Methods Future Research Needs Report

Number 5

Evaluating the Potential Use of Modeling and Value-of-Information Analysis for Future Research Prioritization Within the Evidence-based Practice Center Program

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Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-2007-10066-I

Prepared by:
Duke Evidence-based Practice Center
Durham, NC

Investigators:
Evan Myers, M.D., M.P.H.
Gillian D. Sanders, Ph.D.
Dhurjati Ravi, Ph.D.
David Matchar, M.D.
Laura Havrilesky, M.D., M.Sc.
Gregory Samsa, Ph.D.
Benjamin Powers, M.D.
Amanda McBroom, Ph.D.
Michael Musty, B.A.
Rebecca Gray, D.Phil.

AHRQ Publication No. 11-EHC030-EF
June 2011

This report is based on research conducted by the Duke Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10066-I). The findings and conclusions in this document are those of the author(s), who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested citation: Myers E, Sanders GD, Ravi D, Matchar D, Havrilesky L, Samsa G, Powers B, McBroom A, Musty M, Gray R. Erinoff EG. Evaluating the Potential Use of Modeling and Value-of-Information Analysis for Future Research Prioritization Within the Evidence-based Practice Center Program. (Prepared by the Duke Evidence-based Practice Center under Contract No. 290-2007-10066-I.) AHRQ Publication No. 11-EHC030-EF. Rockville, MD: Agency for Healthcare Research and Quality. June 2011. Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To improve the scientific rigor of these evidence reports, AHRQ supports empiric research by the EPCs to help understand or improve complex methodologic issues in systematic reviews. These methods research projects are intended to contribute to the research base in and be used to improve the science of systematic reviews. They are not intended to be guidance to the EPC program, although may be considered by EPCs along with other scientific research when determining EPC program methods guidance.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The reports undergo peer review prior to their release as a final report.

We welcome comments on the Methods Research Project. They may be sent by mail to Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Elisabeth U. Kato, M.D., M.R.P.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Evaluating the Potential Use of Modeling and Value-of-Information Analysis for Future Research Prioritization Within the Evidence-based Practice Center Program

Abstract

Background. Systematic reviews conducted as part of the Evidence-based Practice Center (EPC) program routinely identify evidence gaps and suggest further research to help close these gaps, but there is little evidence that these suggestions lead to the performance of the needed research. As part of an EPC-wide program to evaluate potential mechanisms for ensuring that research needs identified by systematic reviews are addressed, the Duke EPC reviewed the use of modeling techniques, including value-of-information (VOI) analysis, for prioritizing research gaps, under the assumption that quantitative prioritization could help facilitate the performance of research to address those gaps.

Methods. We first searched PubMed® for relevant literature published in English between 1990 and 2010 using search terms related to research prioritization and VOI analysis to understand how modeling and VOI is currently used in research prioritization. Inclusion/exclusion screening criteria were aimed at identifying articles that focused on research prioritization using a formal framework or process and reported specific prioritization recommendations, with a special emphasis on modeling and VOI.

To supplement this search, we then conducted a nonsystematic review of research prioritization processes used by major research-sponsoring organizations in the United States and abroad. We searched organization Web sites and the results of our literature search, and contacted the organizations by e-mail and/or telephone. Materials were reviewed for information on the focus of the prioritization process and the methods and criteria used for prioritization, again with a special emphasis on modeling/VOI.

Finally, we performed two case studies of the potential use of modeling techniques in research prioritization. First, we developed a model for the use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor antagonists (ARBs) in the management of ischemic heart disease based on the results of a prior comparative effectiveness review, then engaged nine stakeholders in a prioritization process that involved both a consensus-based approach and the use of model results. Second, we adapted a model on the outcomes of treatment of uterine fibroids developed for a previous systematic review and conducted a VOI analysis; these results were then shared with nine participants in a separate consensus-based research prioritization process. In both case studies, we elicited stakeholder feedback on the potential use of modeling and VOI in research prioritization.

Results. Only 6 of the 214 papers identified during the literature search reported using a previously published systematic review as the basis for identifying research gaps. Of the 60 unique modeling-based papers, all but 8 used cost-effectiveness analysis and VOI, with most of these focused on the question of immediate adaptation versus future research for a specific health intervention. The United Kingdom (UK) Health Technology Assessment (HTA) program conducted 19 of the 52 VOI analyses.

Of the 31 research organizations providing information on prioritization processes, only the UK National Institute for Clinical Excellence (NICE), through the HTA program, explicitly included modeling and VOI in their recommendations for future research.

Although the results of the modeling exercises for both case studies provided insight into the underlying decision problems, both models require further development. Despite this, stakeholders from both case study groups reported that the results of the modeling exercises were helpful in thinking about research prioritization, although none thought that modeling alone could substitute for a consensus-based approach. There was some diversity of opinion about the optimal timing of the modeling, with some stakeholders indicating that the results would be more helpful as background to a consensus-based process, while others preferred a parallel, iterative process involving both modeling and consensus.

Conclusions. Outside of the UK NICE/HTA program, systematic reviews were rarely cited as important sources for identifying evidence gaps for research prioritization. Cost-effectiveness and VOI analyses were the most commonly used modeling-based methods, but, outside of the UK, it is unclear to what degree the priorities identified by these methods were translated into actual research funding. Stakeholders in our two case studies found modeling and VOI to be potentially useful tools, but there are a variety of methodological and operational issues that need to be considered and resolved if these methods are to be used to assist with prioritizing research gaps identified through systematic reviews. These include identifying ways to compare the impact of different prioritization methods on the likelihood that priority questions will be answered through research, identifying the appropriate resources (including technical expertise) to conduct the analyses, defining the appropriate timing of the modeling and analyses, and identifying the appropriate level of modeling complexity.

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Background

Identifying and Prioritizing Future Research Needs in Comparative Effectiveness Reviews

The standard for nonindustry-funded biomedical research in the United States, as exemplified by the National Institutes of Health (NIH), has long been: (a) investigator-initiated ideas submitted for peer review almost entirely on the scientific value of the proposal; followed by (b) another layer of peer review at the NIH Council level, where funding decisions are based primarily on the scoring of the initial peer review; followed ultimately by (c) further peer review at the publication and grant renewal stages. As stated by an official at an NIH institute, "The National Institute… strongly believes that the best research relies on the creativity, interests, and expertise of individual … researchers, and investigator-initiated research remains the cornerstone of discovery and innovation in understanding and treating [diseases of interest to the Institute]." This model has been highly successful in generating major improvements in both scientific knowledge and human health.

There are some underlying implicit assumptions behind this somewhat entrepreneurial model:

- Through the literature and other means of scientific communication, the community of researchers will be able to identify the areas of greatest need and opportunity.
- Although research sponsors can provide some direction to specific areas of research through specific program announcements, requests for applications, or other set-asides, the greatest likelihood of significant advances will occur through the generation of multiple ideas, with competition between researchers for funding, publication priority, and other rewards associated with scientific success leading inevitably to progress.
- The most important or valuable "next steps" research will occur either because those next steps are obvious from the current state of the literature, or because less important steps failed to make it through the peer review process.
- The incentives and disincentives for participants in this "market" will align in a way that efficiently results in scientific progress.
- The size of the "market" in terms of number of researchers and available resources will be sufficient to ensure that the probability of progress in important areas will be reasonable.

Despite the overall success of this model in generating scientific advances, dependence on the inherent ability of the scientific marketplace to produce an efficient, steady progression in our ability to prevent and treat disease may fall short in conditions where the underlying assumptions may not be valid. In settings of limited resources, limited numbers of available researchers, or misaligned incentives, there may insufficient numbers of investigators generating competitive proposals to make necessary progress. Mechanisms for communicating specific important next steps may not result in a critical mass of researchers working on those next steps.

The systematic reviews conducted as part of the Evidence-based Practice (EPC) program invariably identify evidence gaps that need to be closed in order to make informed decisions about public health policy and clinical care; many of these reviews explicitly suggest "next-steps" research. In the traditional model of biomedical research in the United States,

dissemination of these descriptions of research opportunity through the usual channels for scientific communication would lead to a number of investigators, perhaps gently prodded by a Program Announcement or other indication of sponsor interest, proposing high-quality research which, through the peer review mechanism, would result in fewer evidence gaps identified in a subsequent review. However, this approach is clearly not working consistently for all reports. For example, despite a clear description of important evidence gaps in a 2001 evidence report on uterine fibroids and several relevant federal funding opportunities in the interim, followup reviews in 2007 and 2009 did not identify any substantial progress.[1]

To help determine best practices for capitalizing on the knowledge gained from systematic reviews to accelerate the development of the evidence base, the EPC program is pursuing several methodological research studies, as well as a set of case studies. Each of the eight EPCs funded through the American Recovery and Reinvestment Act of 2009 (ARRA) – Comprehensive EPC Comparative Effectiveness Reviews for Effective Health Care task order undertook preparing a pilot future research needs report based on an existing Comparative Effectiveness Review (CER). The pilot studies used diverse methods for each step in the process, and guidance from the EPC program on how best to perform these studies is still needed. Although the pilot projects provided case studies of potential methods to employ, formal exploration of the available methods for future research needs identification and prioritization are required. In the present report we explore the use of model-based quantitative sensitivity analysis and value-of-information (VOI) analysis as a tool for prioritizing future research needs. The ultimate goal of this report, as well as the reports by other EPCs that are part of the larger ARRA project, is to assist the Agency for Healthcare Research and Quality (AHRQ) in identifying improved ways to encourage the narrowing of evidence gaps identified through systematic reviews conducted as part of the EPC program.

Models as Tools for Identifying and Prioritizing Research Needs

As part of the EPC program's assessment of methods for addressing future research needs, the University of Minnesota EPC recently conducted a review (currently available only in draft form) of the use of decision and simulation modeling in systematic reviews.[2] The draft report provides an outstanding overview of the use of models in the literature and within the EPC program and is especially clear on the challenges and potential of incorporating modeling into CERs. Since all of these challenges are true for the use of modeling as a tool for research prioritization, we will discuss these aspects of the report in more detail in the final section on Recommendations.

For the purposes of this report, we define a "model" using concepts similar to those outlined in the draft Minnesota report, namely, as an analytic framework for addressing a clinical or health policy decision that involves the use of:

- Data from a variety of sources;
- The application of specific mathematical techniques to synthesize the data;
- Explicit recognition and estimation of the effect of uncertainty in parameter estimates on the optimal decision.

For most CERs, this will involve modeling both the underlying natural history of the disease, either explicitly or implicitly, and the potential impact of the interventions of interest—such as

screening or diagnostic tests, medical therapy, or surgery—on disease natural history, as well as on potential other outcomes of the intervention such as adverse events.

One of the more powerful aspects of the use of modeling is the ability to assess the impact of uncertainty surrounding the values of specific parameters—for example, rates of disease progression, treatment efficacy, adherence to treatment, test sensitivity and specificity, costs of treatment, or productivity losses from illness—on the outcomes being estimated with the model, and whether different parameter ranges alter the optimal decision under a given set of decision rules. This technique, called sensitivity analysis, is a crucial component in any model-based analysis.

Depending on the model and the availability of appropriate data, sensitivity analysis can be done either deterministically (by sequentially varying the value of a given variable or set of variables across the range of potential values) or probabilistically (by running a series of analyses drawing the value of the selected variable or groups of variables from a distribution). Both approaches are subject to limits on the availability of appropriate data and the need to consider potential correlations between parameters. Although the probabilistic approach is preferred in many cases, the need to specify parameter distributions, even in the absence of available data, as well as the additional computational time needed, present additional challenges.

For assisting in research prioritization, sensitivity analysis can be used in two different ways. First, the relative contributions of individual parameters of interest to uncertainty surrounding outcome estimates and the optimal decision can be ranked along two dimensions: quantitatively (those variables that result in the largest range of outcome estimates when varied across the range of reasonable values for each variable) and qualitatively (those variables that result in a change in the optimal decision at some point within the range of reasonable values for that variable).

Although "simply" performing a sensitivity analysis for identifying the most important variables has potential as a tool for research prioritization, there are several major limitations to this approach. First, there is not a standardized way to synthesize the information on both the quantitative size of the effect of parameter uncertainty and the impact of parameter uncertainty on the optimal decision—for example, it is possible that varying the value of a specific parameter across the range of plausible values could have a relatively small impact on outcomes, but that the optimal decision might change somewhere within that range. "Simple" sensitivity analysis also does not account for the potential costs of further research. These costs include not only the resources required to perform the research, but also the costs involved in putting off a decision to adopt an intervention that is truly beneficial, as well as the costs of making the wrong decision. The costs, and ultimately the cost-effectiveness, of future research can be estimated by extending traditional sensitivity analysis into VOI analysis.

Although VOI has been applied in a variety of non-healthcare settings[3,4] and can be considered purely as a method for sensitivity analysis,[5,6] it has been developed most fully for medical and public health interventions by the United Kingdom (UK) National Health Service Health Technology Assessment program;[7,8] the framework used in that program is briefly summarized here.

Simulation models are used to estimate the effectiveness and cost-effectiveness of a particular intervention or interventions, and probabilistic sensitivity analyses are performed. Using this approach, the probability that a given intervention will be cost effective at a given willingness-to-pay threshold can be estimated. Instead of incremental cost-effectiveness ratios,

different options are compared using net monetary benefits. Net monetary benefit for each strategy is calculated as:

Willingness-to-pay threshold * Net quality-adjusted life expectancy – Net costs

At any given willingness-to-pay threshold, the option with the highest net monetary benefit is the "preferred" option. Given the uncertainty in model parameters, the preferred option may vary from simulation to simulation. The upper bound of the opportunity cost of making the wrong decision can be estimated by calculating the expected value of perfect information (EVPI), the difference between the expected outcome (measured as net monetary benefits) given the current uncertainty and the expected net benefit given perfect information.

For example, if we are comparing Treatment X and Treatment Y at a $50,000/quality-adjusted life year (QALY) threshold and perform five simulations, Treatment X might be optimal in three of the simulations, and Treatment Y in two (Table 1; this example is based on one given in Briggs, Schulpher, and Claxton [2006],[9] p. 175).

Table 1. Example of expected value of information

Simulation number	Net benefits X	Net benefits Y	Preferred Option	Maximum benefit	Opportunity cost
1	20	30	Y	30	0
2	15	12	X	15	3
3	18	15	X	18	3
4	14	18	Y	18	0
5	17	14	X	17	3
Expected (average) value	16.8	17.8		19.6	1.8

The currently available information, when synthesized in the model, provides an expected net benefit for each option—this is the average of the individual net benefit calculated during each individual simulation. Because the average for Y (17.8) is higher than for X (16.8), we would choose Y, given the higher value. However, if we knew what the results were for each simulation, we would choose the option with the highest net benefit *in that simulation*. The average of the maximum values for the entire set of simulations is the expected value given perfect information (i.e., knowing in advance which outcome would be optimal). The difference between this value (19.6) and the expected value given current information (17.8) is the expected value of perfect information (1.8).

Alternatively, this can be conceptualized as the opportunity cost based on making the wrong decision. If we choose Treatment Y based on its higher expected value, there is a 60 percent chance that we would be wrong; the difference between the net benefits of Y and X in each simulation where X was preferred (numbers 2, 3, and 5 in Table 1) represents the opportunity cost of choosing Y based on its expected value; the expected overall opportunity cost is the average of these, or 1.8 (identical to the value obtained by subtracting the expected value given current information from the expected value given perfect information).

In this example, the reason that Treatment Y has a higher expected value is the outlier value of 30 obtained in the first simulation. Further research might result in a narrower range of parameter values for treatment Y, and thus an overall lower expected net benefit. The decision model generates estimates of the EVPI for individual patients; these can then be converted to a population-level estimate based on the number of potential patients, the time horizon under

which the intervention will be used, and an appropriate discount rate. If the expected costs of research to reduce uncertainty are less than the population EVPI, then further research could be considered. At the simplest level, using the example above, the EVPI value of 1.8 would be multiplied by the expected number of patients over a given future time horizon, incorporating an appropriate discount rate; this value represents the upper bound of what would be reasonable to spend to reduce uncertainty surrounding Treatments X and Y. As a tool for research prioritization, the population EVPI has two potential applications: (a) as a "go/no go" threshold for deciding whether further research is worthwhile; and (b) in theory, as a way to compare the "cost-effectiveness" of research across different interventions, or even across different clinical problems or therapeutic areas.

The partial EVPI, or expected value of partial perfect information (EVPPI), is a further extension of this concept. In this case, the EVPPI for a specific variable or group of variables is estimated, usually by holding the value of that variable or group of variables constant and performing the rest of the probabilistic analyses; the results provide an estimate of the cost-effectiveness of reducing uncertainty for specific variables. In our example above, the impact of uncertainty in individual parameters (such as costs of side effects or patient adherence to treatment) on the optimal decision between Treatment X and Treatment Y would be estimated; those with higher EVPPIs would be considered of greater priority. These estimates have two potential applications in research prioritization: (a) identifying the variables of greatest importance in reducing uncertainty, and (b) allowing researchers to consider both the relative impact of specific variables on uncertainty and the relative costs of reducing that uncertainty. For example, estimates of the impact of varying degrees of precision for effectiveness estimates can be used in sample size calculations. Alternatively, the EVPPI analysis may show that reducing uncertainty surrounding variables that require less costly study designs may have almost as a big an impact on the optimal decision as variables requiring expensive and time-consuming prospective randomized trials. At the individual level, EVPPI functions as a form of sensitivity analysis[5,6,10] and, at the population level, can provide budgetary guidance.

The Minnesota EPC team reviewed 11 evidence reports or CERs that involved modeling.[2] Although the models were used for a variety of purposes, none of them was explicitly used as a tool to assist with research prioritization, even though the authors of several of the models noted that the usefulness of the models was limited by the lack of available evidence. The draft Minnesota report thoughtfully describes both the potential uses (including VOI) and challenges of incorporating models into systematic reviews. In this report, we focus specifically on the potential use and challenges of using models as tools to assist with research prioritization of the gaps identified by systematic reviews performed as part of the EPC program.

Scope of Current Project

The overarching goal of this project, in concert with a suite of complementary projects conducted across several EPCs, is to inform the development of a set of methods recommendations for use by EPCs in drafting Future Research Needs sections of CERs co-ordinated by the AHRQ. The objective of this project in particular was to explore appropriate uses of modeling or VOI methods for developing and prioritizing research gaps from systematic reviews. We approached this aim by considering and compiling data from multiple sources. These approaches included:

- A systematic review of published literature regarding research priority setting, with a focus on the use of modeling and VOI;

- A review of priority-setting methods or strategies used by organizations involved in sponsoring research, again focusing on modeling and VOI; and
- Two case studies exploring the use of modeling and VOI methods in research priority setting. The case studies were chosen primarily out of convenience. Case Study 1 was chosen because of parallel modeling work on the topic done as part of a separate Future Research Needs project. Case Study 2 was chosen because the Duke EPC had previously written an Evidence Report on the topic incorporating a simulation model; investigators for that report were also involved in a separate, recently completed AHRQ-funded project to develop a research agenda for the topic using consensus-based methods, facilitating comparison of the results of a model-based process to a consensus-based one.

Systematic Review

The systematic review component of the project focused on identification of published literature addressing methods of priority setting, including VOI. The articles of interest in this review were those presenting specific research prioritization recommendations. Although we extracted a range of information on research prioritization, we focus here on applications of modeling and VOI, particularly on the use of modeling and/or VOI as part of systematic reviews.

Review of Individual Group Priority-Setting Processes

Priority-setting methods in practice at selected national and international research sponsoring agencies were reviewed through an assessment of publicly available information (published documents or information accessible from online sources) and contacts to individual organizations via e-mail or phone. These individual contacts offered organizations the opportunity to expand upon data available through print or online access with additional detail. Again, we focus here on aspects relevant to the potential use of VOI.

Case Study 1: ACEIs/ARBs in Ischemic Heart Disease

In the first case study, we elaborated further on work published by the University of Connecticut EPC in a recent CER[11] to identify and prioritize gaps in the evidence supporting the comparative effectiveness of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor antagonist(s) (ARBs) in patients with ischemic heart disease (IHD). The prioritization process used in this case study combined a review of recently published and ongoing studies, development of a decision analytic model to explore engagement of a stakeholder group, and participation of these stakeholders in both qualitative and quantitative exercises, based on a sensitivity analysis approach, of research needs prioritization.

This case study was chosen to parallel work that the Duke EPC was performing for a pilot project on CER research prioritization. Although our investigative team had previously developed a decision model framework for the use of ACEIs and ARBs in essential hypertension patients, the framework and accompanying model was in the early stages of development. The structural modifications and evidence synthesis required for the translation of this model for the prioritization of research related to ACEIs and ARBs in IHD, and the broader goals of our pilot project, meant that we focused this first case study on the use of a decision analytic model and related sensitivity analyses and explored the more in-depth use of VOI analyses in our second case study described below.

Case Study 2: Uterine Fibroids

The second case study for this project involved updating a Markov state-transition model initially developed for a prior evidence report on management of uterine fibroids.[12] This case study also builds on a concurrent AHRQ-supported project titled "Research on the Comparative Management of Uterine Fibroid Disease" being conducted by the Outcome Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Center.[1] The DEcIDE work employed a modified Delphi/nominal group methodology to prioritize research needs qualitatively in the uterine fibroids clinical area. Our update of the previously developed decision model was followed by VOI analyses to establish qualitatively based prioritization rankings for potential research areas identified as knowledge gaps. Stakeholders for this case study were drawn from the pool of technical experts involved in the Outcome DEcIDE work, thus allowing a direct comparison of the qualitative and quantitative approaches by a stakeholder group involved in both methods.

Modeling and VOI as Priority-Setting Methods: Literature Review

Methods

Search Strategy

We performed two PubMed® searches to identify published studies relevant to this review; details of the search strategy and results of our search and screening process are provided in Appendix A.

