Briefing: Weighing the Evidence: Conducting Reviews of Pharmaceuticals in Four Countries
April 22, 2005

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ANNE MONTGOMERY: On behalf of the Commonwealth Fund and the Alliance for Health Reform, we are very pleased to welcome you today to a wide-ranging discussion of how policy makers in the US, the United Kingdom, Germany and Canada approach the complex challenge of assessing the effectiveness of pharmaceuticals. As we'll hear, the approaches and processes that are used to weigh the evidence on drug safety and effectiveness vary, but some of the core questions are the same. For example, what type of evidence is considered and how do the organizations that conduct drug reviews interact with pharmaceutical companies, with consumers, with employers, with the government and other payers, and how transparent are the decision-making processes? We'll be hearing about these and a number of other issues. It promises to be a really interesting discussion. I should have said, I'm Anne Montgomery with the Alliance for Health Reform. I'll now turn it to Robin Osborn at the Commonwealth Fund.

ROBIN OSBORN: Thank you. On behalf of the Commonwealth Fund, I'm delighted to welcome you here and thank you for joining us for this briefing cosponsored with the Alliance for Health Reform. I know I'm speaking for Karen Davis, President of the Fund and Steve Schoenbaum, Executive Vice President, who'd hear with us today when I say how pleased we are to conduct this afternoon's international session here

on Capitol Hill and to be able to bring to the attention of this broad audience of Washington policy makers important developments in other industrialized countries. We're particularly grateful to the Alliance, Ed Howard and Anne Montgomery for their collaboration in organizing this program.

As many of you probably know, the Commonwealth Fund is a private foundation established in 1918 by Anna Harkness with the broad charge to enhance the common good. The Fund carries out this mandate by supporting efforts that help people live healthy and productive lives and by assisting specific groups with serious and neglected problems. The Fund supports independent research on health and social issues and makes grants to improve healthcare policy and practice. Our national programs focus on improving health insurance coverage and access to care, improving the quality and efficiency of healthcare services. Within that context, program priorities include helping people become more informed about their healthcare and improving care for vulnerable populations. Since 1918, the Fund has conducted research and sponsored innovations in healthcare delivery aimed at addressing many of the most urgent health policy problems in the United States. Recognizing, however, that many of the issues of greatest concern to the fund, access to adequate preventive and primary care, the quality of care and responsiveness to patients' concerns, barriers to healthcare for vulnerable populations

long-term care for the elderly and disabled, and ensuring value for money in healthcare are matters of concern to other industrialized countries as well.

As such, the Fund established an international program in health policy and practice. The program is premised on the belief that while healthcare systems may be financed and organized differently, influenced by their individual histories and the cultures in which they operate, there are lessons that can be drawn when policy-makers, researches and journalists look beyond their own borders at the experiences of other countries. I think it's probably fair to say that each country represented here this morning believes it has the best healthcare system in the world, and while our aim is not to dispute that per se, what we hope to do through cross-national comparative research and exchanges such as today's is share country policy experiences and results, highlight innovations and identify where country approaches may offer lessons to be learned. The core countries of the Fund's international program are Australia, Canada, New Zealand, the UK and the United States, and we've been particularly pleased this year to be able to expand our activities to other European countries and to bring in experts from Germany, as well as the Netherlands and Sweden. Key components of the international program include an annual international symposium on healthcare policy, which is cohosted by the US Secretary of Health and Human

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Services, that brings together health ministers from all these countries and leading experts in international health policy survey, annual cross-national comparisons of OECD data, and international working group on quality indicators. These activities produce cross-national data that is valuable both for benchmarking and for comparing US healthcare system performance with other countries.

In the briefing packets distributed today, you'll find three Health Affairs articles, which I hope you'll take a look at. They include the findings from the Fund's most recent international survey on people's experiences with primary care, focusing on issues such as medical errors, same-day access to care, coordination of care, and appropriateness of care for people with chronic illness. The most recent analyses of OECD data by Uve Reinhardt and Gerard Anderson comparing US health spending and utilization with 30 OEC countries and a report on the first ever set of internationally comparable quality indicators comparing the US against other countries on measures such as five-year breast cancer survival rates, survival rates after kidney or liver transplants and preventive measures such as cancer screening and vaccination rates.

This afternoon we have opportunity to look across countries at different approaches to evaluating the relative effectiveness of prescription drugs. Starting with the US project that represents a multi-state collaboration, we'll then

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turn to models that are institutionalized at a national level in the UK, Canada and Germany. What they all share is an aim to inform policy-making through independent, transparent and evidence-based reviews. Their respective structures, operational strategies and the political environments in which they operate, however, differ and we have a unique opportunity today to hear about the impact that they have had and the challenges they face. In addition, the discussion will be further enriched by the opportunity to hear an industry perspective on how best to incorporate the evidence into practice. I know this will be a fascinating and provocative panel with not enough time to do it justice, and so without further ado, I will now turn the program back to Anne Montgomery, who will introduce our speakers.

ANNE MONTGOMERY: Thank you. A few words about our speakers with apologies in advance for the brevity: There are full biographies in your packets and there are also phone numbers and e-mails at the top of the source list if you'd like to contact them afterwards. Our first speaker, Mark Gibson, is Deputy Director of the Center for Evidence-Based Policy, which is home to the Drug Effectiveness Review Project, a.k.a. DERP. He has a background in policy that's very extensive, serving as Chief of Staff to John Kitzhaber when he was President of the Oregon State Senate and a Senior Policy Advisor to Governor Kitzhaber. Mark also played a key role in development of the

Oregon Health Plan, the state's Medicaid program which uses evidence-based evaluations of effectiveness in its prescription drug plan. Next will be Peter Littlejohns, who holds the post of Clinical Director of the National Institute for Health and Clinical Excellence, known as NIHCE, in London. Among many other responsibilities, he leads the research and development program and NIHCE and has held a number of academic and service position within the UK's National Health Service. Then following Dr. Littlejohns will be Peter Sawicki, who directs the new German Institute for Quality and Economic Efficiency in Healthcare that was established in 2003. It's an independent, scientific institute with an ambitious charter, to advise on the quality and economics of the pharmaceuticals and statutory healthcare services in Germany. Andreas Laupacis is President and CEO of the Institute for Clinical Evaluative Sciences in Toronto. He chairs the Canadian Expert Drug Advisory Committee or CEDAC, and much of his current work focuses on pharmacoeconomics and drug policy, and he has wide experience in the design and execution of clinical trials. We're also very pleased to have as our final speaker Dr. Marc Berger, Vice President of Outcomes Research at Merck and Company. He has extensive experience in management of clinical trials and in disease management programs, and has published numerous articles, one of which is in your packets. Dr. Berger was recently tapped to serve on the government's Medicare Coverage

Advisory Committee. I also want to recognize in the audience Dr. Steven Schoenbaum, Executive Vice President for Programs at the Commonwealth Fund. Prior to joining the Commonwealth, he served as Medical Director and President of Harvard Pilgrim Healthcare of New England, and we're very pleased to have you here today. So now we'll turn to the presentations and after each one, if anyone has a question of clarification or two that they would like to ask, please raise your hand, and we'll take one or two questions, and then we will more to the next speaker, and following Dr. Berger's remarks, we'll open it up for general discussion, reactions, and as many questions as you have. So thanks so much, and now we'll turn to Mark Gibson.

MARK GIBSON: I apologize for that false start. You know, every time I sit up behind one of these curved desks like this, it's all I can do to constrain myself from saying, "All those in favor, signify by saying 'Aye,' and we could accomplish a lot, maybe." My name is Mark Gibson. I'm from Oregon, which is not a foreign country, but is sometimes farther away. I'm going to talk about a multi-state collaboration that we have begun out there, and give you some background on that and some of the research that we're doing to help determine the effectiveness, safety and effect on subpopulations of drugs within various pharmaceutical classes. This effort began about four years ago when the Oregon State budget came together and policy-makers realized that they were

going to have about a 60 percent increase in their Medicaid drug spend over the next two years and realized that was unsustainable. They elected to do a preferred drug list as part of their strategy to manage those costs, but when they elected to do a preferred drug list, they wanted to make sure that they were being clinically smart about the way that they put that list together. They wanted to make sure that they weren't just focusing solely on costs, but that they were also focusing on the effectiveness of the medications that they were choosing for their preferred drug list. As a result, the officials in Oregon established a collaboration with the Evidence-Based Practice Center at Oregon Health and Sciences University, and elected to begin to do full systematic reviews of the classes that they were going to consider for the preferred drug list. Systematic review is a key part of our process, and I'll return to that later. When the reports began to come out, Idaho and Washington very quickly got their hands on them and sent up a flare and said, "This is really terrific information. It's better information than we're able to supply to our pharmacy and therapeutics committees. Can we join in an informal collaboration?" The three states in the northwest then got together in an informal way, but very quickly realized that there was far more to do than they could just fund in an informal collaboration, and so they began to reach out to other states to pool their funding and eventually established the

Drug Effectiveness Review Project, which is a three-year project to review the effectiveness, safety and effect on subpopulations of 25 classes of drugs. The other thing the Project does in addition to the systematic reviews is support policy makers in using these systematic reviews in their policy process.

