine Jacobs: Yeah, I’ll just say that if there are any questions that come to mind down the road, please feel free to contact us. And thank you very much for your time.

[ END OF AUDIO ]