In addition to citations identified using these searches of PubMed, a small number of additional relevant citations were identified through manual searching.

Study Selection

We developed criteria for inclusion and exclusion based on the focus and aims of the report in investigating methods for setting research priorities. The criteria used to screen citations for inclusion and exclusion at the title-and-abstract level were as follows:

- Include articles that describe an explicit priority-setting process or provide explicit discussion or examples of VOI analyses.
- Exclude articles focused on establishing priorities for providing health services rather than prioritization of research.
- Exclude non-English articles.
- Exclude articles published prior to 1990.

We retrieved the full text of all potentially relevant literature included at the title-and-abstract screening stage for additional screening. We then conducted a second review for inclusion and exclusion. Criteria applied at this full-text stage were as follows:

- Publication must include research prioritization (excludes health services prioritization or prioritization of other topics).
- Publication must include a formal framework or process for research prioritization (excludes editorials and review articles).
- Publication must include specific research prioritization recommendations, and not only a description of a framework/process.

Data Abstraction

We developed a data abstraction form/evidence table template for abstracting data from all included studies (Appendix B). Abstractors worked in pairs: the first abstracted the data, and the second over-read the article and the accompanying abstraction form to check for accuracy and completeness. Disagreements between abstractors and over-readers were resolved by consensus or by assistance from a third, arbitrating member of the study team.

Results

Two hundred fourteen (214) articles met inclusion criteria. A variety of methods were used for identification of evidence gaps, but almost 40 percent of articles did not specify how research gaps were identified. Only six (2.8 percent) of the papers cited a previously published systematic review as a source of identified evidence gaps; none of these were AHRQ-sponsored reviews. We focus the rest of the result reporting on the characteristics of the modeling/VOI papers.

Sixty-four of the included articles were categorized as using modeling (including VOI) as the primary method for research prioritization. Studies that were primarily methodological but included specific examples were included. Of these, 60 represented at least one unique analysis (the remainder represented analyses conducted for the UK Health Technology Assessment program that were published both as Health Technology Assessments by the UK government and as peer-reviewed journal articles). Table 2 summarizes the basic characteristics of this subset of articles.

Table 2. Characteristics of modeling and VOI studies

Characteristic	Number of studies	Percentage of studies
Sponsor		
UK Government	22	36.7%
National Health Service/HTA program	19	31.7%
Other UK government	3	5.0%
Other European government	7	11.7%
Netherlands	5	8.3%
Other	2	3.3%
Canadian government	4	6.7%
U.S. government	4	6.7%
Foundation or university	12	20.0%
Industry	7	11.7%
Not specified	4	6.7%
Analytic method		0.0%
Cost-effectiveness and VOI	56	93.3%
Other	4	6.7%
Purpose of analysis		0.0%
Specific technology adaptation vs. value of future research	52	86.7%
Study design	5	8.3%
Research prioritization beyond specific intervention	3	5.4%

Abbreviations: HTA = Health Technology Assessment; UK = United Kingdom; VOI = value of information

The most common sponsor of model-based research prioritization analyses were governments with significant involvement in funding health care delivery (35 of 60), with 22 of these funded by the UK Health Technology Assessment program or another UK government research agency.

The majority of the analyses specifically used cost-effectiveness analysis along with formal VOI analysis. Other methods included cost-effectiveness analysis with sensitivity analysis to identify variables contributing the most to uncertainty, but without explicit VOI estimation;[13] combining estimates of population-level utilization of off-label drugs with level of evidence for specific indications to quantify uncertainty;[14] combining estimates of cancer incidence and exposure prevalence with rankings of biological plausibility, existing evidence, and sample size estimates;[15] and using graph-theoretical methods for research prioritization in malaria control.[16]

Not surprisingly, given the sponsors, the majority of the analyses were specifically for the purpose of estimating the cost-effectiveness of specific health interventions and the value of future research for specific questions related to those interventions. Five papers[17-21] addressed issues of study design, while three[14-16] addressed broader research prioritization questions.

Limitations

Reports of research prioritization methods may be particularly susceptible to biases in the types of articles most likely to be published. For example, approximately 40 percent of the identified articles were focused on research interests of a particular provider or specialty group, often in conjunction with specific meetings or conferences, and were published in journals of interest to that group. Research prioritization processes across broader areas (for example, between cancer and cardiovascular disease, or among breast, prostate, and lung cancer) may be conducted at higher institutional levels with less of a natural audience and publication forum (or no perceived need for publication). Conversely, for methods like VOI, where there is still a significant amount of methodological development, publication venues may be limited to a relatively small number of journals. Processes and methods used by industry may be underrepresented because of proprietary interests.

Our search strategy may have missed decision or cost-effectiveness analyses that suggested priorities for future research based on sensitivity analysis but which did not formally include estimation of VOI.

We did not attempt to assess study quality, mainly because we are unaware of any validated system for rating reports of research prioritization methods. We did not systematically attempt to determine whether any of the VOI or other modeling papers we identified resulted in actual performance of research in priority areas; possible methods for determining this include searches of papers that cited the identified articles, documentation of decisions to adapt or defer adaptation of technologies evaluated, or specific announcements of funding opportunities.

Discussion

Approximately 40 percent of the articles identified through our search did not specify what method was used to identify research gaps. Perhaps more disconcertingly for producers of systematic reviews, only 6 of 209 cited a previously published systematic review as a source. Given the volume of high-quality reviews generated by the EPC program, the Cochrane Collaboration, and others, this reinforces the need for identifying better methods for ensuring that reviews are identifying evidence gaps in ways that facilitate translation into actual research.

The majority of the modeling/VOI articles identified were focused on questions of whether to adapt a specific health intervention, based partly on cost-effectiveness considerations, and used VOI to estimate the value of specific additional research on questions related to that decision. We did not identify any papers where EVPI estimates for specific conditions were compared to assist in broader research prioritization questions. Even in primarily methodological studies where several VOI case studies were performed,[7,22] there was no direct comparison of EVPI estimates across interventions. Given the lack of suitable models for the range of conditions/interventions of interest to most sponsors, this is appropriate, but it does represent a potential area for further methodological development.

Within the context of developing a research agenda on the basis of CERs, the type of focused, specific modeling exercise conducted by the Health Technology Assessment group would be most likely to have direct application. In the work described in the next section, we

supplemented our literature review by searching Web sites and directly contacting major institutions involved in research funding for information on internal processes and methods used for research prioritization, again with a specific interest in the extent to which modeling and/or VOI were used for priority setting in the context of “standard operating procedures.”

Current Approaches to Priority Setting: Institutional Perspective

Methods

Based on discussions among the project team and with AHRQ staff, we identified 48 research-sponsoring organizations for consideration. The list was not meant to be exhaustive, but rather to represent a broad range of organizations involved in funding research activities that would be faced with the issue of prioritizing resources. These included:

- U.S. Public Health Service institutions, including various NIH offices and individual institutes, AHRQ, and the Centers for Disease Control and Prevention.
- Comparable agencies in other countries, such as the UK National Institute for Clinical Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), and the Australian Research Council.
- Organizations involved in a variety of activities aimed at reducing morbidity and mortality from specific diseases, such as the American Cancer Society and the American Heart Association.
- Organizations involved in international research activities across a range of conditions, such as the World Health Organization (WHO), the Cochrane Collaboration, and the Gates Foundation.

Research priority-setting practices at these organizations were identified based on publicly available information (primarily through the organizations' Web sites), published literature, or by contacting the institutes directly. We contacted 45 selected institutions (see Appendix C) by email, with telephone followup when necessary, on several occasions over a period of 3 months to request additional information on priority-setting practices and to relay our particular interest in information related to modeling or use of quantitative methods in priority setting. We identified priority-setting methods at two organizations (WHO and the Child Health and Nutrition Research Initiative of the Global Forum for Health Research) based on descriptions in the literature without supplemental e-mail or telephone contacts. Material from the organizations (in the form of e-mail or telephone conversations, sharing of formal documents such as procedure manuals, or referrals to publicly available online documents) were reviewed for information related to the focus of the priority-setting method (such as broad organizationwide allocation of resources versus funding of specific projects), the criteria for priority setting, and specific methods used (such as formal consensus-based methods or quantitative analysis). Our focus was on processes and criteria used to prioritize between broad clinical topics (e.g., cancer versus maternal mortality, breast cancer versus colon cancer versus prostate cancer), specific areas within clinical topics (screening versus primary prevention for colon cancer), specific topics within those areas (improved test sensitivity versus improving patient adherence in colon cancer screening), or specific study designs. We did attempt to identify criteria or processes used to decide funding for individual research projects within a given specific area (such as the probability of successfully answering the research question given the information provided in a research proposal). For the purposes of this report, we focus solely on the results relevant to the use of systematic reviews and modeling and/or VOI as part of the prioritization process.

Results

We were able to determine whether 31 of the 48 research-sponsoring institutions (65 percent) utilized specific priority-setting methods. Of the 17 without information, 12 had no publicly accessible information through published literature or their Web site and did not respond to e-mail or telephone contacts, 3 actively declined to provide information, and 2 responded but the material provided did not describe sufficient details of the prioritization process. The countries represented were the United States, United Kingdom, Australia, Germany, and Canada. The majority of organizations reviewed (26 of 31) described a well-defined priority-setting process.

However, only two organizations reported the use of quantitative or modeling-based approaches. The most explicit use of quantitative methods was by the UK NICE, which recommends use of decision-analytical methods and VOI-based approaches in the framework used to translate uncertainties identified in systematic reviews into both decisions about technology adaptation and recommendations for further research. NICE was also the only organization to explicitly cite systematic reviews as a source for identification of research needs. These detailed assessments for NICE are performed by a network of academic centers under the umbrella of the National Institute for Health Research (NIHR) Health Technology Assessment program. However, the decisions about which topics to consider for reviews are based on a process involving a variety of stakeholders, and it is unclear to what extent modeling/VOI results, even preliminary results, are incorporated into these decisions. Once a detailed review has been performed, the modeling/VOI results and their implications are quite clearly described, but it is unclear by what mechanism those recommendations get translated into the actual performance of research. Among U.S.-based organizations, the U.S. Agency for International Development (USAID) was the only agency that recommended use of analytical tools such as cost-effectiveness and cost-benefit analysis to determine the value of its research efforts. However, in contrast to the situation with NICE, we could not identify specific examples of the use of this USAID recommendation in research priority setting, or even determine whether cost-effectiveness considerations were focused more on the potential cost-effectiveness of the interventions being studied, rather than the cost-effectiveness of the research itself.

Limitations

The list of 48 research-sponsoring organizations we reviewed was neither exhaustive nor random.

Our sample was biased toward developed country organizations with English-language Web sites, although this likely reflects actual funding patterns for health research. Individual institutes and offices of the NIH in the United States accounted for the majority of organizations represented. We did seek information from major sponsors of health research in developing countries, such as the Gates Foundation and WHO. We did not attempt to elicit information on research priority-setting practices from within industry.

Discussion

Our findings were qualitatively quite similar to those of a 2007 systematic review of priority-setting processes among organizations performing health technology assessment.[23] In particular, the authors of the 2007 assessment found that, although almost all of the 12 organizations reviewed included economic considerations as a criterion for conducting a technology assessment, only 2 explicitly considered the efficiency of actually conducting the research—in

other words, the value of further information, whether formally modeled or considered in a more semiquantitative way.

Only the UK NICE, through the NIHR Health Technology Assessment program, described a topic identification process that included an explicit process that included ongoing surveys of the literature. This suggests that, for many organizations, the potential for evidence gaps identified by a given systematic review/evidence report to be incorporated into a research prioritization process depends on the degree to which the stakeholders involved in the prioritization are aware of the review's results and consider them valid. If the majority of current research prioritization activities are taking place without systematic consideration of the results of reviews, then consideration of whether specific methods for presenting and prioritizing research gaps would improve translation into active research may be premature—a more pressing issue would be how to ensure that decisionmakers and stakeholders were even aware of the review's existence.

We identified only one organization that explicitly used modeling-based approaches, specifically cost-effectiveness analysis and VOI analysis, in its research priority setting. Not surprisingly, given the findings of the literature review, this was the UK NICE. In contrast to many of the other organizations, NICE is tasked with making recommendations about adaptation of specific technologies and further research into those specific technologies, rather than making recommendations across broader areas of research (for example, relative allocation of research funds for breast versus prostate cancer). These analyses are usually conducted within the context of specific systematic reviews. The combination of a "menu" of highly specific potential research questions and a context where costs and cost-effectiveness are explicitly part of the decisionmaking process facilitate the potential applicability of VOI to research priority setting. In this context, it is interesting that the only U.S.-based organization that explicitly included cost-effectiveness considerations in its criteria was USAID, which is focused on research in resource-poor settings.

However, there is a subtle distinction to be made. The process by which NICE selects topics for review involves a number of steps and stakeholders. Although "horizon scans" by the National Institute for Health Research (NIHR) Health Technology Assessment program are part of this process, there are a variety of stakeholders involved, and other methods are used. The NIHR, through a network of academic centers, conducts reviews that include modeling and, frequently, VOI, and these reviews inform recommendations for technology adaptation and future research. The degree to which modeling and VOI are incorporated into the initial topic selection by NICE itself is unclear. The technology assessments including VOI provide research prioritization, but the degree to which these are translated into actual research, under whose auspices, and by what mechanism, are also not clear from our review of NICE's publicly available materials.

Our systematic literature review and nonsystematic review of research-sponsoring organizations found that systematic reviews are rarely explicitly used as part of the research prioritization process, and substantial practical experience in the use of VOI for prioritization is largely limited to NICE.

In order to explore the potential use of modeling and VOI in research priority setting for CERs conducted under the EPC program, we conducted two pilot case studies involving EPC reports that included models as part of the report. As mentioned above, the topic areas for these case studies were chosen because of previous or concurrent work, including modeling, by the Duke EPC in these content areas and, in the case of the uterine fibroids study, a concurrent

AHRQ-sponsored project to develop a consensus-based research agenda on comparative effectiveness research for management of fibroids.

Case Study: ACEIs and ARBs in Patients with Ischemic Heart Disease

Background

Despite advances in therapy, ischemic heart disease (IHD) remains the most common cause of morbidity and mortality in the United States. The prevalence of IHD is estimated at 16.8 million adults, and the death rate is 278.9 per 100,000 people, with IHD responsible for more than 35 percent of all deaths nationwide.[24]

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-II receptor blockers/antagonists (ARBs) have been shown to improve clinical outcomes for some patients, including those with heart failure and those with myocardial infarction (MI) and ventricular dysfunction.[25-32] However, the comparative effectiveness of ACEIs and ARBs alone or in combination for patients with IHD remains uncertain. Their potential role in the management of the broader population of patients with known IHD or at high risk for IHD is also unclear.

To address this area of uncertainty, a CER project sponsored by AHRQ was awarded to the University of Connecticut EPC. The subsequent CER reviewed data available through July 2009 comparing the benefits and harms of adding ACEIs, ARBs, or both to standard medical therapy in adults with stable IHD or IHD risk equivalents.

The CER found strong evidence that ACEIs reduced total mortality and nonfatal MI in comparison to placebo among adults with stable IHD and preserved ventricular function, but increased the risk for syncope and cough. There was low to moderate evidence that ARBs reduced a composite of cardiovascular endpoints compared to placebo and were well tolerated. The one available study directly comparing the impact of ACEIs and ARBs on cardiovascular outcomes in patients with IHD revealed no significant difference in the rate of cardiovascular outcomes, but demonstrated higher rates of cough and angioedema among patients treated with ACEIs, and higher rates of hypotensive symptoms among patients treated with ARBs.[33] The same study compared combination therapy with ACEIs and ARBs to monotherapy with each class of agents and found no difference in vascular outcomes, but a higher discontinuation rate in the combination therapy group due to medication side effects.

Although 41 studies including more than 64,000 randomized patients were evaluated in this CER, the authors identified multiple areas where insufficient evidence existed to answer the key questions regarding the comparative effectiveness of ACEIs and ARBs. While there was a high strength of evidence for ACEIs compared to placebo for total mortality, the evidence was insufficient, low, or moderate for the impact of ACEIs or ARBs on several cardiovascular outcomes, including cardiovascular mortality, nonfatal MI, or stroke, suggesting that future research on the impact of ACEIs or ARBs on cardiovascular outcomes may influence their conclusions.

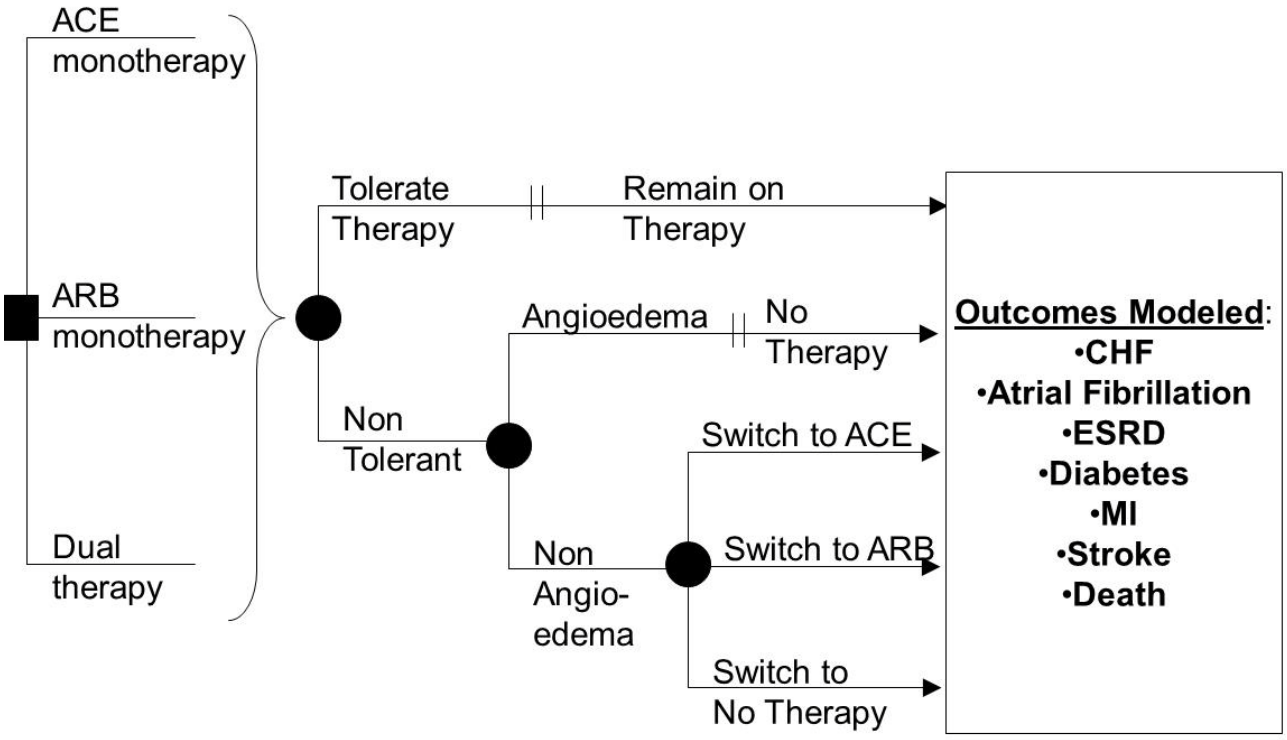
The Duke EPC was recently tasked with performing a pilot project to explore the future research needs of an existing CER and chose the ACEIs and ARBs in IHD report for this case study. Although the pilot project aimed to produce an actual prioritization of the identified research gaps, the timing of this pilot project in relation to this project on broader issues in methods for prioritization setting allowed us to engage a group of stakeholders and to explore the use of qualitative and quantitative prioritization of research needs.

Methods

Decision Model

We developed a decision analytic framework to explore the underlying uncertainties in the use of ACEIs or ARBs in patients with IHD. Figure 1 provides a schematic of the analytic framework. Patients were assumed to start on either ACEI or ARB monotherapy or both (dual therapy). We explicitly modeled potential side effects from treatment regimens through two mechanisms. First, each month patients could be determined to be nontolerant to their drug regimen. The presence of angioedema was modeled separately from other nontolerance. Patients who experienced angioedema were removed from active therapy. Other nontolerant patients could switch to either the alternative regimen or no therapy. We also explored the impact of additional side effects that did not result in therapy modifications through the use of utilities for the varying drug regimens. We tracked patients' outcomes over their lifetime and explicitly modeled development of congestive heart failure (CHF), atrial fibrillation, end-stage renal disease (ESRD), diabetes, MI, stroke, and death.