A quick overview of the organization: It's managed and directed by the states' non-profit organizations that participate. The process itself is administered by the center that I work for, the Center for Evidence-Based Policy, and the research is done by evidence-based practice centers, all of them designated by the Federal Agency for Healthcare Research and Quality. The three that we use most prominently are the Oregon EPC, the EPC at the University of North Carolina Research Triangle, and the EPC at Southern California RAND.

Participating organizations, very quickly: You can see it's a broad cross-section of states that participate, all the way from Alaska down to North Carolina. California is one of our states. Montana actually is not on here. Another state has just joined. The two that are not states are non-profit organizations. One is the California Healthcare Foundation, and they have joined in collaboration with CalPERS out in California. The other is the Canadian Coordinating Office for Health Technology Assessment. They're one of our partners, and a very constructive and influential partner in the project.

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Let me just talk now about the systematic review process, because it lies at the heart of what we do, and is why I think what we do is useful to policy makers. Simply put, the systematic review process is thorough enough that it gives policy makers confidence that they have looked at and considered and accounted for the good quality evidence that's available on a global basis in order to inform their decisions around which drugs they'll use. This process starts out with formulation of key questions. Now, it'll sound axiomatic that you start out your research with a key question, but this is not a simple process when you're starting a systematic review, and we spend a good deal of time looking at the issue of exactly what we'll ask in our systematic reviews. We start out with a template that essentially has three major parts to it. The first part is, what is the relative effectiveness or comparative effectiveness of the different drugs within this class for attaining a given set of outcomes, for a given group of patients? Then the second question is sort of the same format, but it talks about the safety profile, or the adverse event profile of the medications in the class, so what's the comparative adverse event profile of all these medications? And the third questions that we always as is, what does the evidence tell us about any differential impact on members of subpopulations, be it folks on the basis of demographics, on the basis of age or race or gender or ethnicity.

So that's the general template, but there's a lot of work that goes into filling out those questions, and chief among them is determining which outcomes will be the key outcomes that we'll evaluate, and I'll just give you one quick example. Most of us think of a drug class called "statins" as a cholesterol lowering drug class. Now, I would argue that most of us, while we may think we care about our cholesterol, really don't care about our cholesterol, what we care about is dying prematurely of a heart attack or a stroke. So, what we try to do as we focus the systematic reviews is we try to give precedence and preference or an emphasis to real clinical outcomes, clinical outcomes that patients can actually experience. So, while we look at the effectiveness of statins in terms of their ability to lower cholesterol, we also put a great emphasis on whether or not they actually save lives or prevent strokes.

The one other thing I wanted to add about the key questions is they actually illustrate two things about the project. One is its thoroughness and the other is its transparency. So, you can get a sense of the thoroughness from my earlier remarks, but the transparency starts right here. As soon as we have a draft set of key questions ready for a new systematic review or the update of a systematic review, we post those draft key questions on our website, and we open them up to comments from all comers. So, advocacy organizations,

members of the pharmaceutical industry, concerned citizens or concerned medical practitioners out there, all are welcome to look at those key questions and comment. Their comments will be included in our consideration as we finalize the key questions.

Once they're final, we go onto a very important step, and that is determining what kind of research will qualify for inclusion in our studies. It's called the inclusion and exclusion criteria, and essentially we have a hierarchy of evidence. We really are first looking for head-to-head randomized controlled trials comparing the effectiveness, safety and effect on subpopulations of these various medications. Where those don't exist, or where there are an insufficient number of them for us to do a thorough job, then we move down to considering randomized control trials that compare the drugs to placebo. When it comes to the safety aspects, because randomized controlled trials tend to be fairly short in duration, we use observational studies as well because they have a longer timeline that allows us to catch complications and side effects that may show up after general use of the drug.

The next step is to evaluate the quality of the information. Not all studies are created equal. Some are good, some are not very good. We carefully read those studies and we determine which are high quality. Those that are of

high quality are synthesized into a cumulative look at what the research available tells us about the drugs that we have under consideration.

Once that's done, a draft report is published, and once again, this is placed on our website so that anyone, either in the industry, or advocacy groups and others can look at that draft report and send their comments on to us so that we can consider their comments as we finalize the report. And then, the final report is ultimately published on the World Wide Web in the public domain so that anyone can use it.

I want to talk just briefly about the way in which we interact with the industry. I think it's very important. The industry has a lot of great scientists working for it. It has a lot of good information, and one of the things that we do is meet with them on an annual basis to make sure that the lines of communications are open between us. We also ask for them to submit a dossier with any evidence that they think would be important relative to any give class so that we can consider that evidence. The only caveat is, we'll use the same analytic techniques that we use on the studies we find on our own, and we will on request divulge anything that the drug companies send to us. So we make sure that we carry on with our theme of transparency by saying anything that we come in and consider in our reports will be released.

I'm running out of time, so I'm just going to move on to the end. You can see in this, in your handouts, a brief summary of the way Oregon interpreted the first four reports that were there. We can talk more about that in the question and answer session is you would like. There's also a list of the classes that we have reviewed or have under review to date, and we're in the process of selecting our final classes at this point.

Very quickly, our participants use this in a number of different ways. They use it all the way from just using it in terms of provider or consumer education. They also use it to augment the information that their pharmacy and therapeutics committees have in their own preferred drug lists processes or as the primary information, or in support of other levels of government, such as is done by the Canadian Coordinating Office on Health Technology Assessment.

In closing, relevance to other payers, I'm going to—Sorry, we'll catch up here in a second—I want to just make a couple of quick notes here. One is, we believe that our reports are really tough for an individual consumer to use. They're not consumer-friendly. AARP and Consumer Reports or Consumers' Union have begun to translate these reports into more consumer-friendly formats, and I would encourage any of you that are interested to go onto their websites and take a look at those because I think they're very useful. Obviously,

when we look at the challenges of keeping US business competitive—I think General Motors has been in the news lately relative to medical costs. That's another important aspect and obviously Medicare, whether you're trying to avoid the donut hole or help control the federal deficit, having good, quality information to utilize in both purchasing decisions, benefit design and coverage decisions is going to be critical in the future. Thanks very much.

ROBIN OSBORN: Thank you very much. Do we have any questions that you might want to ask now? Yes, please?

MALE SPEAKER: Have you in fact saved the state any money, and if so, how? [Inaudible].

MARK GIBSON: Great question. Have we saved the states money? The answer is yes, and the way in which they've saved money is by utilizing preferred drug lists in order to place a premium on medications that are the lowest priced in the class when they're found to be equally effective, so among drugs in the class that are equally effective, then they're able to select the lowest price, and then insist on having providers utilize those. Most of the states, I'll hasten to add, have an exceptions process that allows a practitioner for a good clinical reason to depart from a preferred drug list, but we find that typically, a state that has a fairly aggressive editing process can get to 80 to 90 percent of a preferred drug in a class in new prescriptions.

On the statins, interestingly enough, when we did our first report, there were only three statins that actually had long-term outcome data that said they actually were effective in decreasing cardiovascular events. Since that time, all of the statins, with perhaps the exception of one have been able to provide us with information that indicates their ability to do that. At that point in time, you go into a fairly interesting discussion about the relative effectiveness of those statins on surrogate indicators, such as cholesterol levels and other lab metrics.

ROBIN OSBORN: Next, please.

MALE SPEAKER: When you're reviewing drugs in any class I'm assuming you're using the blood platelet cells to make comparisons of which drugs [inaudible]. Did you prove the [inaudible] off-label usage for medications? You know, ones today in a different class that are often used [inaudible] others?

MARK GIBSON: The question has to do with off-label use, and do we evaluate that? The answer is, it depends. Generally, the indications and the outcomes we're looking for are pretty close to the label. Our participants have, in a couple of cases, requested that we do an off-label review, so the use of anti-epileptic medications for the treatment of neuropathic pain and the treatment of bipolar disorder was one of those. There are some enormous costs that have been drive

by off-label usage in that particular class, and so they asked us to take a look at that. So it depends on what our participants really believe they need to have the information on.

ROBIN OSBORN: I think we can take one more question, and if you would, please identify yourself as well. Thank you.

JOHN: John [inaudible], a Robert Wood Johnson Fellow. This is a great [inaudible] and sophisticated process that's laid out [inaudible] and how long do they have to do it?