Figure 1. Schematic of decision model



We assumed that all therapies were equally effective in reducing MI, stroke, ESRD, diabetes, atrial fibrillation, and development of CHF compared to standard medical therapy, but also evaluated a range of potential differences between ACEIs and ARBs. We also assumed that there was no difference in a patient's blood pressure for any health state. The model also included estimates of quality of life associated with the different health states. In our base-case analysis we assumed that those patients who were tolerating their given drug regimens did not have an additional disutility associated with therapy. The base-case model assumed a class effect for all

ACEIs and ARBs. Table 3 lists some of the key data estimates used in our analysis. Additional details about the model are found in our pilot project report.[34]

Table 3. Key data inputs for decision model

Variable	Value (Range)	Source
Risk reduction of ACEI/ARB compared with standard medical therapy		
MI	0.83 (0.73 to 0.94)	Baker et al., 2009[35]
Stroke	0.79 (0.63 to 0.97)	Baker et al., 2009[35]
ESRD	0.75 (0.70 to 0.90)	Sarafidis et al., 2008[36]
Diabetes	0.90 (0.83 to 1.0)	Bosch et al., 2006;[37] McMurray et al., 2010[38]
CHF	0.85 (0.75 to 1.0)	Coleman et al., 2009[11]
Nontolerance (first year)		
ACEI	7.8% (6.0 to 9.6)	Yusuf et al., 2008[33]
ARB	6.1% (4.8 to 8.4)	Yusuf et al., 2008[33]
Dual therapy	14.5% (12 to 18)	Yusuf et al., 2008[33]
Angioedema risk (first month)		
ACEI	0.062% (0.051 to 0.073)	Miller et al., 2008[39]
ARB	0.008% (0.006 to 0.012)	Miller et al., 2008[39]
Dual therapy	0.062% (0.051 to 0.073)	Assumed equivalence with ACEI
Utilities		
Utility associated with being on ACEI therapy	1 (0.95 to 1.0)	Assumed
Utility associated with being on ARB therapy	1 (0.95 to 1.0)	Assumed
Utility of having ischemic heart disease	0.95 (0.663 to 1.0)	Nease et al., 1995[40]
Utility of being post stroke	0.64 (0.5 to 0.9)	Mathias et al., 1997[41]
Utility of being post another chronic condition (MI, atrial fibrillation, diabetes)	0.88 (0.7 to 1.0)	Brown et al., 2000[42] Nordmann et al., 2003[43] Tsevat et al., 1993[44]
Utility of living with ESRD	0.62 (0.45 to 0.75)	Lee et al., 2009[45]

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor antagonist; CHF = congestive heart failure; ESRD = end-stage renal disease; MI = myocardial infarction

Prioritization Exercises

The engagement of stakeholders and prioritization exercises used are described in more detail in our pilot project report.[34]

Briefly, nine stakeholders were selected for participation in this project from a variety of backgrounds and perspectives. They included physicians affiliated with academic institutions, representatives of professional societies with a cardiovascular focus or expertise in comparative effectiveness research, a payer institution, industry representatives, the National Heart Lung and Blood Institute, and a patient representative. In selecting members of the stakeholder group, efforts were made to assemble a balanced group of individuals representing a range of perspectives. Efforts were also made to avoid inclusion of researchers whose participation in the prioritization process might result in an unfair advantage in the development of future research proposals.

Project stakeholders participated in three conference calls and three prioritization exercises (Appendix D). Each prioritization exercise built off the findings of the previous exercise. The call and prioritization exercises occurred in the following order:

- Conference Call 1: Introduced stakeholders to the project's objectives and described the key clinical questions, the original CER and its findings, and proposed methods for the prioritization process, including use of a decision model and VOI analyses to quantitatively prioritize future research needs.
- Prioritization Exercise 1: Stakeholders were asked to rate the importance of future research exploring various characteristics using a 5-point Likert scale via an online tool. They were also asked to rank their top five research priorities from the complete list.
- Conference Call 2: Used to review and discuss the results of the initial exercise.
- Prioritization Exercise 2: We distributed additional material to stakeholders, including a list of potential priority-setting criteria to use when considering the appropriate priority for the research questions, the results of the initial survey prioritization, and summary evidence tables from the original CER. Each stakeholder was then asked to rank the 16 research areas from 1 to 16 in order of importance.
- Conference Call 3: Reviewed the findings of the second prioritization exercise, detailed our search of recently published literature and ongoing trials, described the decision analytic model and its key assumptions and data, discussed the model's findings, and then provided an opportunity for the group to discuss the existing ranking.
- Prioritization Exercise 3: Further material was distributed to stakeholders, including the qualitative ranking results and the recently published literature and ongoing trials in each research area. Each stakeholder was then asked to rank the areas from 1 to 16. This final step produced our final ranking.

Each call was recorded and stakeholder feedback elicited both during the call, and through a brief survey sent subsequently to the stakeholders to provide an opportunity for further structured feedback.

Results

Model Results

Table 4 presents the health and economic outcomes for the decision model.

Table 4. Health and economic outcomes

Strategy	Cost, $	Incre-mental cost, $	LY	Incre-mental LY	ICER, $/LY	QALY	Incre-mental QALY	ICER, $/QALY
ACEI	1721		17.985			16.747		
ARB	1998	277	17.990	0.0049	56,198	16.752	0.0054	51,456
Dual	2726	728	17.966	(0.023)	Dominated	16.727	(0.025)	Dominated

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor antagonist; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life year

In the base-case analysis, treatment with ARBs increases life expectancy by 0.0049 years (1.79 days) or 0.0054 QALYs (1.97 quality-adjusted life days) but costs an additional $277, corresponding to an incremental cost-effectiveness ratio (ICER) of $56,198/life-year (LY) or $51,456/QALY. Use of dual therapy is dominated by both monotherapy options (costs more while not increasing life expectancy).

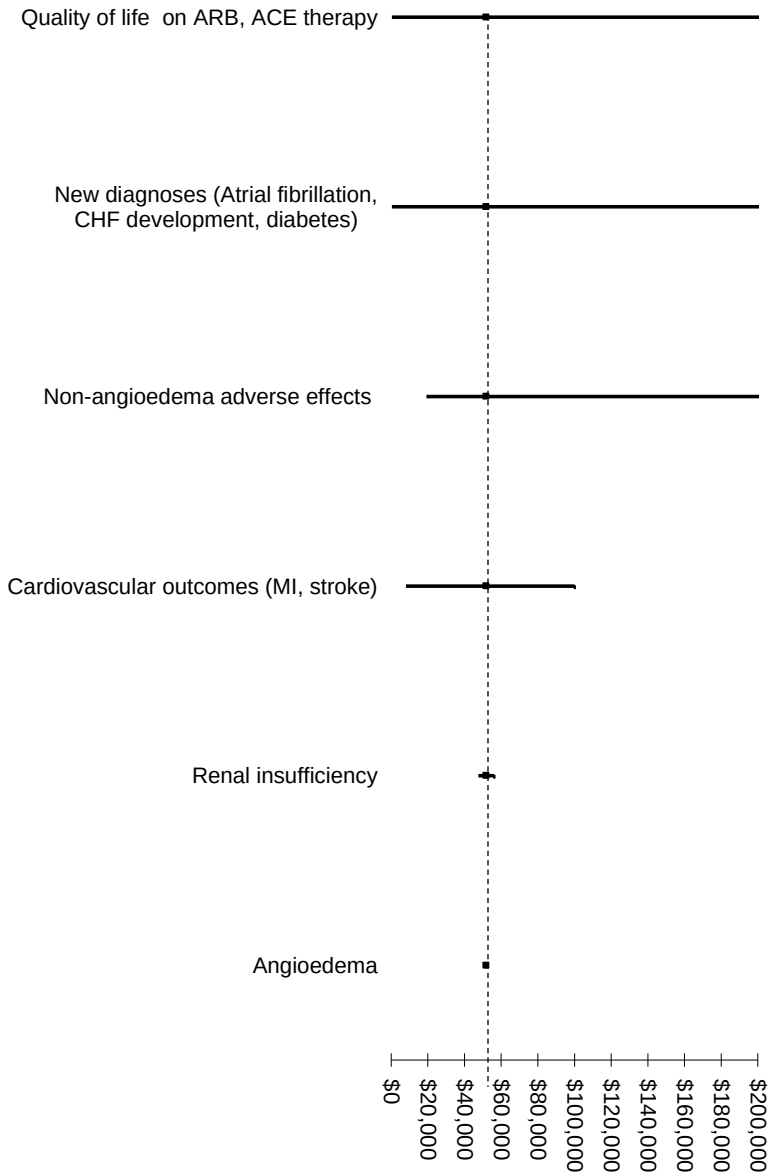
The use of the model allowed us to explore how sensitive our findings were to the data uncertainties—and specifically the data which corresponded to identified potential research

areas. To determine the potential benefit of prioritizing specific research areas for further study, we used the model to explore the impact of reducing uncertainties in the comparative effectiveness of ACEIs and ARBs in patients with ischemic heart disease. Specifically, we explored the impact of uncertainty on new diagnoses, quality of life, cardiovascular outcomes, renal insufficiency, non-angioedema adverse events, and angioedema.

Figure 2 displays a tornado diagram which demonstrates the sensitivity of the model's findings of these key uncertainties and corresponding evidence gaps. This figure demonstrates that the model is most sensitive to the uncertainty surrounding patients' quality of life and the presence of new diagnoses. Uncertainty related to angioedema does not impact the model's findings significantly. Ranges used for the listed variables are found in Table 3.

We presented the model, the underlying data and assumptions, and the findings of our analyses to our stakeholder group. The stakeholders had access to these findings when they prepared their final prioritization of the potential research areas. Note that the use of the decision modeling framework allowed us to explore the relative importance of the underlying uncertainties/research needs concerning the comparative effectiveness of ACEI and ARB therapy for patients with ischemic heart disease—it does not, however, allow a quantitative comparison of these uncertainties with uncertainties in other clinical domains and therefore more formal ranking of these research gaps against those that might be competing for similar resources.

Figure 2. Sensitivity of model findings to key uncertainties. Variables listed below were varied over the range described in Table 3 for uncertainties related to identified research gaps. These represented variables targeting evidence concerning quality of life on ACEI or ARB therapy, new diagnoses of atrial fibrillation, congestive heart failure, or diabetes, occurrence of MIs or stroke, development of renal insufficiency, and angioedema and non-angioedema adverse events.



Results of Prioritization Exercise

Detailed rankings for each of our prioritization exercises are described in our pilot report (see also Appendix E). Most of the rankings remained consistent between the second (qualitative) and third (findings from the decision model) exercises. Notable exceptions included the ranking of research into the incidence of new diagnoses (such as diabetes, atrial fibrillation, or CHF with or without preserved left ventricular [LV] function), which fell from second to sixth. It was instead replaced by an emphasis on research into medication adherence. This change was most likely influenced by the relatively large number of recently published studies (n = 6) and ongoing clinical trials (n = 5) related to new diagnoses that were presented to the stakeholders at this

point in the project and the scarcity of research (no new studies, and one potentially relevant clinical trial) related to medication adherence. This change also emphasizes the importance of providing sufficient clinical/methodological background information to the stakeholders before the prioritization exercises to limit the changes in their rankings based on the gathering of this knowledge later in the process. Of interest, the decision analytic model of ACEI and ARB therapy in IHD patients indicated that uncertainty related to new diagnoses had a significant impact on the model's findings.

Although the overall ranking did not change substantially from the second to the third prioritization exercise, the consensus among the stakeholders in their rankings did improve. The variance in the rankings was greatly reduced, there was much more consistency among the stakeholders and their rankings of the top and bottom five areas. Further research is needed to determine whether this greater consistency was related to incorporation of the decision analytic framework, the additional information provided concerning ongoing trials, or the discussions amongst the investigative team and stakeholder group.

Stakeholder Feedback

In feedback provided during the conference calls and via written comments, all stakeholders found the decision analytic modeling exercise useful in thinking about the prioritization of research areas. Stakeholders did not feel that the modeling results and quantitative prioritization process should replace the qualitative prioritization process, but rather felt that these findings should be conveyed to the stakeholders either in advance or in parallel with the qualitative process. The stakeholders felt that the greatest benefit to the prioritization process came from the opportunity to discuss the model and its findings with the analytic team and other stakeholders; however, they also ranked as valuable the quantitative description of key areas of uncertainty, the rank ordering of priorities, and the details of the underlying model. All of the respondents felt that additional background material on the decision analytic framework and VOI analyses, either as a briefing document or as an online resource, would have been helpful.

Case Study: Uterine Fibroids

Background

Uterine leiomyomata, or fibroids, are benign tumors of the uterine smooth muscle and extracellular matrix and are extremely common in women of reproductive age. Using sensitive imaging techniques, cumulative incidence is as high as 70 percent among white women and more than 80 percent among African-American women by age 50.[46] Most fibroids are asymptomatic; however, in those women with symptoms such as pain or heavy menstrual bleeding, there are limited treatment options. Hysterectomy is curative (in fact, fibroids are the leading indication for hysterectomy in the United States), but there is significant interest in identifying effective alternatives to hysterectomy.[1,12,47,48] Given the high burden of disease (including substantial medical and nonmedical costs[49,50]), significant differences in treatment choices and outcomes among population subgroups, local variation in rates of certain treatments such as hysterectomy,[51] and a range of medical and invasive treatments, management of uterine fibroids is an obvious area for comparative effectiveness research.

The Duke EPC conducted a systematic review on management of fibroids in 2001 that concluded that there was essentially no high-quality evidence available for making decisions regarding the most appropriate treatment for specific patients.[12] As part of the report, there was a detailed list of suggested research questions to address the existing evidence gaps. Subsequently, the Research Triangle Institute/University of North Carolina at Chapel Hill (RTI/UNC) EPC conducted an update in 2007 and noted that "[t]he current state of the literature does not permit definitive conclusions about benefit, harm, or relative costs to help guide women's choices,"[48] with little change noted in the identified evidence gaps.

In 2009, AHRQ awarded a contract to the Outcome DEcIDE Center to develop a specific research agenda for comparative effectiveness research for management of uterine fibroids.[1] As part of this process, Outcome, working with the Center for Medical Technology Policy (CMTP), conducted a priority-setting exercise with a number of stakeholders; Dr. Myers served as co-chair of the Technical Working Group for this project. The large stakeholder meeting took place in March 2010. Because the Duke EPC had developed a decision model as part of the original 2001 report, which was also led by Dr. Myers as principal investigator (PI), the coincident timing of the AHRQ fibroid research agenda project and this project on broader issues in priority setting allowed us to incorporate a pilot exercise comparing the results of the modified Delphi process used with the large group of stakeholders to a formal decision model/VOI analysis.

Methods

Simulation Model

The model is a substantial update of one developed for the 2001 Duke EPC Evidence Report on management of uterine fibroids.[12] At that time, we concluded that "the lack of data necessary to validate, calibrate, and test this model is striking," although we were able to perform a relatively simple "proof-of-principle" analysis comparing relief of symptoms with watchful waiting, hysterectomy, or myomectomy (removal of the fibroids themselves while preserving the uterus). In sensitivity analysis, the main drivers of effectiveness were the probability of menopause and the likelihood of development of new symptoms after hysterectomy.

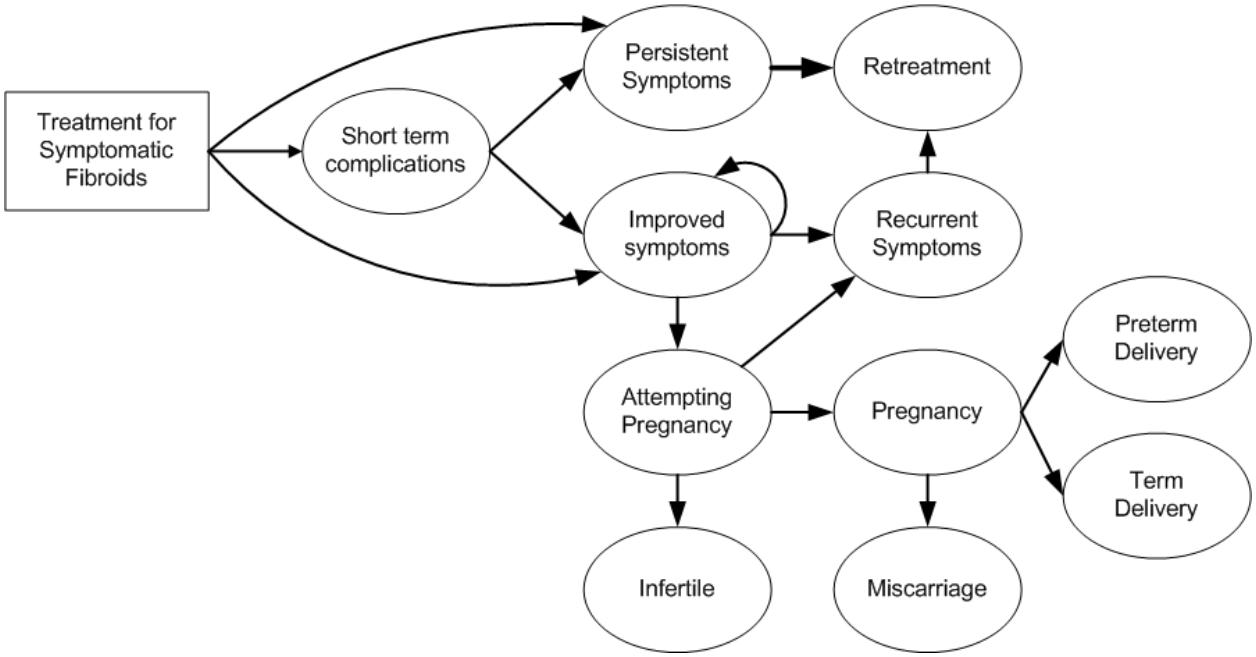
Our updated model is structurally similar to the previous one (Figure 3). Details of the model structure, assumptions, input parameters, and the rationale for our choices are described in detail in Appendix F. Although we attempted to make the model structure as flexible as possible to allow further development as a tool in fibroids research, our focus was primarily on the stakeholders' perceptions of the potential usefulness of the VOI analysis in priority setting rather than on the results of the VOI analysis themselves. In addition, we had time and resource constraints that were similar to those that would be operational if a model were done as part of a CER. Because of this focus and these constraints, we simplified the model and the analysis in a number of ways to facilitate timely completion of the analysis and reasonably simple presentation to the stakeholders

Although population-level values for EVPI and EVPPI would be preferable for purposes of decisionmaking about research investments, we focused this initial analysis, including the results presented to the stakeholders, on individual-level EVPI and EVPPI. Although most of the recent examples of the use of VOI in research prioritization have focused on population-level values, individual level EVPPI can be also be used as a form of sensitivity analysis.[5,6,10,52-54] We chose this approach for several reasons:

- As discussed in the detailed description in Appendix F, the model itself is still something of a work in progress, particularly regarding the potential interaction between the natural ovarian aging process as women approach menopause and treatment efficacy. In addition, the potential impact of incorporating reproductive outcomes into assessing treatment effectiveness for fibroids has not been previously explored. Because of this, we wanted to gain preliminary insight into structural aspects of the model, both to set the stage for further development and to be able to put the results in context for the stakeholders.
- Our primary goal in this case study was to obtain some sense from stakeholders about the potential utility of simulation modeling/VOI as part of a research prioritization process, especially in comparison to the recently completed consensus-based process.[1] Our experience working with stakeholders (or reviewers) with primarily content expertise who are unfamiliar with modeling is that considerable time and effort must be spent on explaining the underlying model structure and assumptions, and providing as much information as possible to ensure confidence in the face validity of the model. By being able to explain how different clinical or epidemiologic parameters affected the per-patient EVPI or EVPPI, we were able to demonstrate that many of the results were consistent with our current understanding of fibroids management.
- Although study feasibility was one of the factors stakeholders were asked to consider during the consensus-based priority setting, explicit discussions about sample size or available budget for specific research areas were not a major part of the process. We were most interested in comparing the relative ranking from the model-based analysis to that generated by the consensus-based process, which we were able to do with patient-level values. Incorporating population-level values would have provided additional information beyond the relative rankings and would certainly be helpful in discriminating between the highest ranking areas.
- There is uncertainty about the size of the potential affected population to be used for population-level estimation. A substantial number of procedures are performed on an outpatient basis, but, because of a lack of national data on outpatient procedures and substantial regional variation in the ratio of inpatient to outpatient procedures,[1] reliable estimates are difficult. Although an inpatient-based value would provide a lower bound

and would be reasonable for the purposes of EVPPI comparisons, we elected not to incorporate this additional level of uncertainty for the purposes of the pilot exercise.

Figure 3. Schematic diagram of fibroids model



Briefly, the model is a Markov simulation that begins immediately following treatment for symptomatic fibroids. The model uses 1-week cycles and follows women for 3 years (based on the available long-term data on treatments of interest) or until age 45. We chose to stop the simulation at age 45 both because we were interested in pregnancy, which is rare after age 45, and to avoid the need to develop a method for modeling the interactions of natural menopausal changes in ovarian function and treatment effects, given our project timetable. We compared outcomes after myomectomy, uterine artery embolization (UAE), or magnetic resonance imaging (MRI)-guided focused ultrasound (FUS), based on published results (but not from a formal systematic review). We chose these three treatments based on current treatment patterns and interest expressed at the larger stakeholder meeting. We did not include long-term complications in the model, both to simplify modeling and presentation and because of a lack of data.

Our primary focus was on several broad areas at the top of the priority list identified by the larger stakeholder group—reproductive outcomes, relative recurrence rates, and the impact of recurrence on quality of life. In order to simplify both the analysis and the presentation, we did not attempt to model all of the possible options for managing recurrent symptoms. Instead, "recurrence" was an absorbing state in the model, with a wide range of possible costs and utilities associated with having recurrent symptoms.

The model was run as a microsimulation, using an age and racial distribution similar to a large prospective registry of women undergoing UAE,[55] and using age- and race-specific probabilities and nonmedical costs as described in detail in Appendix F. For each analysis, we performed between 600 and 10,000 simulations, drawing from the described distributions for each variable. We first performed a cost-effectiveness analysis from a societal perspective, using incremental cost/QALY as the primary outcome, followed by probabilistic sensitivity analyses

using net monetary benefits across a range of willingness-to-pay thresholds from $0 to $100,000/QALY. We then estimated the EVPI for the entire model, followed by the EVPPI for individual variables or groups of variables. This was done by "fixing" the value (usually at the mean) of the variables of interest, then repeating the microsimulation using the remaining variable distributions. The EVPPI values for selected variables of interest were then ranked in descending order. Again, given time constraints, we did not estimate EVPPI for all possible variables, but focused on those identified as important by the modified Delphi process described below. As discussed above, we focused on the effects of different parameters on individual-level EVPPI in our initial review and interpretation of results, and in our presentation to the stakeholders.

Modified Delphi Process (by Outcome DEcIDE Center and CMTP)

The process used to develop a research agenda is described in detail in the Outcome report.[1] Briefly, a Technical Working Group (TWG) subcommittee of eight members with expertise in various aspects of fibroid research and treatment was assembled to provide technical expertise and develop a relatively focused group of research questions for discussion by a larger Stakeholder Committee of 34 members.