MARK GIBSON: Oh, it's a great question! The Evidence-Based Practice Centers, those of you who are working as congressional staff in health policy are probably familiar with AHRQ, the Agency for Healthcare Quality and Research. AHRQ designates evidence-based practice centers around the country—There are actually three of them now in Canada—and they are evaluated and designated as particularly capable of doing the kind of evidence reviews that we're talking about here. So those EPCs and researchers within those EPCs actually do the research. We have a very strict conflict-of-interest policy. None of the researchers are permitted to have any economic relationship with any of the drugs or the companies in the classes that they're reviewing. It takes them usually around nine months to complete a systematic review. Now, they could do that faster. The reason we take nine months is because we insist on transparency all through, and we insist on being able

to get feedback from outside the project to consider as we move forward at both the drafting of the key questions and then evaluation and peer review of the draft report.

ROBIN OSBORN: Thank you for a fascinating presentation. Now we'll move across the pond to the UK and we'll hear from Dr. Peter Littlejohns.

PETER LITTLEJOHNS: Good afternoon, Ladies and Gentlemen. First of all I'd like to say what a great pleasure, indeed, a privilege to share with you my talk today. It's quite an exceptional meeting, I think, and it really is a great opportunity for us to share views. If I'd been asked a few weeks ago, I would have given a different talk because it wouldn't have been the National Institute for Health and Clinical Excellence, it would have been the National Institute for Clinical Excellence, but governments, as you know, can change their policies, and over the last three weeks, the reorganization within the NHS has created this new organization which consists of merging the functions of the Health Development Agency to mean that the new institutes will now be looking at health promotion and disease prevention strategies as well as clinical strategies for the management of disease.

So what is it? It's the independent organization responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health in England and Wales. It aims to identify good clinical and

public health practice using the best available evidence, and we're heard how difficult that is. It's there to create standards for the NHS and local health communities, now broadening out to areas covered by social care as well as healthcare. It helped to resolve uncertainty for the public, patients and the health professionals, identify the evidence gaps and help fill them.

I think you need to see the context of these aims six years ago when there was a new Blairite government coming in, the first time that we had a socialist government after many years of conservatism, and they were very keen to reestablish the underlying principles of the NHS in that all healthcare should be available free of access to all those on the basis of need, rather than the requirement to pay. On that basis, they were aware of the so-called post-code lottery of care, that depending on which part of the country you live in, you had differential access, particularly to expensive cancer drugs.

So what does it do, and what is it? It's part of the NHS. It's a special health authority. It is governed by a board consisting of executive and non-executive members, chaired by Sir Michael Rawlins. It meets in public every two months to debate its issues and underlying it are three, if you like, guidance engines that produce the guidance. The Center for Technology Evaluation that produces technology appraisals, mainly pharmaceuticals, but also devices and other

interventions. The Interventional Procedures Program that assesses the safety and efficacy of new surgical procedures. You'll be aware of the debate around the safety of pharmaceutical industry products, but for many years, surgeons could actually do anything they wanted. The Center for Clinical Practice is much broader and produces clinical guidelines covering whole disease areas, for example, asthma and diabetes, and indeed, it's the way that those particular interventions are delivered so we also provide guidance on the configuration of services. What is the best balance between primary and secondary care? The new Center for Public Health Excellence will be doing the same thing as we've been doing for disease management, but for individual preventative strategies and also healthcare programs.

I haven't got time to go through all of the processes that we use but like to summarize with this slide that any guidance that is issued or produced by the Institute has to achieve these approaches: It all has to be transparent, inclusive, reliable and valid. Interpretation of evidence requires scientific and social value judgments, and being explicit about those values of part of the transparency of decision making, and those values need to be tested with the wider community, and by the wider community, I mean any constituency, be it the industry, patients, professional groups

likely to be affected by that guidance. They have a legitimacy in being part of the creation of that guidance.

Scientific value judgments are based around the strength, reliability and generalizability of the data, and while there is a lot of data out there, unfortunately, in terms of translating it into good guidance, it is often very poor. And so we move quite quickly from systematic reviewing, looking at the evidence to a decision analytical approach using modeling to produce cost-effectiveness. Of course, the validity of the assumptions in that are crucial and all those assumptions are heavily scrutinized by all the stakeholders through an open and consultative process.

William Blake is one of my favorite poets and artists and he said over a hundred years ago that God forbid the truth should be confined to mathematical demonstration, so we take into account social values, but the Institute doesn't have a monopoly on social values. Social values by definition come from the general population. So first of all we take into account the Secretary of the State's directions which include issue of equity and fairness as well as cost-effectiveness and efficiency. We use a very specific health economic methodology based on utilitarian philosophies, but also very technical in terms of the cost per utility that we endeavor to achieve. All our advisory committees and guideline development groups have representatives of all the stakeholders, patients, public,

industry, professional groups on them making the decisions, and we have a very active consultation process which is quite formalized and run through the website.

But finally, we've established the Citizen's Council, a group of ordinary—if they can be called ordinary—individuals who have no background at all within the healthcare sector, and they have been convened. We went on prime time television to recruit them. We had 30,000 expressions of interest. As you can imagine, it's quite difficult to get 30,000 down to 30. They now meet twice a year and debate ethical and moral issues underpinning the NIHCE guidance. The most recent one they've been looking at is orphan drugs. How do you assess the cost-effectiveness of drugs affecting a very few people, almost named individuals costing a lot of money?

At the core of the NIHCE approach is assessment of the differential value of interventions and drugs. Overall, what are the benefits versus the costs? And indeed, in your papers there is an argument that we have a threshold, the so-called 30,000 threshold. What we're saying is, does a drug actually improve life? Does it improve the quality of life? How much are you going to pay for it? But in fact, we don't have a threshold, because cost-effectiveness analysis is just one component of assessing the value of any intervention. What we have is a probability of accepting or rejecting a drug based on cost-effectiveness, but also on other issues of fairness,

equity, the quality of data and indeed, how can you assess one drug where it is the only intervention that is life saving against drugs where there may be ten other drugs? So the issues around debating the value of those two drugs are different. That's why there is a probability of assessment of cost-effectiveness.

Now, this is my favorite slide, because it breaks all the rules of slides; it's multi-colored and totally complicated. But it summarizes the rather messy world in which the Institute works. This is our guideline program. We developed a system to produce guidelines, we quality assure it. So there are only 12 NIHCE employees at the Center. They're supported by guideline review panels consisting of all the stakeholders I've mentioned that quality assure that process. And we've established seven national collaborating centers, again, a consortium of academic, professional and patient groups to produce the guidance according to our specifications, and they manage half a dozen guideline development groups. So all in all, there are about 600 involved at any time producing guidelines, but many thousands if you add in our stakeholders.

Over the last six years we've produced 37 guidelines in these clinical areas, 42 under development. The appraisal program, 87 appraisals completed in all disease areas. But you can see that cancer was the most common and that reflects the concern in the UK that we were falling well behind

international standards in terms of our provision of cancer services.

Again, the intervention procedures, cardiovascular work and obstetrics and gynecology. I think it's amazing how inventive the various surgeons are at attacking the heart and the uterus over the last few years.

Our public health excellence processes are out for consultation, but already we've been given our work program by the Department of Health, looking particularly at areas of inequity of health status, particularly around exercise, underage pregnancies, sexually transmitted disease, and indeed, smoking. These are the public health programs bringing together not just single interventions to achieve therein, but having sweeps of interventions to produce whole programs. Again, we're out for consultation on how these are going to be achieved.

I'd like to finish now looking at the status of the impact of NIHCE guidance. This is the model that the government produced in 1999 for the quality assurance mechanisms within the NHS. Standards will be set nationally, initially by NIHCE and the National Service frameworks, but in the future just by NIHCE. They form parts of core and developmental standards that all NHS organizations are expected to achieve. The responsibility for that implementation, though, is local, and reinforced through CPD and professional

regulatory mechanisms and our quality assurance program called Clinical Governance. There is an expectation that both professionals and their managers will achieve these standards. There is an independent inspector at the Commission for Health orders an inspection that assesses the overall quality of NHS organizations and part of that remit is to assess the implementation and the utility of NIHCE guidance in all its remits.

What's the impact been? Well, the Institute's been running for six years. This is our monthly website, HITS, and at the moment, we're getting four million hits a months for our guidance. Our guidance is issued as full guidance, as the evidence based, and patient leaflets, and sixty percent of those hits come from this country.

We've asked the general public what they thought of NIHCE. These are two national polls. First of all about 25 percent of the public have heard of the Institute, which I'm told for a specialist organization is not bad. Of those 25 percent, quite positive. Considering that the press presents us as a rationing, cost-containment organization, we're rather proud of that figure.

Our elections are in three weeks, and so it's always reassuring around election time to know what the politicians think. This particular survey was done by standing MPs last year before election fever took over, and you can see that

there's quite broad, cross-party support for what the Institute does. Indeed, it's rather worrying that these figures suggest that the percentage of MPs who are satisfied with the Institute's work.

What do the professionals think of us? Well, in 1999 when we were established, like all government initiatives, the professionals were rather suspicious. They thought we were a puppet of Tony Blair. Indeed, [inaudible] are oft about in the medical journals, particularly in the BMJ, there was a debate on the failings of NIHCE, wrong sign referring to the Scottish Intercollegiate Network Guideline program. It distorted national policies. One of their arguments was that we weren't rationing enough. We weren't tough enough in making our decisions. The Lancet probably got it right, because we were trying to achieve a rational approach rather than a rationing approach.