The TWG narrowed the list of evidence gaps identified from previous systematic reviews, translated these gaps into specific research questions, identified ongoing or planned studies that were relevant to specific questions, and helped develop background materials for the larger group. First, the TWG scored the initial list of questions using priority-setting criteria developed by Outcome and CMTP. The TWG then met to discuss and refine the questions, followed by rescoring. Based on this second scoring, a list of the top 12 research questions, along with general and question-specific background materials, was distributed to the larger Stakeholder Committee.

The Stakeholder Committee's main objective was to generate a ranked list of research questions related to management of uterine fibroids. Each question was presented by a member of the TWG, with opportunities for discussion and questions. At the end of the meeting, members voted and generated a prioritized research agenda for uterine fibroids.

Comparison of Modified Delphi Process and VOI

We invited nine stakeholders who had participated in the earlier process to review the results of our VOI analysis and provide feedback on the usefulness of the VOI. These stakeholders were selected to provide diversity of backgrounds and included a gynecologist, an interventional radiologist, a health economist, a patient advocate, an endocrinologist working in industry, a representative from a large third-party payer, the Principal Investigator of the Outcome project, and representatives from the National Institutes of Health (NIH) and AHRQ.

The stakeholders were provided background materials prior to the call, including the detailed description of the model included as Appendix F and several review articles on VOI analysis, as well as a copy of the slide presentation given during the conference calls.

Three 1-hour conference calls were held to accommodate schedules, during which the a slide presentation was given which covered:

- The background of the project and the main purposes of the project—specifically, to assess the feasibility of VOI in a clinical area with a notably low level of quality evidence, to get input from them on the potential utility of VOI as a substitute or

complement to the consensus-based process, and to get input on the optimal timing of VOI if done as part of a larger, multimethod priority-setting process.
- A brief description of the model and the use of sensitivity analysis as a technique to quantify the impact of different parameters on outcomes
- A brief definition of cost-effectiveness and net monetary benefits
- A brief description of VOI, which introduced the concepts of EVPI and EVPPI. Specifically, stakeholders were told that VOI was a method for estimating the value of future research, that population-level values could be used to generate research budgets, and that EVPPI was a method for ranking the relative importance of individual parameters within the model.

Each call was recorded and stakeholder feedback elicited. A brief survey was subsequently sent to the stakeholders to provide an opportunity for further structured feedback. Given the small numbers of participants, we did not formally quantify survey responses.

Results

Model Results

We emphasize that these results are preliminary and that further model refinement and additional analyses may change the results.

Table 5 presents the mean and standard deviations for expected recurrences and reproductive outcomes from the initial model runs, assuming that 25 percent of patients would attempt pregnancy within the first year after treatment and that there are no differences between treatments on reproductive outcomes.

Table 5. Expected recurrences and reproductive outcomes from initial model runs

Outcome	Treatment					
	UAE		Myomectomy		FUS	
	Mean	SD	Mean	SD	Mean	SD
Recurrence	0.095	0.924	0.082	0.275	0.225	0.412
Pregnant	0.087	0.282	0.097	0.296	0.085	0.228
Live birth	0.055	0.228	0.063	0.243	0.055	0.222
Preterm birth	0.012	0.110	0.014	0.111	0.012	0.104
% Preterm	22.4%	-	21.8%	-	22.0%	-

Abbreviations: FUS = focused ultrasound; SD = standard deviation; UAE = uterine artery embolization

The high degree of uncertainty in the parameter estimates is reflected in the very wide standard deviations. Not surprisingly, pregnancy and live birth rates were relatively low, and preterm birth rates were high. Women in their 30s and 40s are less likely to get pregnant and more likely to have a miscarriage, resulting in low live birth rates, while African-American women, who make up approximately half of the population of women receiving fibroids treatment, are more likely to experience preterm delivery, especially at older ages (for example, a 44-year-old black woman is three times as likely to have a preterm delivery than a 25-year-old white woman—*see* Appendix F). The low pregnancy rates create a challenge for studying the effect of different fibroid treatments on reproductive outcomes, since a very large number of women actively seeking to get pregnant would be needed to identify clinically meaningful differences in outcomes. In order to simplify the analysis and presentation, we elected not to further explore the potential impact of differences in treatments on reproductive outcomes in the

VOI analysis—the only pregnancy-related variable left in the model was time between initial treatment and the start of attempts to achieve pregnancy. We kept this variable because it was independent of any treatment effects on reproductive outcomes and, given our underlying assumptions, pregnancy and recurrent symptoms were important competing risks.

The overall EVPI per patient for the model as constructed ranged from $1,050 at a willingness-to-pay threshold of $50,000/QALY to $1,460 at a threshold of $100,000/QALY, reflecting the high degree of uncertainty for most of the model parameters. Table 6 shows the results of the EVPPI for selected variables:

Table 6. Patient-level EVPPI for selected variables

Parameter	EVPPI
Utility after retreatment	$1,053
Time to return to work	$1,047
Time before trying to get pregnant	$1,046
Relative recurrence rates	$1,043
Time between recurrence and retreatment	$1,038
Cost of complicated cases	$1,037
Length of stay (mean of uncomplicated and complicated cases)	$1,030
Cost of uncomplicated cases	$9.50

Abbreviation: EVPPI = expected value of partial perfect information

The majority of the variables considered had EVPPIs close to the overall EVPI, and given the high degree of uncertainty, the observed differences in the estimates may well be insignificant. However, factors related to recurrence and quality of life after recurrence were major drivers of uncertainty.

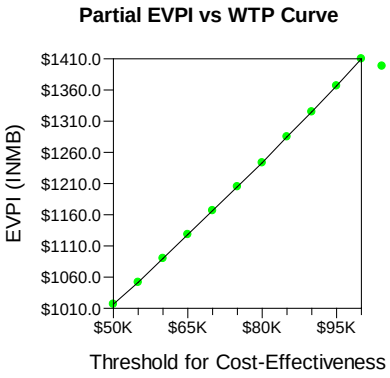
We then compared the overall EVPI for different mutually exclusive subpopulations of interest—first, white versus African-American women, and, second, women who desired future pregnancy versus those who did not (Figure 4). The overall EVPI across the range of willingness-to-pay thresholds was slightly lower for white women than for African-American women. The major modeled differences between white women and African-American women were older age, higher wages, and overall better reproductive outcomes for white women; we did not model other consistent differences, such as more severe symptoms and more extensive disease among African-American women. Given that we constrained the simulations to 3 years or reaching age 45, the lower overall EVPI for white women likely reflects an older mean age, resulting in a greater number of women reaching the end of the simulation before an opportunity for recurrence.

Differences between women desiring pregnancy and those not were much more substantial, with the EVPI for women desiring pregnancy less than half that for women not desiring pregnancy across all levels of willingness to pay. This is largely because, based on our initial results showing an overall low event rate for pregnancy outcomes, we did not model potential treatment-specific differences in reproductive outcomes in this iteration of the model—incorporating uncertainty about the relative impact of different treatments on reproductive outcomes would likely have had a significant impact on the EVPI for this population. Our assumptions that women would not attempt pregnancy while experiencing recurrent symptoms (and, conversely, that recurrent symptoms would not occur during pregnancy), and that a successful pregnancy had a utility similar to relief from symptoms, likely also played a role. Under these assumptions, pregnancy is a competing risk for recurrence, so that overall recurrence rates are lower, and subsequent quality-adjusted life expectancy is higher, among women attempting pregnancy. Since the EVPPI analysis showed that factors related to

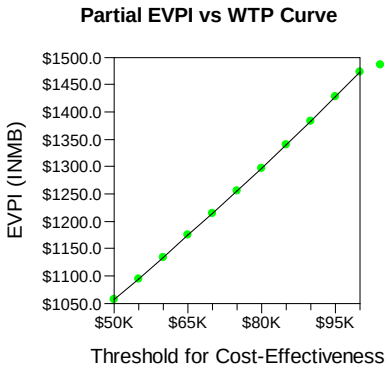
recurrence were the largest drivers of uncertainty, it is not surprising that the overall EVPI would be lower for a subgroup where recurrence risk is inherently lower. This competing risk effect also explains why time to attempt pregnancy was one of the highest ranking variables in the EVPPI analysis.

Figure 4. Expected value of perfect information (EVPI) in select subpopulations of patients
(A) white women vs. (B) African-American women, and (C) women desiring future pregnancy vs. (D) women who have completed childbearing. WTP = willingness-to-pay. Comparisons are valid only between mutually exclusive groups—A vs. B and C vs. D.

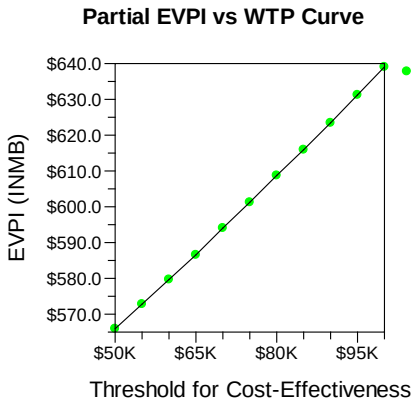
A. EVPI for white women only



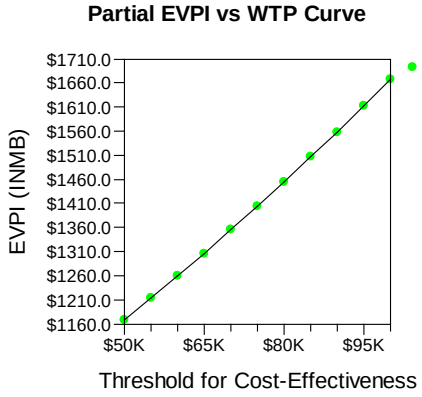
B. EVPI for African-American women only



C. EVPI for women desiring future pregnancy



D. EVPI for women who have completed childbearing



Comparison of Model Results to Qualitative Exercise

The top five research priorities identified by the Stakeholder Committee at the end of the modified Delphi process[1] were:

1. What is the relative effectiveness of available interventional procedures (e.g., UAE) on durability of symptom relief and patient-reported outcomes?
2. What is the relative effectiveness of interventional procedures versus noninterventional approaches as initial therapy on durability of symptom relief and patient-reported outcomes?
3. Can we create validated and reliable classification systems of standard anatomic staging to use in research and clinical care of women with uterine fibroids?

4. Can we create validated and reliable classification systems of patient-reported outcomes (including patient preferences, disease-specific and general quality of life, and patient satisfaction) to use in research and clinical care of women with uterine fibroids?
5. Can we create validated and reliable classification systems of measures of responses to specific symptoms (such as menstrual pictograms, menstrual diaries, hemoglobin) to use in research and clinical care of women with uterine fibroids?

As discussed above, the variables with the highest EVPPI were those related to recurrence and quality of life (in this case, utilities) after recurrence, suggesting relatively close agreement between the VOI analysis and the modified Delphi process in terms of the highest priority areas for future research. Because we did not exhaustively include all possible variables in the analysis, and because the EVPPI values themselves are quite similar, it is possible that this concordance may not be so close with further model development. Three of the top five topics related to development of classification/staging systems for use in comparative effectiveness research in fibroids; although we did not model measurement/classification, extending the model to include these types of parameters is certainly possible (for example, by considering an anatomic staging system as a type of prognostic test, and modeling uncertainty surrounding sensitivity, specificity, and reproducibility).

Stakeholder Feedback

In feedback provided during the conference calls and via written comments, all the stakeholders stated that the VOI exercise was useful. Common themes mentioned included:

- While none of the stakeholders felt that VOI was a substitute for the consensus-based process, all felt that VOI would be a useful complement, with the results either available as background material prior to the in-person consensus meeting, or with the VOI process being done independently and in parallel with a consensus-based process. One respondent noted that the results of a VOI analysis would be helpful in identifying specific decisions that had implications for research feasibility and design, which in turn would be helpful in focusing discussions among a diverse group of stakeholders.
- There was unanimous agreement that the most valuable aspect of the exercise was the opportunity to discuss the model and analysis with the analysts and other stakeholders. The actual results in terms of ranking of research priorities and relative quantification of different areas of uncertainty were also valuable. Although the details of the underlying model were useful to most respondents, this was of overall less importance.
- All of the respondents felt additional background material on VOI, either as a briefing document or an online resource, would have been helpful.

Limitations

Model and Results

As stated above, our focus in this exercise was on updating the preexisting model sufficiently to allow conducting a limited VOI analysis for purposes of presenting those results, both alone and in the context of the results of an independent consensus-based research priority-setting process, to a select group of stakeholders with relatively limited experience with the concepts of cost-effectiveness analysis or VOI analysis. Given this focus and time and resource constraints,

we made a series of decisions, detailed above and in Appendix F, which limit the direct applicability of these results to priority setting for research on uterine fibroid management. These include:

- Our sources for parameter estimates were not based on a formal systematic review, or on analytic methods such as network meta-analysis, which would have been preferred for generating comparative estimates across three different treatment options.[56,57]
- We did not include all possible treatment options, including hysterectomy and medical therapies, in the analysis. We also simplistically modeled recurrence—a more sophisticated approach would be to include a range of possible treatment options for recurrent symptoms.
- We did not exhaustively estimate EVPPI for every variable in the model.
- We constrained our analysis to 3 years of followup or reaching age 45. It is possible that longer time horizons would have affected our results, and it is likely that incorporating a potential interaction between treatment effects and declining ovarian function with age would have had some substantial effects.
- We did not model potential differences between treatments on reproductive outcomes. It is likely that uncertainty surrounding these results would affect the EVPI for the minority of women who are interested in future pregnancy.
- We did not estimate population-level EVPIs as part of the formal analysis, for the reasons described above. We provide one overall preliminary estimate below for overall research into management of fibroids, but this is itself subject to the uncertainty surrounding the size of the affected population. Our estimates of EVPI for subpopulations, or our estimates for individual EVPPI, have more value at this point as indicators of how individual components of the model (differential age distribution between subpopulations, competing risks between pregnancy and recurrence, constraining the simulation to women under 45) are driving affecting the outcome, rather than as formal estimates of the upper limit of research funding for a particular area for further research.
- Overall population-level EVPI estimates would have allowed comparison of the value of future research in fibroids to future research in other clinical areas.

Comparison to Modified Delphi Process

Similarly, our comparison to the modified Delphi process used by the Outcome/CMTP team was limited by a number of factors:

- Our choice of topic was driven by the presence of a preexisting model, institutional experience with the topic, and serendipitous timing. However, because of the size and number of evidence gaps for this particular clinical area, the model resulted in large and closely clustered EVPPIs for a majority of the variables considered. A topic with more discrete evidence gaps might have resulted in more clear-cut model results, and allowed a more detailed comparison to the consensus-based results.
- Our stakeholder group was limited in size, due to both resource and regulatory constraints. Broader representation among the entire stakeholders would have been extremely helpful to get a better sense of the potential utility of VOI. The small sample size also precluded any quantitative assessment of stakeholder perceptions of VOI.
- Dr. Myers, who did most of the model development and analysis, was also chair of the TWG for the consensus-based process. Although his familiarity with the clinical topic,

the underlying evidence gaps, and the workings and outcomes of the consensus-based process undoubtedly helped facilitate the VOI process, it is possible that an analyst less involved in the alternative process would have produced results which differed in some meaningful way from the current results.

- Although our top rankings were similar to those resulting from the modified Delphi process, it is possible that at least some of that agreement is due to decisions about the scope and structure of the analysis made in order to facilitate the comparative process. Comparison of results from a more fully developed model to those from the consensus-based process will be informative.
- Our results as presented emphasized the use of VOI as a type of sensitivity analysis for comparison of relative importance of different parameters. Providing population-level estimates of EVPI and EVPPI to the stakeholders, as would have been done in a fully developed VOI analysis, might have resulted in different feedback from the stakeholders.

Discussion: Fibroids Case Study

Simulation Model Results

Although we do not believe the model results as presented are directly applicable to priority setting for uterine fibroids, the model does provide some valuable insights:

- The prioritization of specific areas for research is likely to differ between women interested in future pregnancy compared to those who have completed childbearing.
- Sample sizes required to determine differences in reproductive outcomes between treatments are likely to be fairly large.
- The overall EVPI for fibroids appears to be quite large. Comparison of EVPI results across different areas is difficult for a number of reasons, especially in this case where the model is still a work-in-progress. In one of the few VOI analyses conducted for a U.S. population, Hassan and colleagues[52] estimated an EVPI for colorectal cancer screening of $216 per subject, less than 25 percent of the estimated values calculated here. One obvious next step after further model refinement is to estimate the population EVPI, which is a function of the expected number of patients affected, the expected duration of use of a given treatment or treatments, and the societal discount rate.[58] In the 2007 Nationwide Inpatient Sample, there were approximately 250,000 admissions with procedures performed for a primary diagnosis of uterine fibroids,[1] which, given the increasing use of outpatient treatments, is likely an underestimate of the potential population. Assuming another 20 percent of cases done as outpatients (approximately 300,000 patients annually) and a 3 percent annual discount rate, the population EVPI based on our preliminary results ranges from $1.5 billion over 5 years at a willingness-to-pay threshold of $50,000/QALY to $3.8 billion over 10 years at a threshold of $100,000/QALY (the comparable 5-year population EVPI for colorectal cancer screening, which affects approximately 15 million people annually, was $15 billion[52]).

Specific areas for further model refinement include:

- Incorporating uncertainty about relative treatment effects on reproductive outcomes.
- Incorporating the effect of natural menopause, as well as any interactions between treatment and declining ovarian function.

- More precise delineation of parameter distributions through collaborations with researchers with appropriately large datasets.
- Estimation of population-level EVPI for subpopulations and EVPPI for model parameters.

Comparison to Modified Delphi Process

The results of our VOI analysis, in terms of ranking of areas of uncertainty, were concordant with the areas of highest priority identified through the modified Delphi process used by the Outcome/CMTP group to develop a research agenda for comparative effectiveness research for fibroid management. It is possible that this agreement is at least partially due to decisions made about the scope and structure of the analysis in order to facilitate this specific comparative project, and comparison of these results to those from a more fully developed model is in order. We also emphasize, as noted above, that the actual differences between specific EVPPIs are quite similar, and it is possible the relative ranking might change with additional model refinement. Despite these and the other limitations discussed above, the stakeholders who reviewed these results felt that VOI analysis had the potential to be a valuable part of any research priority-setting process, primarily either as background or in parallel with a more traditional consensus-based approach.

We discuss the potential implications of these results for incorporation of VOI into future research needs assessments, along with suggestions for further methodology development, in the next section.

Discussion and Recommendations

Use of Systematic Reviews in Research Priority Setting

Although we did not systematically attempt to quantify the use of systematic reviews in research prioritization, explicit mention of systematic reviews as sources for identification of evidence gaps was rare in either our literature search or review of existing prioritization processes. The most formalized use of reviews was for health technology assessments in the UK, which either directly cited previously conducted reviews as evidence or conducted reviews specifically for the purposes of the technology assessment.

Systematic reviews may play an indirect role in many research prioritization processes that is not captured in published reports or descriptions of standard operating procedures. For example, it seems reasonable to assume that at least some content experts involved in consensus-based processes would be aware of published reviews and incorporate the findings of these reviews, and their interpretation of these findings, into their deliberations. However, we would suggest that, if resources are going to be devoted to formalizing and prioritizing research recommendations arising from systematic reviews in the hope of answering important unanswered questions, then some additional research is needed to identify any barriers beyond the format in which those recommendations are presented. A complex VOI analysis with specific recommendations for research priority areas, appropriate study designs, and optimal sample sizes presented with compelling graphs will not result in closing of evidence gaps if the review is not read and used by stakeholders involved in sponsoring and conducting clinical research.

Because of this, further research is needed into the research prioritization process itself. Although a comprehensive discussion of research into research prioritization is beyond the scope of this report, we believe that maximizing the probability that an EPC report will influence future research requires more than identification of best practices for reporting and prioritizing evidence gaps—identifying and removing barriers to the use of that report by key stakeholders involved in the clinical research enterprise is also needed.

Use of Modeling and VOI in Research Priority Setting

Although our literature review suggests a growing interest in the application of modeling and VOI to research priority setting, and there is considerable experience in the use of VOI in the UK health system setting, the available evidence does not allow us to draw any inferences about how modeling or VOI compare to other methods for establishing research priorities, either in general or in specific contexts. Even in the setting of the UK Health Technology Assessment (HTA) program, we could not readily determine whether the results of the VOI-based research recommendations have been translated into ongoing or completed studies. Consensus-based processes were the most common type of method in both the literature review and the review of research funders, but there is no clear way to compare the outcomes of these methods to modeling; for that matter, there is no clear agreement on what outcomes can and should be measured in order to assess the comparative effectiveness of different research prioritization methods.

Again, a comprehensive discussion of the issues involved in comparing different prioritization methods is beyond the scope of this report, but, at the simplest level, one would hope that a research prioritization process would ultimately result in the performance of research

in the areas identified as highest priority, and that the results of this research would resolve some uncertainty about an important clinical or public health question. As suggested above, there are factors other than the methods used for prioritization which may affect whether the results of a specific process get translated into research results, but, at the least, we would suggest that some effort be directed into development of measures to help evaluate different research methodologies. Some examples of these measures include:

- Measures focused on the process itself. These could include the resources (including both costs and time) required to conduct the process, and feedback from participants in the process and decisionmakers who use the results of the process.
- Specific allocation of resources aimed at the top priority areas. At the intramural level, this can be measured by specific budget line items. At the extramural level, this can be measured by the issuance of specific program announcements, requests for applications/proposals, or other specific solicitations, along with funding levels.
- Performance of research focused on specific priority areas. This can be measured by funded grants/contracts.
- Dissemination of results of prioritized research. This can be measured by meeting presentations, publications, or impact factor of publications.
- Measurable differences in health outcomes or decreased unexplained variation in practice patterns. This can be measured using many of the standard tools of health services research.

Incorporating VOI into Future Research Needs Assessments for the EPC Program

Although we believe that our two case studies on using modeling with an emphasis on sensitivity analysis (ACEIs/ARBs for IHD) and individual-level VOI analysis (management of uterine fibroids) provided valuable insights into the potential use of these techniques for research prioritization as part of future reviews, it should be emphasized that these were pilot projects with a number of limitations, many of which are described in the sections of the report detailing the studies. In this final section of the report, we summarize the overall general limitations and "lessons learned" and suggest further methodological work (without assigning priority ranks to specific questions).

- Many of the specific issues discussed below—timing and resource allocation issues for model development in the context of a systematic review; availability of appropriate expertise to develop and interpret the model; the role of interaction between modelers, stakeholders, and decisionmakers in model development and interpretation; appropriate education for stakeholders and decisionmakers in the use and misuse of models—were also identified as issues in the Minnesota EPC's draft review of the general use of models in systematic reviews[2] and in the UK HTA program's assessment of its initial pilot studies of VOI as part of their health technology assessments.[7]
- Given the extensive and almost exclusive experience of the UK HTA program with VOI, direct consultation with this group should be undertaken if further consideration is given to the potential use of VOI as part of EPC reports.
- As mentioned above, the choice of clinical topics was based on familiarity with the topic, existing models on which to base our analyses, and concurrent related AHRQ-sponsored projects. Our original intent was to conduct full VOI analyses for both topics, including

population-level analyses; however, time and resource constraints, including availability of stakeholders, precluded this. Because we used different topics, stakeholders, modeling outputs, and comparator prioritization methods, we cannot draw any inferences about the relative usefulness of sensitivity analysis or individual-level VOI (although this was never our intent). Although VOI is more attractive from a decision theoretical perspective and has the advantage of helping to identify appropriate budgeting levels, the modeling is more difficult and computationally intense, and the interpretation of results, especially for stakeholders unfamiliar with decision analysis and modeling, is more difficult. Further studies of modeling as a tool for research prioritization should allow direct comparison of the relative utility of a simpler versus a more complex approach.

- Because we did not conduct or present "full" VOI analyses, including presentation of population EVPI and EVPPI to the stakeholders, we cannot draw any inferences at all about the potential usefulness of these methods compared to sensitivity analysis or patient-level VOI.
- In both case studies, the time and resources needed to develop useful models was substantial, even though (a) both models were extensions of previously developed models, and (b) our emphasis in both cases was on providing a minimal set of results to introduce stakeholders to potential applications of modeling in priority setting, rather than on detailed and comprehensive consideration of the full range of research options. This suggests that the decision to develop or adapt a model and apply it to research prioritization setting needs to be made relatively early in the systematic review process. Alternatively, if formal research prioritization is a separate process that occurs after the completion of the review, sufficient time must be allotted for model development. This suggestion is consistent with the draft Minnesota report as well.
- One of the challenges in developing models in parallel to the systematic review process is that, although many of the key parameters needed for the model will be identified through the systematic review designed to answer key questions, there will be additional data needs that will likely require additional literature searches or primary data analysis. Identifying the need for these additional data, as well as estimating the resources required to obtain them, can be difficult during the initial development of a proposal, particularly if the need for a model has not been specified.
- One of these additional data needs is likely to be cost data. In both case studies, we required estimates of costs in order to generate cost-effectiveness estimates for sensitivity and VOI analyses. Although it would certainly be possible to use sensitivity analysis to identify those variables contributing to the greatest uncertainty regarding noneconomic outcomes (even using VOI methods without incorporating costs[5,6]), and to use this information to inform research prioritization, avoiding the use of costs in an exercise that explicitly recognizes the existence of limited resources would require substantial cognitive dissonance, and would make VOI impossible. Use of modeling and VOI as part of research prioritization for systematic reviews would require explicit resource allocation for obtaining relevant cost data, either as part of the review or as part of a subsequent prioritization process.
- Both sets of stakeholders stated that they found the model results helpful. In the fibroids case study, the presented results were roughly concordant with the results of the consensus-based process in which the stakeholders had previously been involved. In this setting, it may have been that having their initial results confirmed by an alternative

method increased their certainty about their initial rankings. Because of this (unplanned) concordance, we have no idea how stakeholders would respond to results that differed from their previous rankings. Eliciting these data would require either a much larger sample of stakeholders, so that at least some who had different rankings would be included, or performing enough comparisons across multiple clinical areas so that the frequency of disagreement between model-based and consensus-based rankings could be estimated. If concordance is generally high, then additional work would be needed on the value of stakeholder certainty in generating research recommendations. If concordance is low, then identifying ways to resolve these differences, or to determine which method is more likely to result in research results, is needed.

- Although none of the stakeholders felt that review of model results alone should be used instead of a more traditional consensus-based approach, all felt that the model results were very useful in conjunction with a consensus-based approach, with the participants roughly evenly divided on whether the results would be more helpful as part of the background preparation for the consensus-based approach or as part of an iterative process in parallel with the consensus-based approach. Since when the modeling occurs has significant implications for resource allocation and overall timing of the prioritization process, evaluative studies comparing these two possible approaches in more detail could be useful.
- All of the participants felt that having more background material on modeling and VOI, either directly or as an easily accessible resource, would have been helpful. This need for further stakeholder education was also identified by both the Minnesota EPC and the HTA program. One possible solution would be the development of an EPC-wide reference available via the Web that would provide appropriate background to stakeholders.
- The optimal composition of the stakeholder group and timing of their involvement in the prioritization process is unclear. The Technical Expert Panel (TEP) supporting the systematic review would have familiarity with the clinical area and the state of the available evidence, which might facilitate integration of modeling results into recommendations for future research. However, this potential function of the TEP would need to be explicitly considered during the selection of members to ensure adequate representation by potential decisionmakers. Additionally, if the research prioritization process extended beyond the completion of the systematic review, the longer time commitment for TEP participation would require additional resources and might prohibit the participation of some potentially important experts or stakeholders. The alternative approach, convening a separate group of experts/stakeholders explicitly for the research prioritization process, would ensure the most appropriate membership, but could require additional time and effort in familiarizing the group with the underlying issues.
- Based on these initial pilot studies, we believe that the use of modeling, including VOI, is worth further evaluation as a method for identifying and prioritizing future research needs for reviews conducted as part of the EPC program. We would recommend:
  - Incorporating these methods into several new reviews, in order to better assess the incremental costs associated with conducting them.
  - Conducting the full range of possible analyses, from sensitivity analysis through population-level estimation of EVPI and EVPPI, for each review.

- Devising methods for assessing the relative costs and effectiveness (in terms of stakeholder evaluations) for the varying types of analyses.

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Acronyms and Abbreviations

ACEI(s)	angiotensin-converting enzyme inhibitor(s)
AHRQ	Agency for Healthcare Research and Quality
ARB(s)	angiotensin II receptor antagonist(s)
ARRA	American Recovery and Reinvestment Act of 2009
CADTH	Canadian Agency for Drugs and Technologies in Health
CER	comparative effectiveness review
CHF	congestive heart failure
CMTP	Center for Medical Technology Policy
DEcIDE	Developing Evidence to Inform Decisions about Effectiveness
EPC	Evidence-based Practice Center
ESRD	end-stage renal disease
EVPI	expected value of perfect information
EVPPI	expected value of partial perfect information
FUS	focused ultrasound
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
IHD	ischemic heart disease
LV	left ventricular
LY	life-year
MI	myocardial infarction
MRI	magnetic resonance imaging
NICE	National Institute for Clinical Excellence
NIH	National Institutes of Health
QALY	quality-adjusted life year
RTI	Research Triangle Institute
TEP	Technical Expert Panel
TWG	Technical Working Group
UAE	uterine artery embolization
UK	United Kingdom
UNC	University of North Carolina at Chapel Hill
USAID	U.S. Agency for International Development
VOI	value of information/value-of-information
WHO	World Health Organization
WTP	willingness to pay

Appendix A. Literature Search and Screening Results

Search Strategies

We performed two PubMed® searches to identify published studies relevant to this review. These searches were structured as described below.

Search #1: Designed to identify articles addressing methods of priority setting, using the following search strategy (no date restrictions, search date October 22, 2010):

> ("Research"[Mesh] OR "Health Services Research"[Mesh]) AND (exercise[title/abstract] OR tool[title/abstract] OR tools[title/abstract] OR model[title/abstract] OR models[title/abstract] OR method[title/abstract] OR methods[title/abstract] OR "models, theoretical"[MeSH Terms] OR "costs and cost analysis"[MeSH Terms] OR "resource allocation"[MeSH Terms] OR "investments/economics"[Mesh Terms]) AND ("health priorities"[MeSH Terms] OR "priority setting"[title/abstract] OR "research priorities"[title/abstract] OR "research priority"[title/abstract])

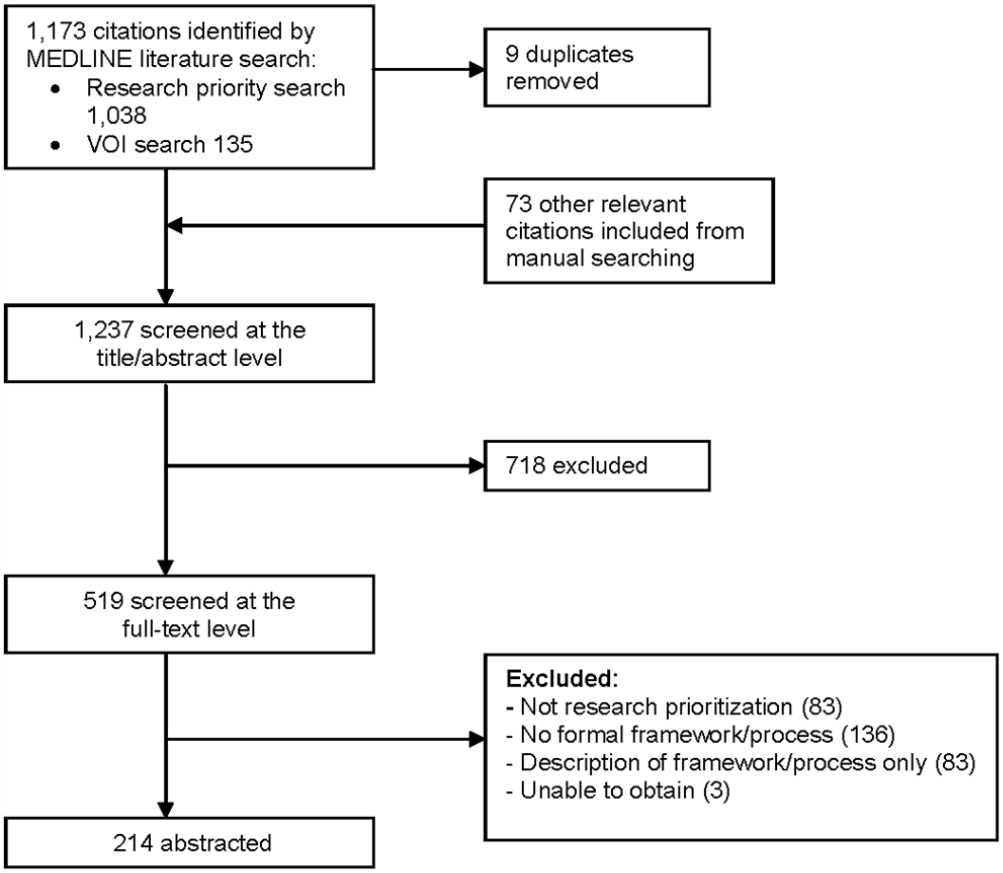
Search #2: Designed to identify articles specifically addressing VOI, using the following search strategy (no date restrictions, search date December 1, 2010):

> "value of information"[title/abstract] AND (("Decision Making"[Mesh] OR "Decision Theory"[Mesh]) OR ("Research"[Mesh] OR "Health Services Research"[Mesh]) OR research[title/abstract])

Literature Screening Results

Figure A1 summarizes the results of our literature search and screening.

Figure A1. Literature flow diagram



Appendix B. Data Abstraction Form

Study	Study characteristics and participants	Focus of prioritization effort	Identification of research gaps	Prioritization considerations and methods	Use of prioritization results/study output
Study ID and location: [enter information] 1st author_____ Year_____ Article #_____	**Location:** [enter country]_____ **Study type:** [check one/delete all but one] ___Methodological with case study ___Practical application of priority setting framework/process (e.g., report of consensus conference) **Sponsoring organization:** [check multiple items, if appropriate] ___NIH ___AHRQ ___Other US govt Describe:_____ ___Non-US govt Describe:_____ ___WHO ___NGO ___Professional society ___Advocacy group (e.g., AHA, ACS) __Industry	**Focus of prioritization effort:** [check one/delete all but one] ___Provider/specialty based (e.g., research questions in acute care nursing) ___Broad disease area (e.g., breast cancer vs. prostate cancer vs. colon cancer) ___Specific disease (e.g., screening vs. improved treatment for breast cancer) Describe:_____ ___Specific interventions (e.g., mammography vs. MRI for screening high-risk women) ___Specific methods (e.g., RCTs vs. registries for CER)	**Identification of research gaps:** [check multiple items, if appropriate] ___Systematic review specifically for this article ___Cited systematic reviews ___Non-systematic review specifically for this article ___Cited non-systematic review ___Formal survey prior to conference/ work group meeting ___Formal survey at conference/work group meeting ___Non-specific consensus of participants ___Other Describe:_____ ___None ___Not specified	**Prioritization considerations:** [check multiple items, if appropriate] ___Burden of disease ___Cost of illness ___Feasibility ___Impact on practice ___Clinical variations (gap between current practice and best practice) ___Inclusiveness (relevance of research area to broad range of individuals with regard to age, sex, socioeconomic status and race or ethnicity) ___Value of research ___Other Describe:_____ ___Not specified **Prioritization methods:** [check multiple items, if appropriate] 1. Consensus based methods: ___Qualitative survey ___Quantitative survey	**Use of prioritization results:** [check multiple items, if appropriate] ___Allocation of research funds (e.g., RFA/RFP) ___Setting a research agenda __Adoption/further research for a particular technology or intervention ___Advocacy ___Not specified **Study output:** [check multiple items, if appropriate] ___Ranked list of priorities (yes/no) ___Identification of broad research questions without ranking ___Cost-effectiveness of therapy/intervention ___Cost-effectiveness of research ___Cost-effectiveness of research and EVPI

Study	Study characteristics and participants	Focus of prioritization effort	Identification of research gaps	Prioritization considerations and methods	Use of prioritization results/study output
	___Academic Specify source of funding: Govt___ Industry___ Nonprofit___ Not reported__ **Participants:** [give N for each category as appropriate] Researchers____ Sponsoring agency____ Other agencies____ Payers____ Industry____ Advocacy org____ Patients____ Providers/ clinicians____			___Delphi ___ Other (e.g., deliberations among work group members/panel, voting) 2. Modeling- based approaches: ___VOI analysis ___Cost effectiveness ___Probabilistic decision analytic model ___Other Describe:_____ ___Not specified	

Appendix C. Details of Research-Sponsoring Organizations

List of Organizations Sponsoring Research

Note: Organizations that declined participation or did not provide a response are noted with an asterisk.

National Institutes of Health: Centers, Programs, and Individual Institutes

1. Division of Program Coordination, Planning and Strategic Initiatives, Office of Director, NIH*
2. Office of AIDS Research
3. Office of Behavioral and Social Sciences Research (OBSSR)
4. Office of Strategic Coordination (OSC), Office of Director, NIH*
5. Office of Research in Women's Health
6. National Cancer Institute (NCI)
7. National Eye Institute (NEI)
8. National Heart, Lung and Blood Institute (NHLBI)
9. National Human Genome Research Institute (NHGRI)
10. National Institute of Aging(NIA)
11. National Institute of Alcohol Abuse and Alcoholism (NIAAA)
12. National Institute of Allergy and Infectious Diseases (NIAID)
13. National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS)*
14. National Institute of Biomedical Imaging and Bioengineering (NIBIB)*
15. National Institute of Child Health and Human Development (NICHD)
16. National Institute on Deafness and other Communication Disorders (NIDCD)*
17. National Institute of Dental and Craniofacial Research (NIDCR)
18. National Institute of Digestive and Kidney Diseases (NIDDK)*
19. National Institute of Drug Abuse (NIDA)
20. National Institute of Environmental Health Science (NIEHS)
21. National Institute of General Medical Sciences (NIGMS)*
22. National Institute of Mental Health (NIMH)
23. National Institute of Neurological Disorders and Stroke (NINDS)*
24. National Institute of Nursing Research (NINR)*
25. NIH Consensus Statements

Agency for Healthcare Research and Quality (AHRQ)

26. United States Preventive Services Task Force (USPSTF)
27. Developing Evidence to Inform Decisions about Effectiveness Network (DeCIDE) Centers
28. Centers for Education & Research on Therapeutics (CERTs)
29. Topic Selection for Systematic Reviews

Other U.S. Government Sponsors of Research

30. Centers for Disease Control and Prevention (CDC)*
31. Centers for Medicare and Medicaid Services (CMS)*
32. Veterans Administration (VA)*
33. U.S. Food and Drug Administration (FDA)*
34. U.S Agency for International Development (USAID)

International Agencies and Groups

35. National Institute for Clinical Excellence (NICE)
36. Cochrane reviews and protocols
37. Canadian Agency for Drugs and Technologies in Health
38. Canadian Institutes for Health Services Research and Policy
39. German Research Foundation
40. German Federal Ministry of Education and Research
41. Australian Research Council
42. World Health Organization

Nongovernmental Sponsors of Research

43. American Cancer Society
44. Bill and Melinda Gates Foundation
45. Robert Wood Johnson Foundation*
46. American Heart Association
47. March of Dimes*
48. Children's Health and Nutrition Research Initiative of the Global Forum for Health Research

Summary Table

1.	Agency for Health Care and Quality (AHRQ)	
	a. Focus	• Identifying, Selecting, and Refining Topics for Comparative Effectiveness Systematic Reviews
	b. Criteria	• Appropriateness—applies to Medicare and/or Medicaid populations, priority condition designated by the Department of Health and Human Services (DHHS) • Importance-disease burden, cost-of illness, strong stakeholder support, uncertainty or controversy surrounding issue • Desirability of new research/duplication • Feasibility • Potential value-potential for significant health and economic impact, potential for change and potential risk from inaction; addresses inequities, vulnerable populations, and has clear implications for resolving dilemmas in health and health care decisions
	c. Methods	• Consensus-based; expert-panel (topic prioritization group) with input from multiple stakeholders.
	d. Source	• Whitlock et al., 2010[1]
2	AHRQ- Centers for Education and Research on Therapeutics (CERTs)	
	a. Focus	• Prioritizing new research

	b. Criteria	• None
	c. Methods	• Investigator-initiated research prioritized by peer-review process; no other formal prioritization process.
	d. Source	• Response to Duke EPC review of research priority setting methods
3	AHRQ- DEcIDE (Developing Evidence to Inform Decisions about Effectiveness) Network	
	a. Focus	• Prioritizing new research
	b. Criteria	• Appropriateness—applies to Medicare and/or Medicaid populations, priority condition designated by the Department of Health and Human Services (DHHS) • Importance-disease burden, cost of illness, strong stakeholder support, uncertainty or controversy surrounding issue • Desirability of new research/duplication • Feasibility • Potential value-potential for significant health and economic impact, potential for change and potential risk from inaction; addresses inequities, vulnerable populations, and has clear implications for resolving dilemmas in health and health care decisions
	c. Methods	• Consensus-based
	d. Source	• Response to Duke EPC review of research priority-setting methods
4	U.S. Preventive Services Task Force	
	a. Focus	• Identifying research priorities for clinical preventive services
	b. Criteria	• Public health importance (burden of suffering, and expected effectiveness of preventive services to reduce that burden); • Potential for a Task Force recommendation to affect clinical practice (based on existing controversy or the belief that a gap exists between evidence and practice); • New evidence (e.g., new studies or new analysis of previous data) that has the potential to change prior recommendations; • Need for a balanced portfolio of topics.
	c. Methods	• Consensus-based
	d. Source	• http://www.uspreventiveservicestaskforce.org/uspstf08/methods/procmanual2.htm
5	National Institute of Clinical Excellence (NICE), UK	
	a. Focus	• Topic selection for the Institute's clinical practice, health technologies and public health programs
	b. Criteria	• Identified as priority by the health service or the government • Impact on the financial or other resources of the NHS or society in general • Interventions that the NHS could stop using without impairing cost-effective patient care, thus freeing up resources for use elsewhere in the NHS • Significant morbidity or mortality • Interventions or practices that could: -significantly improve patients' or carers' quality of life -reduce avoidable morbidity -reduce avoidable premature mortality -reduce inequalities in health? • Variations in clinical practice • Variation in access to interventions or treatment • Significant public concern
	c. Methods	• Consensus based; expert panel deliberations with input from stake holders
	d. Source	• http://www.nice.org.uk/niceMedia/pdf/boardmeeting/brdnov06item4.pdf