To finish, now the British Medical Journal, you may know that Richard Smith, its editor, finished this year, and on his closing editorial he talked about the triumph of NIHCE, "NIHCE may prove to be one of Britain's greatest cultural exports along with Shakespeare, Newtonian physics, the Beatles, Harry Potter and Teletubbies [laughter]." Talking to my chairman, Sir Michael Rawlins, he was pretty happy with the first three. He was rather worried about the others, and I had to explain to him what a Teletubby was. But, it was typical

Richard Smith. It was praise, but could to better. There's always a sting in the tail, and if you're read that editorial, you'll know about that because of what's in the last paragraph. Thank you for your attention. I'm very happy to take questions.

ROBIN OSBORN: Thanks very much. I'd like to have the first question, actually picking up on a comment that Mark Gibson had made about the challenge of developing information on drugs for consumers, and with NIHCE's orientation to involvement of citizens on the citizen's council, and to incorporation of public values into the process, how do you address the challenge of providing information to your citizens' council and to the public in general about the drugs and the choices that you're recommending?

PETER LITTLEJOHNS: Well, as I emphasized in my talk, it's much easier if they're part of the production of our guidelines in the first place, so when issues, if around appropriate outcomes that are relevant to patient groups, to individuals with the disease, having them there, debating and incorporating their views, it is important.

But we're also aware of translating that into evidence that can be used and we have a patient support unit located within the Institute consisting of half a dozen people who spend their time working with the groups, educating them before they come into our guideline development groups so that they

can participate fully. At the end of the day, it's also through the public media. We made a decision very early on that rather than treating the medica as part of the problem, we would treat them as part of the solution, so we unashamedly work very closely with the media, professional groups, professional media, but indeed, the popular media, to try to get them to understand, and most of the controversial guidelines we issue we do in a formal press release with invited media people there.

ROBIN OSBORN: Thank you. We have time for one additional question now. Yes, Sir? Can you please identify yourself?

MALE SPEAKER: Yes. [Inaudible], this is going to be about decentralization of something, and some particular surgery being far more frequent than [inaudible] for another surgery, more frequent in Arizona and New Mexico. Since you have a national health [inaudible], do you have any such problem of uniformity of care [inaudible] on a national basis? And also, this is true [inaudible] heard about national health, that someone at my age would have to wait a lot longer for surgery than somebody your age.

PETER LITTLEJOHNS: [Laughs.]

MALE SPEAKER: I put that wrong.

PETER LITTLEJOHNS: Right. I think two issues there. Certainly, I think because of the national nature of the Health

Service even before NIHCE existed, that we didn't have such diversity of interventions and unrated interventions that you have in this country, but as I said, that there certainly were difference, and they were unacceptable differences. I think we need to distinguish between those that are acceptable in terms of the mix of patients, the age groups, the interaction and even the requests of patients, because what NIHCE is doing is not dictating how clinicians should offer care, but to facilitate the debate and discussion between the professional and their patient about how that decision should be a joint decision. We certainly have evidence of reduction in some of the poorer areas, particularly around provision of cancer drugs. But there are other areas where we've still got a lot of work to do.

Coming on to your issue of access, that's certainly been a priority of the previous two administrations, and judging by the promises in the last week that's going to be the aim for the next organization. But we certainly don't have any what we call ages policies, and the actual access to service depends really on the speed of the local services and what the government is doing. I have to be careful, because that's supposed to be [inaudible] at the moment, not talking about government policy. What they're doing is identifying that if local services can't provide enough services within a certain period of time, then patients have the freedom to go anywhere,

and you could extend that even into the EEU in certain contexts.

ROBIN OSBORN: Thank you very much. We'll now move to Dr. Peter Sawicki who'll tell us what's going on in Germany.

DR. PETER SAWICKI: Yes, I will try to do that in a few seconds. First of all, let me thank you for the invitation. It's pleasure to be here with you, and I will try to describe to you very briefly the philosophy and the structure of the German evidence-based policy making in healthcare. As you may know, we do have a solidarity system in Germany, where everybody's insured and everybody pays for so-called statutory health insurance funds, and from that everything is paid for those who need it. The major problem is to decide what is the need of a single person and what is the need of the population, and I will show you some of our problems now with respect. This is the topic here with the pharmaceuticals here. Well, there are of course a lot of other topics, but this is the one that I have to cover during this ten minutes talk.

First of all, a very interesting thing that you can see on this slide that happened to Germany during the last 14 years is the change in prescriptions and the change in expenses for the health insurance system. AS you see, there are fewer prescriptions per year, starting with about one billion 14 years ago, and now it's 30 percent less, so the doctors prescribe less and this is due in most cases to more rational

prescribing and more evidence-based prescribing. And we have here arrived in the same time in the expenses, and this rise is a 50 percent between 1991 and 1993, so we have the one less prescriptions and we pay more for this.

Politicians used to calculate this and they thought that if this goes on for the next five years, our solidarity system may be damaged because the people will not be willing to pay so much money if it's not proven that this money is well spent. So what we are now trying to do is find a scientific method of how to spend the money well within the solidarity system.

The second thing you may already know is that we do not have a government system of controlling this and making the decisions but a self-administration of healthcare in Germany. In 2004 health reform took place in Germany, and this was a little bit changed now. The major institute now takes all the discussions, the Federal Joint Committee and this consists of patients, physicians and representatives of sickness insurance funds. Of course, there's some legal supervision of Ministry of Health, but this is entirely independent of the state. This is very important to the population of this country, a little bit afraid of the government no matter which party is on at the time.

The second institute is the Institute for Quality and Efficiency in Healthcare, and both are independent of each

other, but they work and cooperate with each other. This institute produces the scientific evidence on which the decisions which are made by the Federal Joint Committee are made. This is only scientific, and this takes also into account the social part of the decision, which is of course, also important. The task of the new Institute of Quality of Healthcare is very briefly, evaluation of the benefit of diagnostic and therapeutic medical procedures, evaluation of evidence-based guidelines recommendations for disease management programs, very important evidence-based information for patients and physician is the major fore-task of our institute. If we base these decisions upon evidence of course you know that you would have a lot of different studies, and these studies have different qualities and the results have also different meanings from all the different studies, and there is some kind of error you make when you base your decision upon these studies, and the further down the slide you get, the lower the error, but it will never be zero. You can just diminish the probability of making a mistake within your process, but it will never reach zero.

The major problem we have now is that the available evidence is not sufficient evidence. The evidence you need to make a sound decision, it’s not equal to the evidence you have after a thorough search in the literature. This is something we, and everybody has to cope with at any of the institutes.

What do you do then, if you have a different amount of evidence published, and you need something more to be sure that you do not make a mistake? This is something we have now thought about, and one of the first aspects of this is that the sufficient evidence to show a benefit from a pharmaceutical agent usually requires good quality data from randomized controls, usually. This means that it doesn't always have to be the case, but the larger the gap between the sufficient and the available evidence, the stronger the need for extensive explanation of a positive decision. There are ways to explain that, but you have to explain if you decide, if you do not have the evidence that you want to have. Nevertheless, if you make the public pay for something then you have to explain why and you have to have good reason for that. So the gap between available and sufficient evidence must be put into a relation, into, for example, nature and severity of the disease. If the disease is fatal and you are desperate you will have a lower grade of decision gap, a negative to the therapeutic effect. For example, antibiotics or insulin. If the effect is so big you see it without proper randomized control trials, and the availability of alternatives. If you already have a good treatment for a disease, then you must be very cautious to introducing new ones because it not only may cost more, but it may harm the people.

Effects and benefits: We go more for the benefits and less for effects, and the reason is that this is not equal in many cases. One was the question you put with the cholesterol. We'll come to that in a moment. The proof of benefit is influencing patient-relevant outcomes, and this in most cases is mortality, morbidity and disease related life-quality.

The proof of effectiveness or even efficiency is not necessarily a proof of patient-relevant benefit. I will show you several mistakes from the history of medicine on that. For example, cholesterol. You can lower cholesterol, which is of course, associated with a bad prognosis if this is high with clofibrate, but this results in an increase of mortality. There are even several examples where you reduce the so-called surrogate markers, the non-patient relevant markers, like cholesterol or arrhythmia or Vitamin A in your blood, and the effect that matters goes in the opposite direction. That's with Clofibrate. Arrhythmia is of course, bad for you, after a myocardial infarction. You have a bad prognosis if you have arrhythmia, but if you diminish your arrhythmia with the arrhythmic agents, this results in an increase in mortality. Vitamin A concentrations in blood are negatively associated with poor prognosis of, for example, lung cancer, but if you give in randomized controlled trials Vitamin A and beta-carotene to smokers, for example, you will increase the risk of lung cancer and also increase the risk of mortality. Bone

density, the higher bone density the lower the risk for fracture. But if you increase bone density with sodium fluoride, you will increase three-fold the risk of fracture. Heart attack and hormone replacement therapy, of course you know this example. Everything changes in the right direction. Fibrindizen [misspelled?] went down, the insulin resistance went down, blood glucose went down, cholesterol went down, but what happened was that these post-menopausal women had more strokes and more heart attacks with hormone replacement therapy. So surrogate markers may be in many cases misleading, so we are very cautious to use the surrogate markers, and we want to have relevant patient-oriented outcomes with morbidity, mortality and life-quality.

The second step is to recognize that the proof of benefit in scientific trials does not necessarily mean benefit for the population. This may also go in different directions. I will show you a recent example for that. Rofecoxib, Vioxx, and I will not talk now about the cardiovascular side effects, which you have probably all read in the newspapers, but about the gastrointestinal complications of Vioxx. This slide is a figure taken from the vigor study, and the vigor study showed that you can reduce bleeding, gastrointestinal bleeding when using Rofecoxib with the conventional painkiller, naproxen, and one would expect that this would translate, if you replace all the agents with the newer Vioxx, in the reduction in bleeding

in the community. But this is only shown in trials. In population, different aspects also ruled. For example, the way the drug is marketed, the way the physicians use this drug, which patients are given such a drug. I will who you also here a very recent paper from Ontario, in fact, from Canada, where Mondavi [misspelled?] looked on the association between the prescription rates of celecoxib and rofecoxib, the cox-2 inhibitors, and the development of the hospital admission rate for bleeding. What you see is that the prescription rates went up, the 40 percent, of course, and at the same time, the admissions to hospital for gastrointestinal bleeding also went up. So this goes in completely different directions. You may result in a different outcome. You may come out with a different outcome, nevertheless. You can't explain causality, of course, because this is a population-based study, but the things you do and the things you look at in randomized control trials may be different from what you see when you investigate populations.

In the end, I would like to come to the point, which is of major importance, the single patient. I'm still treating patients myself. So the proof of benefit in the population is not the benefit for the individual patients, so the patient has to decide for himself or for herself whether he or she wants to take the risk to get a benefit. So what we are also doing is very straightforward patient information where we describe the

probability of benefit and the probability of harm, and also the extent of uncertainty of this information in a way that every patient can understand it, and can make then his or her own decision whether he or she wants to undergo this intervention and to take this drug, in some cases, life long.

We just started six months ago. That's when the Institute opened, and we do not have a lot of results, like Littlejohn from NIHCE has, of course, but we will try also to in five or six years to have such a good editorial in the British Medical Journal. That is our aim for the future. Thank you very much.

ROBIN OSBORN: Thank you very much. I think what we might do is move on directly to Dr. Andreas Laupacis from Canada and then save questions for the end because we're getting a little behind on time. Thank you.

DR. ANDREAS LAUPACIS: Good afternoon. Thanks for inviting me. I'm just going to give you one slide on sort of a set up of drug policy in Canada. In Canada, the federal government has regulatory responsibilities around drugs in terms of deciding which drugs can be marketed, but for the actual administration and payment of drugs, like all other health services in Canada, it's almost entirely a provincial or territorial responsibility, so there's a slightly odd division of responsibilities.

In-patient drugs in Canada are covered out of the hospital global budget. Outpatient drugs are publicly reimbursed if they are on a formulary, and if patients are eligible. In Ontario, the province I come from, anybody who's 65 years of age or older will have their drugs paid for free of charge with an annual copayment, I think, of $100 Canadian, which is like about $80 US, provided that that drug is on the formulary. I will spend most of my time today talking about the issues of getting that drug on the formulary or it not being on the formulary.

In Canada, in terms of outpatient drugs, 46 percent of drugs in total are paid by these public plans. Many patients like myself who are not eligible because I'm not yet 65, do have private coverage, so that 34 percent of drugs in Canada are paid out of private, and the maximum price for a drug is established nationally by a national organization, and that price is based simply upon the median price that is charged in seven other countries. So it has nothing to do with the value of the drug. It's basically, we're gonna pay a maximum of the median of seven other countries—the US is one of those countries—and in very marked distinction to my understanding of your system here, there is very, very little price negotiation in Canada around drugs. It's basically, the drug company will say, "We're charging the maximum price we're allowed to charge; take it or leave it." And if organizations like the one I'm in

charge of go to them and want to negotiate, they'll say, "Well, prices up here are already a lot lower than they are in the United States, and we're not going to go any lower."

So I'm going to spend most of the talk then talking about the reimbursement committees, because that's actually how we regulate the cost of drugs and the use of drugs, because we don't have much flexibility around price right now. There have traditionally been a number of provincial committees, and I think next to Australia, Canada's probably the country that has the most experience with using cost-effectiveness evaluations to make decisions about the reimbursement of drugs.

Most recently there's now a national committee—this is the one that I chair—called the Canadian Expert Drug Advisory Committee, which is making national recommendations about the reimbursement of drugs. All of these committees make recommendations based upon a review of the drug's cost effectiveness, and I would remind you that there are two words in cost-effectiveness; in my opinion the most important one is effectiveness. A drug cannot be cost effective if it isn't clearly effective, and in many instances, an extremely expensive drug, if it is extremely effective, is actually cost-effective.

The recommendations options that we have is to make a drug general listing, which means that if a physician pulls out a prescription pad and writes a prescription it will be paid

for by the province or territory, no questions asked, limited listing, which would be say, we suggest you pay for this drug under these particular clinical circumstances, or we suggest that you not pay for this drug at all. It's important to understand that patients can actually obtain any drug that is approved by our equivalent of the FDA that's not on the list if they want to pay for it.

So, the Common Drug Review, which is this new national evaluation of drugs is a single process for reviewing new drugs. We're right now only reviewing new chemical entities and providing formulary-listing recommendations. It's important to understand that this committee is basically saying to the ten provinces and three territories. "We would recommend that you do or do not fund this drug," but the ultimate decision is left to the ministers of health in each of those 13 jurisdictions. The Common Drug Review is funded in an arm's length basis by the provincial, territorial and federal governments, and it consists of a systematic review of the available clinical evidence, a review of pharmacoeconomic data, and then a listing recommendation made by the committee that I chair, which is an independent committee and as I mentioned, the drug programs may accept or reject our recommendation. So the process, very briefly, is that the drug company submits information about effectiveness and cost-effectiveness if they want their drug to be on the formularies. The CDR commissions

an independent clinical and economic review of that submission. That review is sent to us and it's also sent to the company for comments. The committee then reviews the review by the experts and the drug company's comments on that review. The committee consists of 11 individuals, eight physicians, three pharmacists. There are no health economists on it. There are no public members, which is a controversial issue, and there are no representatives of the government or the payer. If we say no, the drug company may appeal. We consider that appeal as quickly as we can, but they can only appeal once. If the recommendation is a do not list the second time, that's it, although they can resubmit if new information becomes available in terms of a clinical trial. The average time for this whole process from drug company submission to a positive decision is five months. It's obviously longer for a negative decision because we have the appeal process. Our recommendations are made publicly available, and one of them's in your package, and you can look at them at the CODA website, and to date of the 22 drugs that the committee's evaluated, nine have resulted in a recommendation to fund in some way or other, and 13 in a recommendation not to fund, which is similar to what the provincial drug plans have been doing in the past.

So, with that rather fast review of the sort of set up, what I'd like to do is spend a bit of time on my perception of what the perspectives are out there about this process, so the

perspectives of the committee then, the 11 experts, is that I think in general we think the process has gone relatively well. We have not ended up in court and we have not very often ended up on the front page of the newspapers. We have noted, though, that it is not easy to find methodologically sophisticated, clinically savvy, unbiased reviewers who are willing to do these reviews in literally two to three months, so that's a challenge. We do have concerns about the possibility that there are important randomized trials that we are actually not obtaining information about from the pharmaceutical companies, and unfortunately the people, in my opinion, that set up the CDR set it up in such a way that we do sometimes get unpublished information from the drug companies, but we cannot actually comment on it publicly in our reasons for recommendation without their approval. So in some of our recommendations you'll see this slightly bizarre thing that says, "We reviewed three randomized trials. This is the result of the one, and by the way, we can't tell you about the other three." Usually, those have been negative and I think the reviewer could kind of figure that out from looking at the thing. I think it's unfortunate, if we're talking about using public dollars for this that we're not making this all public.