5.a	National Institute of Clinical Excellence (NICE), UK	
	a. Focus	• Translating uncertainties identified in systematic reviews into research recommendations
	b. Criteria	Suggested criteria for evaluation • Importance to patients or the population • Relevance to NICE Guidance • Relevance to NHS • National priorities • Current evidence base • Equality • Feasibility
	c. Methods	• Consensus-based; • Decisionmaking framework employed recommends use of value-of-information methods (as and when necessary) to reduce evidence gaps and help prioritize future research
	d. Source	http://www.nice.org.uk/media/46F/72/ResearchRecommendationManual.pdf
6	Cochrane Reviews	
	a. Focus	• Topic selection for systematic assessment of health care interventions
	b. Criteria	• Burden of disease, magnitude of problem, urgency • Importance to developing countries • Avoidance of duplication • Opportunity for action
	c. Methods	• Consensus-based
	d. Source	• Waters et al, 2003[2]
7	World Health Organization	
	a. Focus	• Improving the use of research evidence in guideline development
	b. Criteria	• High burden of illness • No existing guidelines or recommendations of good quality • Feasibility of developing recommendations • Implementation is feasible • Interventions that will likely require systems changes • Interventions where there might be conflict in choices between individual and societal perspectives
	c. Methods	• Consensus-based;
	d. Source	• Oxman et al., 2006[3]
	National Institutes of Health and Individual Institutes and Centers within the NIH	
8	National Heart and Lung Institute (NHLBI), NIH	
	a. Focus	Identifying institute-level research priorities

	b. Criteria	• Alignment with the NHLBI Strategic Plan • Magnitude of the public health need (disease severity, number affected, current therapy) • Existence of scientific opportunity (new concepts or tools, likelihood of significant advance) • Rate of research progress • Opportunity to attract disciplines new to NHLBI research areas • Need to foster multidisciplinary research • Expression of congressional interest
	c. Methods	• Consensus-based with input from researchers, advisory council and a variety of stake holders • Extramural, investigator initiated research (70% of research funding) is prioritized using peer-review system • Institute-initiated research (30%) is prioritized by NHLBI staff through working groups and advisory council of outside experts. • Proposed research in applications with direct costs of $500,000 or more in any one year are prioritized based on whether research is: 1. relevant to NHLBI mission, 2. complements outgoing or new NHLBI programs, 3. adds to existing knowledge, 4. has reasonable costs and 5. has appropriate plans for data sharing
	d. Source	• Response to Duke EPC review of research priority-setting methods
9	National Institute of Aging (NIA), NIH	
	a. Focus	• Identifying institute-level research priorities
	b. Criteria	• Responding to needs identified by NIH/presidential/congressional leaders • Burden of illness/disease prevalence/trends among aging population groups • Scientific opportunity • Special areas or needs identified using bibliometric and portfolio analysis
	c. Methods	• Consensus-based with ongoing input from research community and advisory groups and advocacy organizations
	d. Source	• Response to Duke EPC review of research priority-setting methods
10	National Institute of Allergy and Infectious Diseases (NIAID), NIH	
	a. Focus	• Identifying institute-level research priorities
	b. Criteria	• Need or gap • Scientific opportunity • Portfolio diversification • Public health need
	c. Methods	• Consensus-based through the mechanism of scientific workshops, program reviews, research advisory committees, blue ribbon panels and input from stakeholders
	d. Source	• Response to Duke EPC review of research priority-setting methods (See Appendix)
11	National Institute of Dental and Craniofacial Research (NIDCR), NIH	
	a. Focus	• Identifying institute-level research priorities
	b. Criteria	• Prevalence and impact of related diseases and criterion • Current state of science (and available opportunities) • Responding to needs identified by NIH/Presidential/Congressional leaders
	c. Methods	• Consensus-based with input from research community, professional societies, patient organizations, Board of scientific councilors and ad-hoc advisory groups
	d. Source	• Response to Duke EPC review of research priority-setting methods
12	National Institute on Drug Abuse (NIDA),NIH	
	a. Focus	• Identifying institute-level research priorities

	b. Criteria	• Emerging and significant public health needs • Key scientific opportunities • Filling gaps in current knowledge base
	c. Methods	• Consensus-based with input from research community, professional societies, patient organizations, Board of scientific councilors and ad-hoc advisory groups, U.S. Administration representatives and Members of Congress • Input on the priority setting process from: -NIDA Council –The National Advisory Council on Drug Abuse with 18 members including 12 scientific experts, 6 knowledgeable members of the general public, and ex-officio members who provide liason with other government entities. Council advises on the institute's program portfolio and helps determine the overall merit and priority of grant applications -Subcommittees of the Advisory Council to systematically review NIDA's portfolio and issue recommendations to the director -Conferences and symposia: Variety of meetings to solicit potential scientific research in particular areas identified as a priority • Monitoring of emerging health needs: Monitoring of national and regional drug abuse trends to identify and prioritize specific areas of research
	d. Source	• Response to Duke EPC review of research priority-setting Methods
13	National Eye Institute (NEI), NIH	
	a. Focus	• Identifying institute-level research priorities
	b. Criteria	• Not explicitly specified; broad criteria such as scientific opportunity as interpreted by panel of experts in the strategic planning process
	c. Methods	• Consensus-based
	d. Source	• Response to Duke EPC review of research priority-setting methods
14	NIH Consensus Development Program	
	a. Focus	• Prioritizing topics for evidence-based consensus statements addressing controversial issues important to health care providers, policymakers, patients, researchers, and the general public
	b. Criteria	• None
	c. Methods	• Informal consensus-based process
	d. Source	• Response to Duke EPC review of research priority-setting methods
15	Office of Research on Women's Health, NIH	
	a. Focus	• Developing strategic research priorities for women's health research for the coming decade
	b. Criteria	• Not explicitly specified
	c. Methods	• Regional scientific workshops and public hearings with participation from leading scientists, women's health advocates, public policy experts, healthcare providers, and the general public; participants provide both written as well as public testimony. Ideas from regional workshops integrated with additional input from NIH community over the course of a 18-month national planning effort to develop strategic research priorities for women's health research.
	d. Source	• Response to Duke EPC review of research priority-setting methods
16	National Human Genome Research Institute (NHGRI), NIH	

	a. Focus	• Setting institution-wide priorities for investigator-initiated research as well as institute-initiated research.
	b. Criteria	• Not explicitly specified; broad priorities are scientific merit and fidelity to the institute's mission
	c. Methods	Priorities set using consensus-based methods in consultation with the research community and stakeholders through the following methods: • Workshops and conferences sponsored by NHGRI • Concept clearance from the National Advisory Council for Human Genome Research • Request for White Papers • Regular long-range planning activities (see www.genome.gov/Planning)
	d. Source	• Response to Duke EPC review of research priority-setting methods
17	Office of Behavioral and Social Research (OBSSR), NIH	
	a. Focus	• Behavioral and social research across NIH
	b. Criteria	• Not explicitly defined;
	c. Methods	• Consensus-based methods
	d. Source	• Response to Duke EPC review of research priority-setting methods
18	National Institute of Child Health and Human Development (NICHD),NIH	
	a. Focus	• Identifying institute-level research priorities
	b. Criteria	• Responsiveness to existing and emerging public health needs • Disease burden (incidence, severity, and costs of specific disorders) • Considerations such as unmet needs associated with rare disorders

	c. Methods	• Consensus-based with input from many sources, including:
		  • Formally instituted advisory and review panels including National Child Health and Human Development Advisory Council, the National Advisory Board for Medical Rehabilitation Research and the NICHD board of scientific councilors
		  • The extramural scientific community, including individual researchers and professional societies;
		  • Patient and provider organizations and voluntary health organizations, which may provide input directly or indirectly, through Congress and the media;
		  • Congress and the Administration;
		  • NIH leadership and colleagues at other NIH ICs;
		  • Formally constituted advisory and review panels described below;
		  • NICHD staff scientists;
		  • Research programs of other Federal agencies such as the Department of Defense and the Department of Education;
		  • International public health and research organizations; and
		  • Individual members of the public

	d. Source	• Response to Duke EPC review of research priority-setting methods
19	National Cancer Institute	
	a. Focus	• Setting institutional priorities
	b. Criteria	• Not explicitly defined
	c. Methods	• Consensus-based process with input from multiple stakeholders; consensus developed through multiple forums including state-of-science workshops, scientific advisory boards program reviews, meetings
	d. Source	• Response to Duke EPC review of research priority-setting • http://www.cancer.gov/aboutnci/servingpeople/BudgetProcess

20	USAID	
	a. Focus	• Identifying priority problems for research
	b. Criteria	• Relevance (to USAID's strategic priorities) • USAID's unique role • Importance of the problem • Consistency • Feasibility • U.S. Institution's unique role
	c. Methods	• Consensus-based methods; • The research policy framework of USAID recommends use of appropriate analytical tools (e.g. cost-benefit analysis, cost-effectiveness analysis) to facilitate use of these criteria and to determine the relative value of USAID research efforts
	d. Source	• Response to Duke EPC review of research priority-setting methods; (http://www.usaid.gov/policy/ads/200/polframe.pdf)
21	Office of AIDS Research	
	a. Focus	• Trans-NIH AIDS research agenda and priorities
	b. Criteria	• Public health need • Scientific opportunity
	c. Methods	• Consensus-based methods
	d. Source	• Response to Duke EPC Review of Research Priority Setting Methods; (http://www.usaid.gov/policy/ads/200/polframe.pdf)
	c. Methods	• Consensus-based methods; Input from internal staff, research community, other NIH institutes and centers, • Portfolio analysis • Concept mapping • Request for information in the NIH guide asking for members of the public, advocacy groups, scientific organizations, researchers etc to identify priorities for future research investments
	d. Source	• http://obssr.od.nih.gov/pdf/bBSSR%20StrategicPlanOBSSR%20FINAL.pdf • http://obssr.od.nih.gov/pdf/OBSSR_Prospectus.pdf
22	National Institute of Alcohol Abuse and Alcoholism	
	a. Focus	• Institute-level priorities
	b. Criteria	• Multiple; not specified explicitly
	c. Methods	• Consensus-based methods; Input from public, scientists, NIAAA advisory council and working groups
	d. Source	• Response to Duke EPC review of research priority setting methods
23	National Institutes of Environmental Health Sciences	
	a. Focus	• Setting institute-wide priorities
	b. Criteria	• Scientific opportunity • Public health importance • Impact on research portfolio (focus on research areas where NIEHS has genuine strengths)
	c. Methods	• Consensus-based methods using with input from variety of sources such as National advisory environmental health services council, annual leadership retreat, board of scientific counselors, research workshops, semi-annual center director's meetings, and the general public
	d. Source	• Response to Duke EPC review of research priority setting methods

24	National Institute of Mental Health (NIMH)	
	a. Focus	• Setting institutewide priorities
	b. Criteria	• Multiple; not specified explicitly
	c. Methods	• Consensus-based methods
	d. Source	• Response to Duke EPC review of research priority setting methods
25	Institute for Health Services and Policy Research (IHSPR), Canada	
	a. Focus	Priorities for health services research across Canada-
	b. Criteria	Multiple; not specified explicitly
	c. Methods	Consensus-based; Research priorities identified with input from a broad range of stakeholders and potential partners (input is typically obtained through a range of mechanisms including key informant interviews, town hall meetings, in-person meetings with partners, etc.), refined by various subcommittees of the board (comprised of IHSPR's board members and a few key experts from the researcher and decision maker communities), and vetted by Institute Advisory Board for final approval. Specific example: IHSPR in partnership with Canadian Health Services Research Foundation (CHSRF) implements a national consultation process-Listening for Direction (LFD)- a pan-Canadian priority setting exercise undertaken every three years to identify pressing short, medium and long-term priority issues of the health system decision makers and managers from across the country with regards to health services research and policy.
	d. Source	Response to Duke EPC review of research priority-setting methods
26	American Cancer Society	
	a. Focus	Prioritization of research portfolio
	b. Criteria	None
	c. Methods	Primarily investigator initiated, peer-reviewed research; A small portion of ACS research goes to focused research and the specific areas are chosen by panels of outside scientists and ACS volunteer leadership
	d. Source	Response to Duke EPC review of research priority-setting methods
27	American Heart Association	
	a. Focus	Prioritization of research portfolio
	b. Criteria	None
	c. Methods	None; Primarily investigator initiated research; No formal prioritization process
	d. Source	Response to Duke EPC review of research priority-setting methods
28	German Research Foundation	
	a. Focus	Prioritization of research portfolio
	b. Criteria	Primarily science driven;
	c. Methods	Does not set research priorities

	d. Source	Response to Duke EPC review of research priority-setting methods
29	Australian Research Council	
	a. Focus	Prioritization of research portfolio
	b. Criteria	None
	c. Methods	Does not set research priorities; acts on guidance received from Australian government on areas of research of national priority
	d. Source	Response to Duke EPC review of research priority-setting methods
30	Canadian Agency for Drugs and Technologies in Health	
	a. Focus	Priority setting for health technology assessment
	b. Criteria	Disease burden Clinical impact Alternatives Budget Impact Economic Impact Available Evidence
	c. Methods	Deliberative process incorporating ranking using specific criteria
	d. Source	Husereau et al., 2010[4]
31	Child Health and Nutrition Research Initiative of the Global Forum for Health Research	
	a. Focus	Priority setting for research into child health and nutrition issues in developing world
	b. Criteria	Answerability Effectiveness Deliverability Maximum potential for disease burden reduction Effect on equity
	c. Methods	Deliberative process incorporating ranking using specific criteria involving both stakeholders and investors in research
	d. Source	http://www.chnri.org/

References to Summary Table:

1. Whitlock EP, Lopez SA, Chang S, et al. AHRQ series paper 3: identifying, selecting, and refining topics for comparative effectiveness systematic reviews: AHRQ and the effective health-care program. J Clin Epidemiol 2010;63(5):491–501.
2. Waters E, Doyle J, Jackson N. Evidence-based public health: improving the relevance of Cochrane Collaboration systematic reviews to global public health priorities. J Public Health Med 2003;25(3):263–266.
3. Oxman AD, Schunemann HJ, Fretheim A. Improving the use of research evidence in guideline development: 2. Priority setting. Health Res Policy Syst 2006;4:14.
4. Husereau D, Boucher M, Noorani H. Priority setting for health technology assessment at CADTH. Int J Technol Assess Health Care 2010;26(3):341–347.

Appendix D. Prioritization Tools—
ACEI/ARB Case Study

The material presented below represents the tools used in each of three prioritization exercises conducted with the stakeholder group.

Prioritization Exercise 1

The following survey was administered to stakeholders electronically on July 19, 2010, using SurveyMonkey™ software. In this survey, stakeholders were asked to use a 5-point Likert scale to rate the importance of further research in the areas of the 16 identified research gaps. Possible responses ranged from "Not at all important" to "Very important." A free text field was offered to allow stakeholders to enter additional research areas for consideration. Stakeholders were also asked to rank their top five research priorities from the complete list of options, including any additional considerations entered into the free text field.

Page #1

1. Participant Information

1. Please provide your name

Name:

Page #2

2. Patient/Population Subgroup Differences

2. With respect to impact on modulating ACE-I/ARB effectiveness or harms in patients with stable ischemic heart disease, to what extent do the following patient/population characteristics warrant further research?

Please indicate your rating of each characteristic below.

	Not at all important	Somewhat unimportant	Neutral	Somewhat important	Very important
Demographic differences (such as age, race, gender)					

Co-morbidities (such as hypertension, congestive heart failure with or without preserved LV function, diabetes, peripheral arterial disease, chronic kidney disease, prior coronary revascularization; single vs. multivessel coronary artery disease)	☐	☐	☐	☐	☐
Concurrent medications (such as anti-platelet agents, lipid lowering medications, other anti-hypertensives)	☐	☐	☐	☐	☐
Genetic differences (such as ACE or Angiotensin II receptor gene polymorphisms)	☐	☐	☐	☐	☐

Page #3

3. Medication Characteristics

3. With respect to impact on modulating ACE-I/ARB effectiveness or harms in patients with stable ischemic heart disease, to what extent do the following ACE-I/ARB characteristics warrant further research?

Please indicate your rating of each characteristic below.

	Not at all important	Somewhat unimportant	Neutral	Somewhat important	Very important
Dose-response (impact of medication dose or dosing interval)	☐	☐	☐	☐	☐

Class effect (impact of differences between specific agents within each class)	☐	☐	☐	☐	☐
Benefit relative to alternative medication classes (calcium channel blocker, diuretic, or beta-blocker)	☐	☐	☐	☐	☐

Page #4

4. Health Care Delivery

4. With respect to impact on modulating ACE-I/ARB effectiveness or harms in patients with stable ischemic heart disease, to what extent do the following issues warrant further research?

Please indicate your rating of each characteristic below.

	Not at all important	Somewhat unimportant	Neutral	Somewhat important	Very important
Adherence (including differential adherence within and between medication classes)	☐	☐	☐	☐	☐
Strategies to enhance greater evidence-based use of ACE-I/ARBs	☐	☐	☐	☐	☐

Page #5

5. Outcomes/Adverse Effects

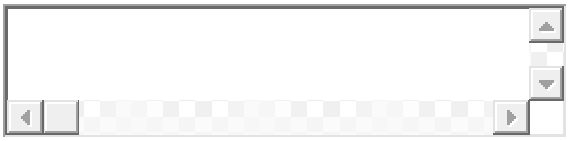
5. With respect to impact on choice of ACE-I/ARB in patients with stable ischemic heart disease, to what extent do the following outcomes warrant further research?

Please indicate your rating of each characteristic below.

	Not at all important	Somewhat unimportant	Neutral	Somewhat important	Very important
Cardiovascular outcomes (such as cardiovascular death, non-fatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure control, measures of atherosclerosis, etc)	☐	☐	☐	☐	☐
Incidence of new diagnoses (such as diabetes, atrial fibrillation, congestive heart failure with or without preserved LV function)	☐	☐	☐	☐	☐
Progression of renal insufficiency or development of dialysis dependence	☐	☐	☐	☐	☐
Development of angioedema	☐	☐	☐	☐	☐
Development of non-angioedema adverse effects (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)	☐	☐	☐	☐	☐
Patient quality of life	☐	☐	☐	☐	☐
Utilization and cost of therapy	☐	☐	☐	☐	☐

6. If there are other outcomes or adverse effects that in your opinion should be considered in Question #5 above, please list them here and include your rating of each outcome or adverse effect using the following scale:

1 - Not at all important
2 - Somewhat unimportant
3 - Neutral
4 - Somewhat important
5 - Very important



Page #6

6. Ranking of Top Selections

7. Please list your top 5 selections for further research from the options presented in previous questions (including question #6) in order from #1 to #5. In your ranking, consider #1 to be the most important. The options from previous questions are reproduced below.

	1 - Most Important	2	3	4	5
Demographic differences (such as age, race, gender)	☐	☐	☐	☐	☐
Co-morbidities (such as hypertension, congestive heart failure with or without preserved LV function, diabetes, peripheral arterial disease, chronic kidney disease, prior coronary revascularization; single vs. multivessel coronary artery disease)	☐	☐	☐	☐	☐

Concurrent medications (such as anti-platelet agents, lipid lowering medications, other anti-hypertensives)	☐	☐	☐	☐	☐
Genetic differences (such as ACE or Angiotensin II receptor gene polymorphisms)	☐	☐	☐	☐	☐
Dose-response (impact of medication dose or dosing interval)	☐	☐	☐	☐	☐
Class effect (impact of differences between specific agents within each class)	☐	☐	☐	☐	☐
Benefit relative to alternative medication classes (calcium channel blocker, diuretic, or beta-blocker)	☐	☐	☐	☐	☐
Adherence (including differential adherence within and between medication classes)	☐	☐	☐	☐	☐
Strategies to enhance greater evidence-based use of ACE-I/ARBs	☐	☐	☐	☐	☐

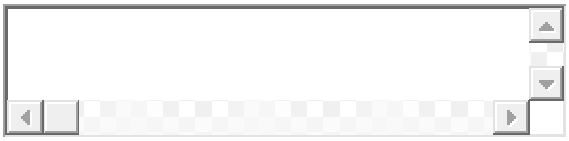
Cardiovascular outcomes (such as cardiovascular death, non-fatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure control, measures of atherosclerosis, etc)	☐	☐	☐	☐	☐
Incidence of new diagnoses (such as diabetes, atrial fibrillation, congestive heart failure with or without preserved LV function)	☐	☐	☐	☐	☐
Progression of renal insufficiency or development of dialysis dependence	☐	☐	☐	☐	☐
Development of angioedema	☐	☐	☐	☐	☐
Development of non-angioedema adverse effects (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)	☐	☐	☐	☐	☐
Patient quality of life	☐	☐	☐	☐	☐
Utilization and cost of therapy	☐	☐	☐	☐	☐
Other outcomes or adverse effects (specify from your response to question #6)	☐	☐	☐	☐	☐

If Other was selected above, specify the selection here.

Page #7

7. Additional Comments

8. Please use the space below to add any additional comments you would like to share as part of this survey or for discussion during the Stakeholder teleconference on 22Jul2010.



Page #8

8. Thank You

Thank you for your time in completing this survey -- we will be discussing the responses with the group during our next Stakeholder teleconference on July 22nd at 2pm ET.

We look forward to your continued participation in this project.

Prioritization Exercise 2

The following qualitative prioritization exercise was conducted with stakeholders on July 28, 2010. In this exercise, stakeholders were provided with a PDF document including the results of Prioritization Exercise 1 and a list of priority setting criteria that could be used when considering the appropriate priority for the research questions. Summary tables describing the evidence base regarding the comparative effectiveness of ACE inhibitor and ARB therapy in patients with IHD[1-2] or hypertension[3-4] were also distributed to the group. Stakeholders were asked to prioritize each research area in order from 1 to 16.

(1) Please consider the information provided with respect to the following hypothetical scenario:

You have been asked to serve on a national advisory panel for an organization interested in funding research on the comparative effectiveness of ACEIs or ARBs for patients with ischemic heart disease.

The organization has a limited research budget and has tasked you with prioritizing the most important areas for future research. You are to use your own judgment based on your knowledge and experience as to which topics would have the greatest impact on patient outcomes.

Please rank the following 16 areas of future research from 1 to 16, with 1 indicating the highest priority, and 16 the lowest priority.