There is a clear tension between making promising drugs available quickly and real-world cost-effectiveness, so the CEDAC committee operates at the—and Peter spent some time

talking about in the real world cost-effectiveness. Our equivalent of the FDA is sort of operating, in my opinion, in the area of sort of trying to make drugs available fairly quickly, so an example would be an Iressa, which is a drug for lung cancer. We looked at the evidence and actually recommended against funding that because we were not convinced that the drug actually did impact upon clinically important outcomes. That drug, though, had been approved by our equivalent of the FDA, and so there was that kind of tension where patients sort of said, “How could you not recommend funding?” It turns out that the subsequent two randomized trials actually have shown no impact upon mortality, so to date that recommendation not to fund stands. It’s a disappointment to many of us on the committee that there are some jurisdictions across the country who are taking a long time to make up their mind whether they’re gonna follow our recommendation or not, so-called “policy–making by dithering,” and other jurisdictions have been fairly fast off the mark. To date I’m not aware of any jurisdictions that have actually gone against our recommendation, but there are a bunch that are taking about 10 to 12 months at least to make up their mind. And then there are concerns—this is very important because we don’t have the public involvement, and I want to make it quite clear that this committee looks at cost-effectiveness, and in some instances, as Peter mentioned, there are other issues that are just as

important, if not more important, so there's the issue around Fabry's disease. Again, when we looked at the evidence around the drugs for Fabry's disease a few months ago, we came to the conclusion that there was no evidence that they were cost-effective. It may be that society, though, given that this is a rare disease, no other treatments, might then decide that despite that, they would reimburse the drug. As I mentioned, there's no price negotiation, which I personally find disappointing.

My sense of the perspective from the patients and the public: To date there's been relatively little public interest, certainly not 25 percent of Canadians would know about CEDAC or the CDR like they do about NIHCE, but there has been great interest from patient groups, and there is concern from these groups that the public and patient voice is not being heard, and actually the Common Drug Review now is looking at options of incorporating the public into it, whether it's having public members on the committee, whether it's having something like the citizens' council, that to my knowledge has not been decided. And there is this concern that this process is not appropriate for these orphan drugs for very, very rare diseases. If there's a problem with the Canadian healthcare system it is access to care. Actually in the public, there's more concern around access to rapid hip and knee replacements than there is frankly right now on average to access to drugs.

In terms of the public formularies, I think the provinces and territories are in general satisfied with the process. They point to the Vioxx story as justification for a restrictive formulary. In British Columbia, Vioxx was never reimbursed. They were never convinced that the drug was cost-effective and always had concerns about its overall risk/benefit ratio, and they are now sort of pointing to the fact that they believe that having a restrictive formulary actually saved the lives of some British Columbians in terms of avoiding cardiovascular disease. As I mentioned, to date the listing decisions have all followed CEDAC recommendations, although some are taking some time. Despite all this, though, and despite our saying no to 13 out of 22 drugs, there is still enormous pressure on drug budgets in Canada, and the drug budgets are going up in the last two years, somewhere between 10 to 15 percent per year. So, this is not a cost-cutting exercise. If it was a cost-cutting exercise, we're incredibly incompetent at it.

And then there is political pressure related to the drugs for orphaned diseases, which in my opinion is likely to increase in the future as we get anticancer drugs that are incredibly expensive that are targeted at very small subgroups of people with cancer who have a particular genetic subtype for example.

From the perspective of the physicians, they are aware of the problems of increasing drug costs, however, their major interest is to provide the best to their patients, and therefore they're ambivalent about this process. They're frustrated with the slowness of getting access to drugs sometimes and the formularies to them sometimes seem out of date because we're always focused on the new drug and not very often going back to look at the decisions that were made four, five, six, seven years ago.

From the industry perspective, there is concern in Canada voiced by industry about restricted access and the time delays. They do emphasize the apparent contradictions sometimes between the regulator, for example, saying you can sell Iressa, and the committee like ours saying we suggest that you not pay for it. And there is a fair amount of political activity in terms of industry linking the obvious much less investment in research in Canada than there is in the United States, for example, to the fact that we have restrictive drug policies which doesn't make it attractive for industries to invest in Canada.

So in summary, in Canada there's a long history of drug formularies based upon cost-effectiveness, with, as opposed to you folks, little price negotiation. I think actually the landscape is going to markedly change over the next—well, it's changing already. We're going to switch from the blockbuster

drugs like the statins and the Vioxxes and Celebrexes to, I think, smaller market extremely expensive drugs, which is going to change the way these committees work, because as I said before, Canadians can pay for these drugs if they want to, if they're not on the formulary, but if the drug costs $50,000 a year, there's very few Canadians that can afford that kind of money.

You know, and in the end I certainly disagree with Robin and her introductory comments. I sure don't think Canada's got the best healthcare system in the world. I don't think anybody knows who's got the best healthcare system in the world. Drug policy is a mix of scientific evidence, judgment, altruism, self-interest and politics that superimposed on a complex, semi-rational, constantly changing overburdened system. That's at least the way it feels like in Canada. My suspicion is that you guys are at least as bad off as we, and I wish you good luck [laughter]!

ROBIN OSBORN: Thanks very much for a great presentation. Again, we'll try to hold any questions or comments until the end. We have one more speaker, Marc Berger, who comes to us from Merck and we've designated him as providing the industry perspective. Thank you.

DR. MARC BERGER: Well, first, thanks very much for being invited to be on this auspicious panel, and let me say that what I'm going to give is not necessarily an industry

perspective. It will represent the perspective that I hold and that my company endorses. Probably there's a diversity of opinion within the industry just as there is a diversity within the opinion across governments, stakeholders and everything else.

The colors on my computer at home are much better than this, so it's in your packet, and hopefully you'll be able to read it, but since I don't come to talk on Capitol Hill very often, I thought I'd echo some words I heard many years ago. What do we know? When do we know it? And the thing I'll add here is, when will we learn what we want to know? I'm not going to dwell on parts of my talk because my colleagues have really made a lot of points for me, but I'm going to go down into some of the weeds around this area of how we know what we know, which is really a very difficult issue. This is a relatively new field, and making sure we get it right is something everybody strives towards, but I don't think we have an agreement yet about how to do that.

So, first a couple of statements about what I believe, and I think what my company also believes, and that is Merck supports comparative effectiveness to inform best practice guidances and coverage policies. It makes sense for us to make these important public policy decisions with the best available evidence. But these evidence reviews really look at the impact across very large populations, so we believe that population-

based evidence-based medicine should not preclude access to non-preferred interventions that are medically necessary for individuals. That is, there always are some people who may not benefit or be able to tolerate a preferred drug. They should also, as appropriate, have access to those non-preferred drugs. Now, whether that's through an exception policy or whether it's based on subpopulations, the fact is, what makes sense on average for the whole population, as we've heard a couple times, may not make sense for an individual patient.

Finally, comparative effectiveness analysis should not start with the premise of saving money in the short run. The fact is that the march of new medical technology and drugs is one of the engines that's driving increases in healthcare costs, but it's also one of the things that is driving improvements in health outcomes. People are living longer. They are living better, and in part that can be attributed to the march of technology and at least at an aggregate level, economists would say this is very much worth it. What's at issue though, is this politically acceptable? Do people see this as affordable? And what choices are we making?

So, we have a problem, and the problem is that you've heard there's a gap between what we'd like to know and what we do need to know. It's a limited supply of good quality comparative effectiveness information. Unfortunately, this will never go away. No matter what happens in the future, even

when the day comes when we have perfectly automated electronic medical records and everything seamlessly put together, we're still always going to have incomplete information at the time that we need to make the decisions. As you heard, that leads to a desire to look at all the best available evidence within an evidence-based medicine framework, and we know that there's some evidence that's of better quality in terms of certainty around what you think you know, and what we've heard here already from others is that consistent evidence from head-to-head randomized control trials provide the greatest certainty. But what I'll also tell you is there is no universally accepted approach to evaluating the evidence in the US today, and there are still open methodological questions that I think my colleagues on this panel would all admit to in terms of how you evaluate evidence in specific situations. And there is no consensus about what represents adequate information to assess comparative effectiveness, so that means whenever you take whatever you think you know, and now you want to translate it into a policy recommendation, different places will assess evidence differently so that, we've heard that in a very restrictive formulary that we heard about where they didn't let Vioxx in a formulary, in fact they only accept RCT data, the articles in your packet that talks about that. There are other places which accept different levels of evidence. We don't have an agreement from government to government about what

level of evidence you should be accepting in terms of making decisions about access to new technology.

So with that problem statement, let me give you my take home points. That is, RCTs may provide us the highest quality evidence, but as you've heard from others, it only tells us a part of what we need to know, and ideally we need to have a mix of other information. EBM is the appropriate approach that uses the best available evidence, including RCTs, observational data, decision models that can provide us with comparative effectiveness information. What we will say, though, is that we need to make our policy goals more explicit because by making those policy goals explicit it would drive what would be the choice of comparative effective methods that are appropriate for achieving those policy goals. Also, by making those policy goals explicit, we could develop a coherent strategy to fill in the gaps. How are we going to set our research priorities?