Research Area	Ranking (1 = Most Important, 16 = Least Important)
Impact of demographic differences (such as age, race, gender) on ACEI/ARB effectiveness or harms in patients with stable ischemic heart disease (IHD)	
Impact of co-morbidities (such as hypertension, congestive heart failure with or without preserved LV function, diabetes, peripheral arterial disease, chronic kidney disease, prior coronary revascularization; single vs. multivessel coronary artery disease) on ACEI/ARB effectiveness or harms in patients with stable IHD	
Impact of concurrent medications (such as anti-platelet agents, lipid lowering medications, other anti-hypertensives) on ACEI/ARB effectiveness or harms in patients with stable IHD	
Impact of genetic differences (such as ACE or Angiotensin II receptor gene polymorphisms) on ACEI/ARB effectiveness or harms in patients with stable IHD	
Impact of the dose response (impact of medication dose or dosing interval) of ACEI and ARBs on their effectiveness or harms in patients with stable IHD	
Impact of class effect (impact of differences between specific agents within each class) of ACEI and ARBs on their effectiveness or harms in patients with stable IHD	
The benefit of ACEI/ARBs relative to alternative medication classes (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD	
The impact of ACEI/ARB adherence (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD	
Strategies to enhance greater evidence-based use of ACEI/ARBs	
The impact of ACEI/ARB in patients with stable IHD on cardiovascular outcomes (such as cardiovascular death, non-fatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure control, measures of atherosclerosis, etc)	
The impact of ACEI/ARB in patients with stable IHD on incidence of new diagnoses (such as diabetes, atrial fibrillation, congestive heart failure with or without preserved LV function)	
The impact of ACEI/ARB in patients with stable IHD on progression of renal insufficiency or development of dialysis dependence	

Research Area	Ranking (1 = Most Important, 16 = Least Important)
The impact of ACEI/ARB in patients with stable IHD on development of angioedema	
The impact of ACEI/ARB in patients with stable IHD on development of non-angioedema adverse effects (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)	
The impact of ACEI/ARB in patients with stable IHD on patient quality of life	
The impact of ACEI/ARB in patients with stable IHD on utilization and cost of therapy	

(2) List of potential priority setting criteria that may be used when considering the appropriate priority for the research questions*

1. Disease burden
   The proposed research will reduce disease burden (Prevalence, mortality, morbidity) on afflicted individuals and their families, caretakers, and communities.
2. Cost
   The proposed research has potential to lead to substantial cost efficiencies or cost savings for patients, health plans, or public health programs, through reduction of unnecessary or excessive costs.
3. Variation in care
   The proposed research will reduce unexplained variations (overuse, underuse, misuse) in prevention, diagnosis, access, and/or treatment protocols.
4. Appropriateness
   The proposed research involves a healthcare drug, intervention, device, or technology available (or soon to be available) in the US and is relevant to Section 1013 enrollees (Medicare, Medicaid, SCHIP, other federal healthcare programs)
5. Information gaps and duplication
   The proposed research will fill substantial gaps in the current body of evidence, and there is no other research planned or in progress that will answer the research question, thereby contributing to reduced clinical uncertainties, changes in use and/or coverage of a technology or set of technologies (i.e., improvability of evidence or value of information).
6. Gaps in translation
   The proposed research is likely to improve translation of research findings or existing recommendations into clinical practice or identify improved strategies for research translation.

***Reference:** Institute of Medicine. Initial national priorities for comparative effectiveness research. Washington, DC: Institute of Medicine, 2009.

(3) For information only

The results of the initial ranking of these priorities by the stakeholder group using:

(a) The Likert scale

Comorbidities subgroups
Progression of renal insufficiency or development of dialysis dependence
Utilization and cost of therapy
Demographic differences
Concurrent medications
Benefit relative to alternative medication classes
Strategies to enhance greater evidence-based use
Cardiovascular outcomes
Incidence of new diagnoses
Genetic differences
Adherence
Patient quality of life
Dose-response
Class effect
Development of non-angioedema adverse effects
Development of angioedema

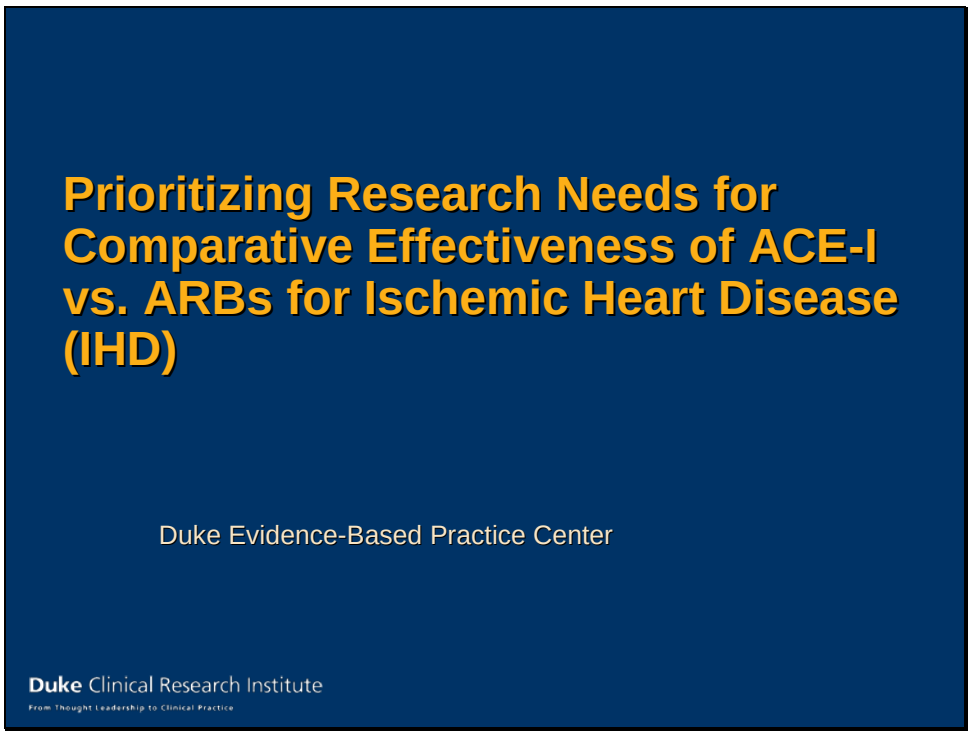
(b) Top 5 ranking

Cardiovascular outcomes
Incidence of new diagnoses
Benefit relative to alternative medication classes
Strategies to enhance greater evidence-based use
Demographic differences
Adherence
Patient quality of life
Comorbidities
Class effect
Genetic differences
Utilization and cost of therapy
Concurrent medications
Progression of renal insufficiency or development of dialysis dependence
Dose-response
Development of angioedema
Development of non-angioedema adverse effects

Prioritization Exercise 3

The following PowerPoint slideshow was presented during a conference call held with stakeholders on September 3, 2010. During this call, the group discussed the results of Prioritization Exercise 2, findings from the Duke EPC's search of recently published literature and ongoing trials, findings from the decision analytic model analysis, and potential changes to the existing ranking based on the body of newly available information.

Slide 1


Prioritizing Research Needs for Comparative Effectiveness of ACE-I vs. ARBs for Ischemic Heart Disease (IHD)
Duke Evidence-Based Practice Center
Duke Clinical Research Institute
From Thought Leadership to Clinical Practice

Slide 2

Agenda

- Update on project focus
- Qualitative prioritization results
- Description of decision analytic model
- Model assumptions and key data
- Model results
- Quantitative priority setting process
- Group discussion

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Slide 3

Project Focus: Update

- Two future research projects
- Today's focus: Pilot project and prioritization of evidence gaps
- Larger methods project: VOI analysis using ACE/ARB in IHD as case study

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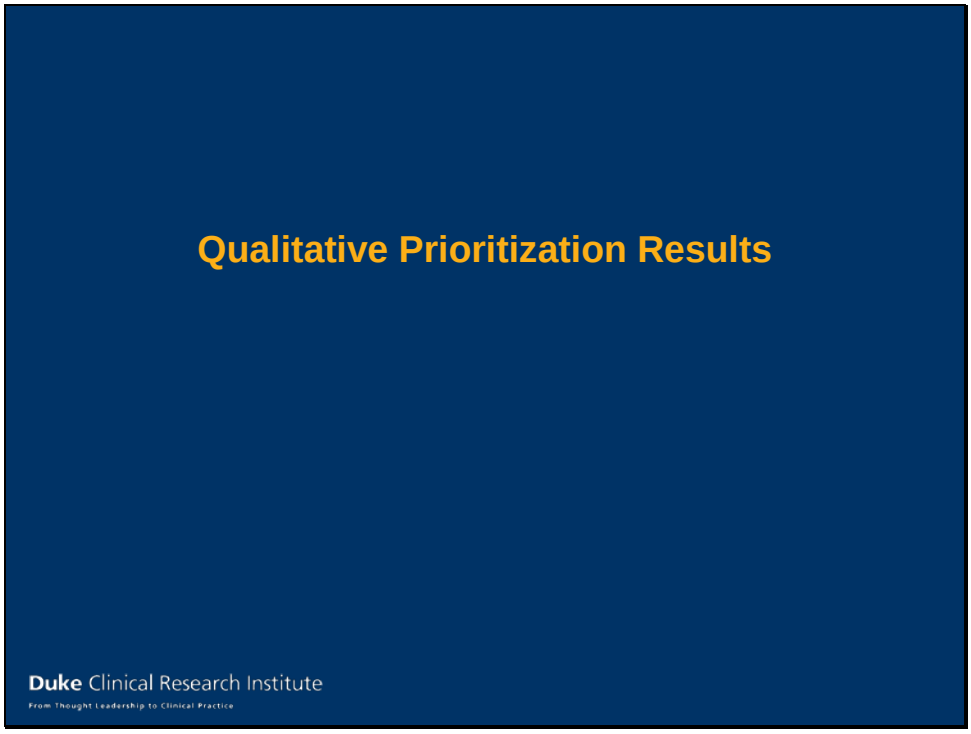
From Thought Leadership to Clinical Practice

Slide 4



Slide 5

#	RESEARCH AREA
1	Strategies to enhance greater **evidence-based use** of ACE-I/ARBs
2	The impact of ACE-I/ARB in patients with stable IHD on incidence of **new diagnoses** (such as diabetes, atrial fibrillation, congestive heart failure with or without preserved LV function)
3	Impact of **co-morbidities** on ACE-I/ARB effectiveness or harms in patients with stable IHD
4	The impact of ACE-I/ARB in patients with stable IHD on patient **quality of life**
5	Impact of **demographic differences** (such as age, race, gender) on ACE-I/ARB effectiveness or harms in patients with stable ischemic heart disease (IHD)
6	The impact of ACE-I/ARB **adherence** (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD
7	The benefit of ACE-I/ARBs relative to **alternative medication** classes (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD
8	The impact of ACE-I/ARB in patients with stable IHD on **cardiovascular outcomes**
9	The impact of ACE-I/ARB in patients with stable IHD on **utilization and cost** of therapy
10	The impact of ACE-I/ARB in patients with stable IHD on progression of **renal insufficiency** or development of dialysis dependence
11	Impact of **concurrent medications** (such as anti-platelet agents, lipid lowering medications, other anti-hypertensives) on ACE-I/ARB effectiveness or harms in patients with stable IHD
12	Impact of **genetic differences** (such as ACE or Angiotensin II receptor gene polymorphisms) on ACE-I/ARB effectiveness or harms in patients with stable IHD
13	Impact of **class effect** (impact of differences between specific agents within each class) of ACE-I and ARBs on their effectiveness or harms in patients with stable IHD
14	Impact of the **dose response** (impact of medication dose or dosing interval) of ACE-I and ARBs on their effectiveness or harms in patients with stable IHD
15	The impact of ACE-I/ARB in patients with stable IHD on development of **non-angioedema adverse effects** (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)
16	The impact of ACE-I/ARB in patients with stable IHD on development of **angioedema**

Slide 6

Prioritization Descriptive Statistics

	Evidence-based use	New diagnoses	Co-morbidities	Quality of life	Demographic differences	Adherence	Alternative medication	Cardiovascular outcomes	Utilization and cost	Renal insufficiency	Concurrent medications	Genetic differences	Class effect	Dose response	Non-angioedema adverse effects	Angioedema
Rank	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Average	5.8	5.9	6.3	6.8	6.9	6.9	7.6	7.6	8.4	8.5	9.0	9.9	10.5	11.4	11.6	13.1
Minimum	1	2	1	3	4	1	2	1	3	2	4	3	1	8	4	6
Maximum	16	15	12	13	12	15	13	16	15	14	12	16	16	15	16	16
StDev	6.5	4.5	4.0	3.3	2.5	5.2	3.3	6.3	4.7	4.7	2.6	4.7	4.8	2.5	3.9	3.5
Variance	42.2	20.7	15.6	10.8	6.4	27.3	11.1	40.0	22.3	22.0	6.9	21.8	22.6	6.3	14.8	12.1
Median	3	4	5	6	7	6.5	7.5	6.5	8	9.5	9.5	11	12	11	13	14.5
1st Quart	1.0	2.8	3.8	4.8	5.5	2.0	6.0	1.8	4.5	4.5	7.8	7.0	8.5	9.8	9.8	12.3
3rd Quart	7.8	8.3	9.5	7.8	7.3	10.0	8.8	13.5	12.3	11.8	11.0	12.0	13.3	13.3	14.0	15.3

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Slide 7

Ongoing/New Studies of Evidence Gaps?

#	RESEARCH AREA	Ongoing Trials	New Published Studies
1	Evidence-based use	1	2
2	New diagnoses	5	8
3	Co-morbidities	1	7
4	Quality of life	0	3
5	Demographic differences	0	2
6	Adherence	1	1
7	Alternative medication	5	3
8	Cardiovascular outcomes	7	18
9	Utilization and cost	1	1
10	Renal insufficiency	12	7
11	Concurrent medications	2	1
12	Genetic differences	1	3
13	Class effect	1	4
14	Dose response	0	2
15	Non-angioedema adverse effects	4	2
16	Angioedema	0	1

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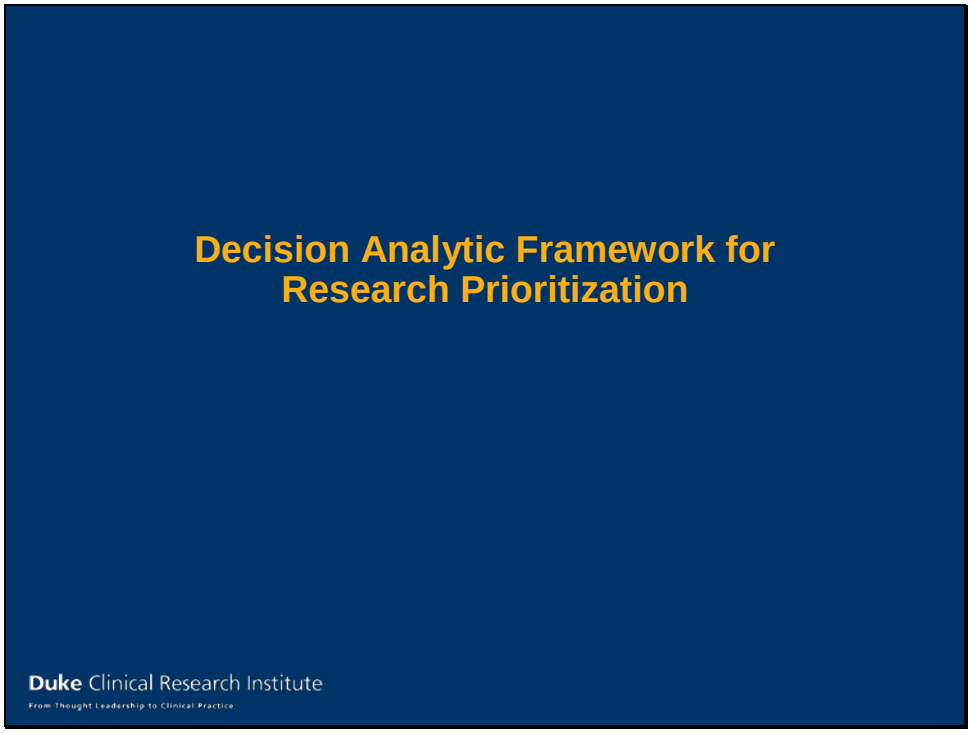
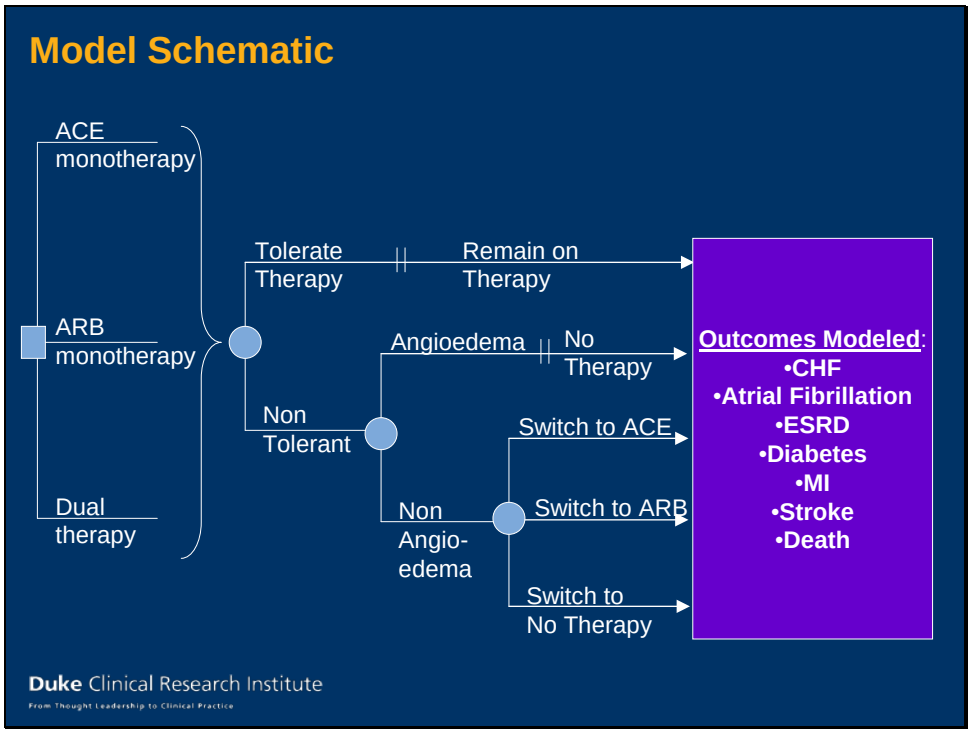
Slide 8



Slide 9



Slide 10

Key Model Assumptions

- Assume all therapies are equally effective in reducing MI, stroke, ESRD, diabetes, atrial fibrillation, and development of CHF compared to standard medical therapy
- No difference in BP for any health state (many paths to BP lowering)
- Class effect for all ACE-I and ARBs
- Intolerance to one class (ACE-I or ARB) results in switching therapies
- Angioedema with either class disqualifies a patient from switching to the other class

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Key Data Estimates

- Risk reduction of ACE/ARB compared with standard medical therapy
  - MI = 0.83
  - Stroke = 0.79
  - ESRD = 0.75
  - Diabetes = 0.90
  - CHF = 0.85
- Non tolerance (first year)
  - ACE = 7.8%
  - ARB = 6.1%
  - Dual therapy = 14.5%
- Angiodema risk (first month)
  - ACE = 0.062%
  - ARB = 0.008%
  - Dual therapy = 0.062%

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PRELIMINARY Results

Strategy	Cost, $	Incr Cost, $	LY	Incr LY	ICER, $/LY	QALY	Incr QALY	ICER, $/QALY
ACE	1721		17.985			16.747		
ARB	1998	277	17.990	.0049	56,198	16.752	0.0054	51,456
Dual	2726	728	17.966	(0.023)	Dominated	16.727	(0.025)	Dominated

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Impact of Evidence Gaps?