So, I'm not going to dwell on this, but suffice it to say, there are methodologic challenges when you don't have good randomized controlled head-to-head trials, and combining results from non-head-to-head studies can be done within evidence-based framework, however, frequently they're looking at different populations, different durations of followup, non-comparable dosing, variation of how they define end points and the protocol specified procedures, all of which makes it

difficult to just say this is all comparable. And as I've said, this situation is never going to be relieved, because even if we have ways to boost our supply of other available evidence, the fact is, RCTs are expensive, they take a long time to do, and therefore, we are not going to, generally speaking, expect that we're going to do an RCT for every situation, for every comparative question that we have for each subpopulation defined by age, gender, disease history, previous treatments, all of the things that you would need to do to gt that highest quality of evidence.

So, obviously the perfect cannot be either the end of the good and so we go ahead and we assess what we have based upon the information that we have. Even when we have RCTs, good head-to-head RCTs, we also recognize that indeed is not perfect information, because what an RCT tells you about comparative efficacy is, what happens under ideally managed situations where patients are very compliant and you have a very selective population so that you can really measure the signal very well between the different therapies. That's not what happens in the real world, and as you heard here from an earlier speaker, that what you see in an RCT may not translate into what happens in a real-world situation. Now, that may be because the populations that are being treated are very different, it may be that there's a lower adherence in general population—it can be for a variety of reasons.

So what do you do in the absence of good head-to-head RCTs or other good information? Well, in the old days the option was, let's not make any inferences and let's leave it up to the individual practitioner and patient to say, "Based on as best as I understand the evidence, this is what I think is right for the individual patient." I think those days are gone.

Option two is to give formulary preference to treatment options with more complete information regarding risks and benefits. You've heard that several years ago when the Oregon Health Sciences University Evidence-Based Practice Center was doing their review for statins, at the time there were three statins which had proven long-term effectiveness information in terms of decreasing mortality. They recommended that those are the ones that should go on formulary. That's not the same as what the policy makers ended up deciding at the time because there were other statins on the market which there was an anticipation may some day have additional information about their effectiveness. Is that the right thing to do? I don't know. One thing I do know is that a lot of these studies that have developed those long-term effectiveness information have been performed and funded by pharmaceutical companies, and by not providing them with the incentive, by giving them extra credit for having done those kinds of studies, you provide a disincentive to getting the additional information we'd like to

have. The question is today, if statins came to be reviewed, would they be approved today based on lipid lowering? The fact is, they were back then, and in fact, millions of patients got lots of benefit, and there were expert panels, including the National Cholesterol Education Panel which recommended the use of statins in advance of where proving they actually had the mortality benefit because it was anticipated that based upon the best available evidence, they were going to have a real benefit to patients. This is a real question that we need to talk about.

Option three is to use the best available evidence and a rigorous comparative effectiveness framework, however, where there needs to be some additional discussion about how you make that decision and how you translate those recommendations into policy decisions? I'm not going to go into this because you heard it better from better experts than I about what EBM includes. It includes rigorous literature synthesis, metaanalysis decision modeling, and what you've already heard from the other speakers is that the assumptions that you have in using this approach all require judgment and therefore can be open to question, and therefore, the legitimacy of any decisions that we made need an inclusive and deliberative process and transparency about the key assumptions and how the decisions are made, and that these kinds of decisions have associated with them a lower level of certainly.

What I haven’t heard anybody talk about today is what do you do about that certainty? The question that we need to be asking and which has not gotten as much attention, I think, in the public policy discussion is, given the fact that you’re making decisions with imperfect information and you may have a chance for error, what is your tolerance for error, and what kind of error? There are two principle kinds of error. Statisticians call it Type 1 and Type 2. Type 1 is an error of commission, or false positive, thinking there is a difference when there is none. So you think that Drug A is more effective than Drug B, or you think that Drug A is safer than Drug B, when in fact there is no difference. And then there’s the reverse kind of error, the error of omission or false negative, thinking there is no difference when there is one. Depending on the situation, you would think that you would have a different tolerance for those kinds of errors. We would argue that when you have serious life-threatening health conditions, there’s a greater willingness to accept less-than-perfect information as decisions must be made by doctors and patients. On the other hand, when there are asymptomatic populations who are at risk for developing a condition, there’s a greater desire for certainty. In both of those situations you might have different tolerance for Type 1 and Type 2 error.

The recognition that we don’t have a resolution to the tension that was raised here about having as rapid of access as

appropriate to new technology that might provide benefit and at the same time knowing the full risk/benefit/cost profiles for new technologies is being played out today in many ways. Certainly CMS is weighing in on this right now, the Center for Medicaid and Medicare Services, and they issued a draft guidance in April about coverage which evidence development, and they talk about in there wanting to not slow the access to technologies that are believed to have benefit, but at the same time recognizing that they may not have complete information, and they talk about now asking for additional evidence to be developed, and that can be done either through observational studies, practical trials, or randomized control clinical trials. I'm not going to go into the differences between those, although we can get into that within the question and answer period if people desire.

We believe that the future should focus on having a really good conversation at the policy level with all stakeholders about how we should set our priorities for generating needed comparative information. How do we fill in those gaps? One could argue that not all those gaps are equal, and therefore, if we have limited resources to fill those gaps in, we should be able to make good prioritization about that. How should we decide what is the most appropriate method to generate that information? Some ways of generating this information are more expensive than others, like randomized

control trials. They provide greater certainty, but they're more expensive. Some methods, like doing database studies are less expensive but provide less certainty. How do you titrate the right method to the question that's at hand? And at least in the US there needs to be greater public acceptance of priority setting. We need to assure consumers that the primary purpose of evidence-based medicine is not cost containment, but it's to make sure that we're providing access to the best therapy that we know that has the best evidence and is right for the patient, and that we legitimize decision-making through deliberative and transparent process. Potential criteria that we could use for priority setting might be around thinking about the value of the information. Now, there is formal value of information analysis, and that's also discussed in one of the articles in your packets, but basically it says that you can pretty much know where you're going to get a bigger bang for your buck in getting more information based upon the clinical and economic burden of a disease, the potential for change, care practices, the existence of safe and effective alternatives, and the consequences of not having the information. In terms of how you select the correct methods, here's where we need to have a better discussion around what is the level of certainty desired that is needed to make good recommendations?

So, we would recommend that we need to have developed a coherent strategic approach to evidence requirements for decision making based upon the level of certainly that is required and the value of obtaining additional information. I know that AHRQ has recently made some recommendations around priorities around different disease areas, but that doesn't get down low enough into the details about what kind of method you need to have to answer what kind of question around what kinds of treatment alternatives. We believe that having a coherent approach would support more consistent decisions about studies and analyses to be performed and that consistency could promote greater acceptance of public priority setting. If you want more information about this, my article with my coauthors Steve Teutsch and Bill Weinstein is in the packet, and I'd be happy to answer any questions.

ANNE MONTGOMERY: Great. Well, thank you very much. Thanks to all the speakers for some really excellent presentations, and now, as Ed Howard often says, it's your turn. So you have question cards. There are these green ones in your packets, and please write questions on them if you choose and our staff will collect them if you hold them up. We also have microphones on the left and the right, so while you're getting ready, I'll just remind you also that if you need to leave at any point, if you could fill out the blue evaluation form, we'd be really grateful. Okay, well, we did

get a couple of e-mail questions ahead of time, so maybe I'll just start with one, and it's for Peter Littlejohns. NIHCE has made a few controversial decisions about whether the NHS should extend coverage to certain drug therapies in the last several years, so could you discuss a couple of those controversies and how they were resolved, and whether they resulted in any changes in the way that NIHCE does its reviews?

PETER LITTLEJOHNS: Thank you. I think probably that the one that I think caused the most concern was around the management of [inaudible] and the beater interferons, and that went through many cycles including appeals, and our appeal process is a quasi-legal one where it's outside the main appraisal process. But finally in the end we did still come to the conclusion that on the basis of the evidence presented to us, it wasn't cost-effective, but we did encourage governments and the industry to look at how it could become cost-effective. In that context, the national government did work with industry to develop a cost/risk sharing process where patients were monitored and if they indeed didn't benefit, and therefore the actual effect of the drug was outside what we call cost effectiveness, then there was a reduction in price. So I think that's an example where we stuck to our guns in terms of the process and the implications for the NHS, but in the end patients, and I think also the country got the best deal. Interestingly enough, though, that process, even though our

guidance was adhered to in terms of the main stakeholder being the government and industry as opposed to individual professionals, not surprisingly, it was presented in the press as government not supporting the NIHCE view, so I think there's implications there for both the Institute, government and industry.

ANNE MONTGOMERY: Great! Thank you very much. We have a question on a green card. It's generally, I would say, for many of the panelists. Why are European countries more likely to approve a given drug years before approval is granted in the US? Any takers? So that's not true? Weigh in!

DR. PETER SAWICKI: Well it's not always the case. There are several examples. For example, for erosarustatin [misspelled?], it is already approved in the United States and it's not approved in Europe, so there are other examples the other way around. There are different decision boards and I think this is the reason for approving or not approving a drug, but in most cases this is with regard to the "me too" drugs. A very new drug that really is an improvement in the care of a patient is approved on this, and the other side of the Atlantic Ocean.

ANNE MONTGOMERY: Okay. Go ahead, and please identify yourself.

HERB CHATTMAN: Herb Chattman, I work for Bloomberg Radio. For Dr. Laupacis, could you respond to Dr. Berger's

implication that in rejecting a majority of the drugs that you passed upon that you acted on possibly inadequate evidence and that you've force the minority of patients that could benefit from some of these drugs that are not in the formulary to pay out-of-pocket for it, and also aren't you even slightly, having talked about even wanting to negotiate the price of drugs further down, aren't you even slightly ashamed at having off the cost of research and development to us?

DR. ANDREAS LAUPACIS: Let me address the latter. I guess since you folks have got so much of the research and development you've got all the great paying jobs, so we're kind of jealous of that.

I think the question about would we have approved statins now is a provocative one, actually. I'm old enough as a clinician to remember when cholestyramine first came out and, you know, we may well not have. And maybe one way down the road is I think this idea of having conditional listing. You can think about conditional listing in two ways. As I understand it, the FDA is saying, "We're going to give you conditional listing, in terms you can market your drug as long as you do this." And certainly in Canada, some of the drug formularies are interested in looking at conditional listing in terms of reimbursement, to sort of say, "Okay, you say that your drug is going to decrease admissions to the Emergency Department for asthma, for example. We're not convinced by

that, but we're actually convinced enough by the evidence to think it's a reasonable possibility, and so we will actually conditionally pay for this drug for the next three years with these conditions," and then there's the negotiation with the pharmaceutical company about what the condition is, the idea being that if the condition is met then great, it becomes an unconditionally funded drug. If it isn't, then they could decide not to fund it at all, or the company pays back some money or whatever. I'm aware of two such contracts in Ontario, and it will be interesting to see whether that works out, because in a way, that would be the best of both worlds. It would allow patients to have access to some drugs that they might not get now. Sitting on these formulary committees, one becomes relatively conservative because one realizes that if one says yes it's much, much more difficult to say, "Whoops, we made a mistake, and you know what, that drug wasn't cost-effective. And you know, it's just striking with the Vioxx—I'm sorry to be picking on Vioxx with someone from Merck here all the time—but in Ontario we only listed Vioxx and Celebrex only for people who had had a previous GI bleed or had failed on three different NSAIDs, yet the uptake, the day, the month afterward was just phenomenal, so to withdraw that is very difficult. So because of that, the committee's become very conservative. If we had this conditional listing it might get patients to have access to the drug yet give the drug plans the

comfort that if the drug isn't as good as we thought it was, we're not going to be stuck paying for it forever. And maybe with the statin example, if they were coming along now as a new class, it might be a good thing to try out.

PETER LITTLEJOHNS: Just had a comment on that. I certainly have some sympathy with what Marc is saying, that the inflation systems that we've got just were set up to look at safety and efficacy, but we're now moving into a whole new complicated world of long-term safety and efficacy but also clinical and cost-effectiveness, and the variability of population versus individuals. So we're actually in the process where we need to redefine very explicitly what those data sets are and we're beginning to work with CMS trying to identify how you can look at long-term and followup and coming back to my colleague's point that it's not a yes/no is a drug safe or not. It is a conditional process where it is legitimate to go back and to reassess safety, clinical and cost effectiveness.

ANNE MONTGOMERY: Thank you very much. Questioner at the microphone?

MARY AGNES KERRY: Yeah. I'm Mary Agnes Kerry with Congressional Quarterly. This question is for Mark Gibson and Marc Berger, but if others want to jump in, go ahead. I guess I'm just trying to understand. Will we get to a point in the United States where we can have information that guides health plans and consumers on which drug is more effective than the

other? I think that's what the lawmakers were trying to do on the Medicare bill with the funding on that. Dr. Berger just laid out all the complexities on this. Of course there'll be political pressure from constituents, from lawmakers, from the drug industry itself. Is it too difficult of a system to develop for this country to get this kind of information to guide people?

MARK GIBSON: Thanks. I think it's a great question. I think Marc put his finger on it when he said it has to do with your tolerance for risk, and you know, risk can go both ways. I would say relative to the previous question that there was an assumption in that question that open access to any drug was a positive thing, and if you look at the history of hormone replacement therapy and some other examples out there, that's clearly not the case. So what we're trying to do, I think all of us, is to figure out where we can have confidence that there is an increased benefit for patients on the general or specific basis. So I think, will we ever have the perfect information that each consumer needs to select exactly the right for them? I don't think that will ever happen. I don't think it would be cost-effective to do that. On the other hand, can we do a much better job of determining when there's reason to believe that a drug is better for a given patient so that they should be willing to pay a price premium for it, or is there sufficient evidence that a particular drug is better than others in a

class that a payer, whether it be the government or a private insurer or someone else should be willing to pay a price premium for it? I think we can approach a level of confidence that will allow us to make those decisions. I would also say that I think that level of information is critical to the creation of a functional marketplace around pharmaceuticals, which I would argue does not currently exist. I know that they compete. I know that they compete hard for their margins, but when it comes to the payers, without the comparative information that we're talking about, it's very difficult to foster price competition in the industry.

DR. MARC BERGER: Let me say that we can make great strides down this path, and we're looking at a number of major transformations that are going to enable this. The first is that we have introduced the idea of measurement as part and parcel to the delivery of medicine. Thirty years ago, you know, when I was taking care of patients, I knew I was taking good care of patients because I'm a doctor, and therefore I knew I was taking good care of patients. That was all that was needed. We don't really go by that any more. We try and collect some data to say how are we doing, what are the outcomes? We look at large providers of managed care and we say, how are they doing on performance measures, and we look at practice variation and we say that cannot be justified based upon differences just in severity of population, so this is

only a new movement that really has been around for 25 years or so, and really only has gained speed in the last 15 years, so the desire for more information to really know better about what we're getting in terms of the quality of our healthcare and now what are we getting in terms of the quality of the drugs that we're purchasing is part of a new movement, and we're building information infrastructures, although we're probably not investing in it nearly as much as we should, and it's going to probably take us longer to get there.

The second thing, at least that's happening in the US which I think is going to drive this is the consumerism movement, and as more and more of costs are offloaded onto the individual patient through coinsurance, increased copay and whatnot, the patients are going to demand better information and they're also demanding to be more of a shared decision-making process with their physician. Again, 30 years ago I'd say, "Here take this," and they'd say, "Okay. Thanks, Doc." Not anymore! And people don't accept that, and so, they're going to be demanding better information. But in order to make this day come further, we have to do a much better outreach and education of the general public about their needing to be an active participant in their getting their healthcare, they're demanding information, they're demanding that investments are being made to improve healthcare delivery, and for them to begin to understand that, guess what, every medicine has risks

an benefits associated with it. It's not like it's a magic pill. That's why you have a doctor who has to prescribe it. There are benefits and risks, and it's not like if I take this it's guaranteeing that I will get better from this condition. We need to do a better way of helping the public to understand that medicine can improve the likelihood they're gonna get better, have some risks that they may get some harms, but the overall risk/benefit relationship is one that makes a whole hell of a lot of sense, especially in comparison to doing nothing for whatever their clinical condition is.

ROBIN OSBORN: Thank you very much. We have a question sort of building on the previous discussion, for any of the panelists, I think. Do you have a sense of how clinicians are responding to the recommendations of these different organizations and panels, and particularly those that are not binding in terms of setting reimbursement policy? Are clinicians changing their prescribing patterns at all? Any evidence of that?

DR. PETER SAWICKI: Yeah, for example, we produced a patient and clinician information upon this Lipitor atorvastatin last year, and this changed the prescription rate from forty—not only this, but also the difference in pricing of this Lipitor atorvastatin. This changed because it reduced the number of prescriptions 40 percent of statins to five percent of statins in Germany. So I think that the doctors and

patients want to have this information; they want to know whether the more expensive drug is really better, and if such an independent panel says it's not better, it's not worthwhile, then maybe even worse than those statins that are on the market longer, they will change the prescriptions.

ANNE MONTGOMERY: Mark?

MARK GIBSON: I think in the US it's a less certain translation to the practice of medicine and that our system doesn't really encourage that to a large extent because of its plurality and because of the incredible marketing presence that exists from the industry, I think. We found in our experience that on a voluntary basis, provided with the clinical information from our studies, practitioners tended to shift market share by about 30 percent, and it really took something like a formulary decision or some kind of an administrative step to cause them to make a shift larger than that in their prescribing.

ANNE MONTGOMERY: Great. Well thank you very much. Unfortunately, I think it's a bit after 2:00, and we're going to have to wrap up, but I do want to thank our speakers for an absolutely wonderful discussion of some very complex and very fascinating trends and mechanisms and processes, and I hope you'll join me in giving them a hand [applause]. And please fill out your blue evaluation form and follow up with the

speakers if you like. As we say, we have their phone numbers and e-mail. Thanks again for coming.

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