- How sensitive are our findings to uncertainty in the evidence?
- Initial modeling exploring impact of uncertainty of
  - New diagnoses
  - Quality of life
  - Cardiovascular outcomes
  - Renal insufficiency
  - Non-angioedema adverse events
  - Angioedema

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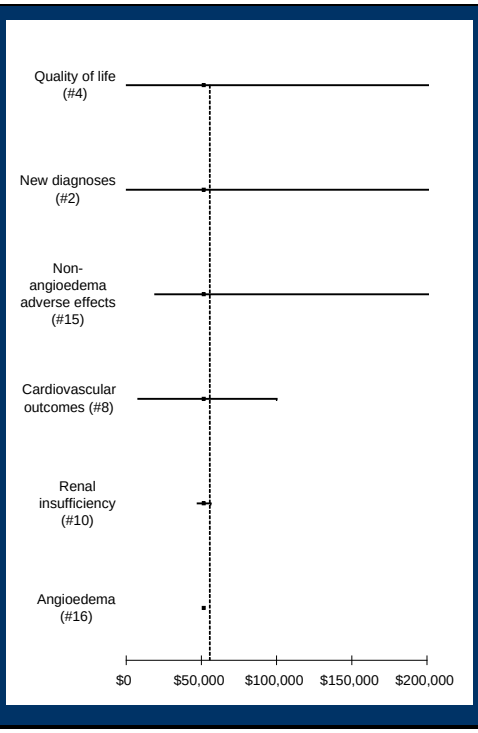

Slide 15

Next Steps: Value of Information Analysis

- Include distributions for model parameters
- Model will give distributions of results
- Allows quantification of uncertainty
- Can then (formally) identify relative importance of different sources of uncertainty
- Value of information
  - Expected value of perfect information (reduce all uncertainty)
  - Expected value of partial perfect information (reduce particular sources of information)

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Slide 16

Slide 17

#	RESEARCH AREA
1	Strategies to enhance greater **evidence-based use** of ACE-I/ARBs
2	The impact of ACE-I/ARB in patients with stable IHD on incidence of **new diagnoses** (such as diabetes, atrial fibrillation, congestive heart failure with or without preserved LV function)
3	Impact of **co-morbidities** on ACE-I/ARB effectiveness or harms in patients with stable IHD
4	The impact of ACE-I/ARB in patients with stable IHD on patient **quality of life**
5	Impact of **demographic differences** (such as age, race, gender) on ACE-I/ARB effectiveness or harms in patients with stable ischemic heart disease (IHD)
6	The impact of ACE-I/ARB **adherence** (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD
7	The benefit of ACE-I/ARBs relative to **alternative medication** classes (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD
8	The impact of ACE-I/ARB in patients with stable IHD on **cardiovascular outcomes**
9	The impact of ACE-I/ARB in patients with stable IHD on **utilization and cost** of therapy
10	The impact of ACE-I/ARB in patients with stable IHD on progression of **renal insufficiency** or development of dialysis dependence
11	Impact of **concurrent medications** (such as anti-platelet agents, lipid lowering medications, other anti-hypertensives) on ACE-I/ARB effectiveness or harms in patients with stable IHD
12	Impact of **genetic differences** (such as ACE or Angiotensin II receptor gene polymorphisms) on ACE-I/ARB effectiveness or harms in patients with stable IHD
13	Impact of **class effect** (impact of differences between specific agents within each class) of ACE-I and ARBs on their effectiveness or harms in patients with stable IHD
14	Impact of the **dose response** (impact of medication dose or dosing interval) of ACE-I and ARBs on their effectiveness or harms in patients with stable IHD
15	The impact of ACE-I/ARB in patients with stable IHD on development of **non-angioedema adverse effects** (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)
16	The impact of ACE-I/ARB in patients with stable IHD on development of **angioedema**

The following prioritization exercise was conducted with stakeholders on September 7, 2010. In this final survey, stakeholders were provided with a Word document including (1) the qualitative rankings as established in Prioritization Exercise 2 and (2) summaries of the recently published literature and ongoing trials that might inform each research area. Stakeholders were asked to consider these findings and then complete a final ranking of the research areas, again assigning priorities from 1 to 16.

Prioritized Future Research Needs for Comparative Effectiveness of ACE-I vs. ARBs for Ischemic Heart Disease: Summary of Recently Published Research and Active Clinical Trials

QUALITATIVE RANKING	RESEARCH AREA	UPDATED RANKING
1	**Research Need:** Strategies to enhance greater **evidence-based use** of ACE-I/ARBs **Recently Published Research:** none **Active Clinical Trials:** (1) Clinical trial of copayment reduction/elimination for post MI therapy **(**Choudhry, N. A Randomized Evaluation of First-dollar Coverage for Post-MI Secondary Preventive Therapies (Post-MI FREEE). ClinicalTrials.gov (ID:NCT00566774).)	

QUALITATIVE RANKING	RESEARCH AREA	UPDATED RANKING
2	**Research Need:** The impact of ACE-I/ARB in patients with stable IHD on incidence of **new diagnoses** (such as diabetes, atrial fibrillation, congestive heart failure with or without preserved LV function) **Recently Published Research:** (1) Comparison of Afib incidence in ALLHAT (lisinopril vs. chlorthalidone vs. amlodipine). No difference in incidence between different classes of medication. J Am Coll Cardiol, 2009; 54(22):2023-31 (2) Effect of valsartan vs. placebo in 9306 pts with impaired fasting glucose on the incidence of diabetes and cardiovascular events. 14% risk reduction for incident diabetes; no effect on CV outcomes. N Engl J Med, 2010; 362(16):1477-90 (3) Small trial of 26 pts on perindopril vs. placebo on outcome of LV structure and function measured by Doppler tissue echocardiography. Found slightly improved LV systolic/diastolic performance on perindopril J Cardiovasc Med (Hagerstown), 2009; 10(10):781-6 (4) Olmesartan vs. Irbesartan vs. telmisartan effects on glucose metabolism in 151 patients with hypertension and impaired fasting glucose. Found less insulin resistence in telmisartan group compared to other two. Clin Ther, 2010; 32(3):492-505 (5) Meta-analysis of 23 trials evaluating ACEI or ARB for prevention of AFib. Overall found odds ratio for afib reduced 33%, but significant heterogeneity between trials. J Am Coll Cardiol, 2010; 55(21):2299-307 (6) Evaluation of ramipril, telmisartan, both, or placebo on development of left ventricular hypertrophy or regression of LVH in patients with this at baseline (subanalysis from Ontarget/Transcend). Less incident LVH and greater LVH regression in telmisartan group compared to placebo. No benefit of dual therapy compared to either alone. Circulation, 2009; 120(14):1380-9 **Active Clinical Trials:** (1) Mechanisms of Ramipril Reduction in the Onset of Type 2 Diabetes. Small mechanistic study looking at glucose metabolism. ClinicalTrials.gov (ID:NCT00574834). (2) Add-on Effects of Valsartan on Morbi- Mortality (KYOTO HEART Study). Evaluates new diagnosis of Afib and DM as secondary outcomes. ClinicalTrials.gov (ID:NCT00149227). (3) Effects of Telmisartan on Ischemic Cardiovascular Events in High-risk Hypertensive Patients (KCPS). New dx of Diabetes is secondary outcome. ClinicalTrials.gov (ID:NCT00863980). (4) Comparison of Valsartan With Amlodipine in Hypertensive Patients With Glucose Intolerance. ClinicalTrials.gov (ID:NCT00129233). (5) Prevention of Diabetes and Hypertension (PHIDIAS). Randomize ~6000 pts to different medication and diet interventions (including ACEI and ARB arms) to prevent development of hypertension or diabetes. ClinicalTrials.gov (ID:NCT00456963).	

QUALITATIVE RANKING	RESEARCH AREA	UPDATED RANKING
3	**Research Need:** Impact of **co-morbidities** (such as hypertension, congestive heart failure with or without preserved LV function, diabetes, peripheral arterial disease, chronic kidney disease, prior coronary revascularization; single vs. multivessel coronary artery disease) on ACE-I/ARB effectiveness or harms in patients with stable IHD **Recently Published Research:** (1) Subgroup analysis of ONTARGET/TRANSCEND (ramipril, telmisartan, or both) looking at outcomes in patients with or without erectile dysfunction. Found ED predicted CV events, but no interaction between treatment effect and ED. Circulation, 2010; 121(12):1439-46 (2) Subgroup analysis of Survival of MI Long Term Eval study (zofenopril vs. placebo in 1400 pts) comparing RR with ACEI for patients with high baseline and low baseline cholesterol. Possible increased benefit of zofenopril in patients with higher baseline cholesterol. Fundam Clin Pharmacol, 2009; 23(5):641-8 (3) In patients with impaired glucose tolerance trial of valsartan vs. placebo for new onset DM or cardiovascular outcomes (n=9300pts). No difference in CV events. N Engl J Med, 2010; 362(16):1477-90 (4) Subgroup analysis of PROGRESS (perindopril vs. placebo) examining interaction between treatment effect and BMI. Found comparable risk reduction across entire range of BMIs. Hypertension, 2010; 55(5):1193-8 **Active Clinical Trials:** (1) Angiotensin Converting Enzyme (ACE) Inhibition and Peripheral Arterial Disease. Ramipril vs. placebo in ~264 pts with PAD. ClinicalTrials.gov (ID:NCT00681226)	
4	**Research Need:** The impact of ACE-I/ARB in patients with stable IHD on patient **quality of life** **Recently Published Research:** none **Active Clinical Trials:** none	
5	**Research Need:** Impact of **demographic differences** (such as age, race, gender) on ACE-I/ARB effectiveness or harms in patients with stable ischemic heart disease (IHD) **Recently Published Research:** (1) Subgroup analysis of PROGRESS study (perindopril vs. placebo in ~ 6100 pts) comparing effects between Asian and Western participants . Found possible greater RRR in Asian participants compared to Western. J Hypertens, 2010; 28(2):395-400 **Active Clinical Trials:** none	
6	**Research Need:** The impact of ACE-I/ARB **adherence** (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD **Recently Published Research:** none **Active Clinical Trials:** (1) Clinical trial of copayment reduction/elimination for post MI therapy **(**Choudhry, N. A Randomized Evaluation of First-dollar Coverage for Post-MI Secondary Preventive Therapies (Post-MI FREEE). ClinicalTrials.gov (ID:NCT00566774).)	

QUALITATIVE RANKING	RESEARCH AREA	UPDATED RANKING
7	**Research Need:** The benefit of ACE-I/ARBs relative to **alternative medication** classes (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD **Recently Published Research:** (1) Renal effects of aliskiren compared with and in combination with irbesartan in 26 patients with type 2 diabetes, hypertension, and albuminuria. Found similar albuminuria reduction with aliskiren and irbesartan. Diabetes Care, 2009; 32(10):1873-9 (2) Cost-utility analysis of ARB compared to ACEI in primary prevention and nitrendipine (CCB) in secondary prevention in Europe--the HEALTH model. Found eprosartan to be cost effective compared to ACEI (~25,000Euro/Qualy) and CCB (~9300Euro/Qualy) Value Health, 2009; 12(6):857-71 **Active Clinical Trials:** (1) Mechanisms of Ramipril Reduction in the Onset of Type 2 Diabetes. Comparison of ramipril and hctz in approx 48 pts. ClinicalTrials.gov (ID:NCT00574834) (2) Aliskiren Versus Ramipril on Antiproteinuric Effect in Hypertensive, Type 2 Diabetic Patients With Microalbuminuria. Approx 120 total patients. ClinicalTrials.gov (ID:NCT01038895). (3) Rationale and Design for Shiga Microalbuminuria Reduction Trial. Valsartan vs. amlodipine in approx 160 pts. ClinicalTrials.gov (ID:NCT00202618). (4) A Study on Ca Blocker Versus AII Antagonists in Hypertension With Type 2 Diabetes. Approx 300pts included. ClinicalTrials.gov (ID:NCT00144144). (5) Comparison of Valsartan With Amlodipine in Hypertensive Patients With Glucose Intolerance. Approx 1150 enrolled. ClinicalTrials.gov (ID:NCT00129233).	

QUALITATIVE RANKING	RESEARCH AREA	UPDATED RANKING
8	**Research Need:** The impact of ACE-I/ARB in patients with stable IHD on **cardiovascular outcomes** (such as cardiovascular death, non-fatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure control, measures of atherosclerosis, etc) **Recently Published Research:** (1) Subgroup analysis of PROGRESS study (perindopril vs. placebo) comparing effects between Asian and Western participants. Found 20% RRR for composite of vascular events in Western pts; 38% RRR in Asian participants. J Hypertens, 2010; 28(2):395-400 (2) Subgroup analysis of EUROPA study (perindopril vs. placebo) looking at CV outcomes in patients already on calcium channel blocker. Addition of perindopril to CCB reduced total mortality by 46% compared to CCB alone. Am Heart J, 2010; 159(5):795-802 (3) Subgroup analysis of ONTARGET/TRANSCEND (ramipril, telmisartan, or both) looking at outcomes in patients with or without erectile dysfunction. Found similar results in patients with or without ED . Circulation, 2010; 121(12):1439-46 (4) Subgroup analysis of Survival of MI Long Term Eval study (zofenopril vs. placebo) comparing RR with ACEI for patients with high baseline and low baseline cholesterol. In 6wk outcomes, found zofenopril provided RRR of 43% for death and CHF in high cholesterol pts; 25% RRR in low cholesterol pts. No difference at 1yr. Fundam Clin Pharmacol, 2009; 23(5):641-8 (5) Subgroup analysis of PROGRESS (perindopril vs. placebo) examining interaction between treatment effect and BMI. Perindopril reduced vascular events similarly across BMI range (average RRR ~22%). Hypertension, 2010; 55(5):1193-8 (6) Small trial (86 pts) post-PCI randomized to quinapril or placebo to evaluate impact on in-stent restenosis. Found quinapril reduced in-stend restnosis from 25.6% (placebo) to 9.3% (quinapril). Am J Cardiol, 2010; 105(1):54-8 (7) Trial (n=247pts) comparing olmesartan vs. placebo for coronary atherosclerosis progression as measured by Intravascular ultrasound. Olmesartan reduced total atheroma volume at 14months compared to placebo from 5.4% vs. 0.6%. J Am Coll Cardiol, 2010; 55(10):976-82 (8) Trial of valsartan vs. placebo for new onset DM or cardiovascular outcomes (n=9300pts). No difference in CV events. N Engl J Med, 2010; 362(16):1477-90 (9) Small trial of 26 pts on perindopril vs. placebo on outcome of LV structure and function measured by Doppler tissue echocardiography. Perindopril improved LV systolic/diastolic performance compared to placebo. J Cardiovasc Med (Hagerstown), 2009; 10(10):781-6 (10) Secondary outcome from ONTARGET/TRANSCEND (ramipril, telmisartan, or both) on development of LVH. Less incident LVH and greater LVH regression in telmisartan group compared to placebo. No benefit of dual therapy compared to either alone. Circulation, 2009; 120(14):1380-9 **Active Clinical Trials:** (1) Left Ventricular Function After Acute Myocardial Infarction (AMI). Treatment With Angiotensin 2-Receptor Blockade (GLOBAL-Study). ClinicalTrials.gov (ID:NCT00125645) (2) Add-on Effects of Valsartan on Morbi- Mortality (KYOTO HEART Study). ClinicalTrials.gov (ID:NCT00149227) (3) Effects of Telmisartan on Ischemic Cardiovascular Events in High-risk Hypertensive Patients (KCPS). ClinicalTrials.gov (ID:NCT00863980). (4) Comparison of Valsartan With Amlodipine in Hypertensive Patients With Glucose Intolerance. ClinicalTrials.gov (ID:NCT00129233). (5) A Trial of Telmisartan Prevention of Cardiovascular Disease (ATTEMPT-CVD). ClinicalTrials.gov (ID:NCT01075698). (6) Candesartan for Prevention of Cardiovascular Events After Cypher or Taxus Coronary Stenting (4C) Trial. ClinicalTrials.gov (ID:NCT00139386). (7) Prevention of Diabetes and Hypertension (PHIDIAS). ClinicalTrials.gov (ID:NCT00456963).	

QUALITATIVE RANKING	RESEARCH AREA	UPDATED RANKING
9	**Research Need:** The impact of ACE-I/ARB in patients with stable IHD on **utilization and cost** of therapy **Recently Published Research:** (1) Cost-effectiveness analysis of ARB monotherapy in patients with HTN (from Netherlands). Modeled cost-effectiveness of 4 ARBs and found olmesartan to be most cost effective option. Am J Cardiovasc Drugs, 2010; 10(1):49-54 (2) Cost-utility analysis of eprosartan vs. enalapril in primary prevention of CVD in Europe. Found eprosartan to be cost effective compared to ACEI (~25,000Euro/Qualy) and CCB (~9300Euro/Qualy) Value Health, 2009; 12(6):857-71 **Active Clinical Trials:** (1) Clinical trial of copayment reduction/elimination for post MI therapy **(**Choudhry, N. A Randomized Evaluation of First-dollar Coverage for Post-MI Secondary Preventive Therapies (Post-MI FREEE). ClinicalTrials.gov (ID:NCT00566774).)	

QUALITATIVE RANKING	RESEARCH AREA	UPDATED RANKING
10	**Research Need:** The impact of ACE-I/ARB in patients with stable IHD on progression of **renal insufficiency** or development of dialysis dependence **Recently Published Research:** (1) Analysis of TRANSCEND (telmisartan vs. placebo in 5927 adults) on outcome of dialysis or doubling of serum creatinine. No difference between two groups, however only 17 patients required dialysis. Ann Intern Med, 2009; 151(1):1-10, W1-2 (2) Cross sectional study of 1119 pts with DM2 evaluating PPAR-gamma2 Pro12Ala polymorphism and ACE inhibitor therapy on new-onset microalbuminuria. Report significantly higher risk for developing proteinuria in Pro/Pro homozygotes, with this group benefiting more from early ACEI. Diabetes, 2009; 58(12):2920-9 (3) RCT of 81 patients with diabetes, hypertension, and albuminuria on ACEI. Pts randomized to losartan add on or spironolactone for 48wks. Found that addition of spironlactone to ACE was better than adding ARB to ACE for proteinuria reduction. J Am Soc Nephrol, 2009; 20(12):2641-50 (4) RCT of 26 pts with diabetic nephropathy comparing aliskirin, irbesartan or both. Aliskirin and irbesartan produced similar reductions in proteinuria. The combination of the two agents reduced proteinuria more than monotherapy. Diabetes Care, 2009; 32(10):1873-9 **Active Clinical Trials:** (1) Triple Blockade of the Renin Angiotensin Aldosterone System in Diabetic (Type 1&2) Proteinuric Patients. ClinicalTrials.gov (ID:NCT00961207). (2) Aspirin and Enalapril in Microalbuminuric Type 2 Diabetes Mellitus Patients. ClinicalTrials.gov (ID:NCT00427271). (3) Effectiveness Study on Fosinopril and/or Losartan in Patients With Chronic Kidney Disease Stage 3 (FLIP). ClinicalTrials.gov (ID:NCT00565396). (4) Safety of Dual Blockage of Rennin-angiotensin System in Patients With Advanced Renal Insufficiency (SDBRAS). ClinicalTrials.gov (ID:NCT00630708). (5) NEPHRON-D: Diabetes iN Nephropathy Study. ClinicalTrials.gov (ID:NCT00555217). (6) Rationale and Design for Shiga Microalbuminuria Reduction Trial. ClinicalTrials.gov (ID:NCT00202618). (7) Comparison of Valsartan With Amlodipine in Hypertensive Patients With Glucose Intolerance. Includes evaluation of renal outcomes as secondary endpoint. ClinicalTrials.gov (ID:NCT00129233). (8) A Trial of Telmisartan Prevention of Cardiovascular Disease (ATTEMPT-CVD). ClinicalTrials.gov (ID:NCT01075698). (9) Preventing ESRD in Overt Nephropathy of Type 2 Diabetes (VALID). ClinicalTrials.gov (ID:NCT00494715). (10) Preventing Microalbuminuria in Type 2 Diabetes (VARIETY). ClinicalTrials.gov (ID:NCT00503152). (11) Effect of Enalapril and Losartan Association Therapy on Proteinuria and Inflammatory Biomarkers in Diabetic Nephropathy: a Clinical Trial on Type 2 Diabetes Mellitus. ClinicalTrials.gov (ID:NCT00419835).	

QUALITATIVE RANKING	RESEARCH AREA	UPDATED RANKING
11	**Research Need:** Impact of **concurrent medications** (such as anti-platelet agents, lipid lowering medications, other anti-hypertensives) on ACE-I/ARB effectiveness or harms in patients with stable IHD **Recently Published Research:** (1) Subgroup analysis of EUROPA study (perindopril vs. placebo) looking at CV outcomes in patients already on calcium channel blocker. Addition of perindopril to CCB reduced total mortality by 46% compared to CCB alone. Am Heart J, 2010; 159(5):795-802 **Active Clinical Trials:** (1) Aspirin and Enalapril in Microalbuminuric Type 2 Diabetes Mellitus Patients. ClinicalTrials.gov (ID:NCT00427271). (2) Effects of ROSIglitazone on Inflammatory Markers and Adipokines in Diabetic Patients Using an Angiotensin Receptor Blocker (TELmisartan) - The ROSITEL Study. ClinicalTrials.gov (ID:NCT00486187).	
12	**Research Need:** Impact of **genetic differences** (such as ACE or Angiotensin II receptor gene polymorphisms) on ACE-I/ARB effectiveness or harms in patients with stable IHD **Recently Published Research:** (1) Cross sectional study of 1119 pts with DM2 evaluating PPAR-gamma2 Pro12Ala polymorphism and ACE inhibitor therapy on new-onset microalbuminuria. Report significantly higher risk for developing proteinuria in Pro/Pro homozygotes, with this group benefiting more from early ACEI. Diabetes, 2009; 58(12):2920-9 (2) Sub analysis of RCT (n=217 pts) of losartan vs. three other htn med. Evaluates CYP2C9 genotype and activity of rennin-angiotensin system. No impact on efficacy of losartan. J Hypertens, 2009; 27(10):2001-9 (3) Sub analysis of LIFE RCT (losartan vs. atenolol) in 3503 high risk pts. Evaluated effect of ACE gene insertion/deletion and 12 other polymorphisms on clinical outcomes and response to treatment in the LIFE study. (none influenced treatment response) Pharmacogenet Genomics, 2010; 20(2):77-85 **Active Clinical Trials:** (1) Association of Angiotensin II Type 1 R Gene Polymorphism and Diabetic Nephropathy in Type 2 Diabetes. ClinicalTrials.gov (ID:NCT01069549)	
13	**Research Need:** Impact of **class effec**t (impact of differences between specific agents within each class) of ACE-I and ARBs on their effectiveness or harms in patients with stable IHD **Recently Published Research:** (1) Telmisartan vs. olmesartan on metabolic parameters in 65 overweight and obese patients with hypertension. Found that Telmisartan may have greater impact than olmesartan on insulin resistence Nutr Hosp, 2010; 25(2):275-9 (2) Telmisartan vs. eprosartan on insulin sensitivity in 50 overweight hypertensive patients. Found that Telmisartan may have greater impact than eprosartan on insulin resistence Horm Metab Res, 2009; 41(12):893-8 (3) Telmisartan vs. losartan vs. candesartan on uric acid levels in 42 hypertensive patients. Found uric acid levels declined in telmisartan, candesartan, but not losartan arms. Arzneimittelforschung, 2010; 60(2):71-5 (4) Olmesartan vs. Irbesartan vs. telmisartan effects on glucose metabolism in 151 patients with hypertension and impaired fasting glucose. Found telmisartan had most favorable effects on insulin resistence. Clin Ther, 2010; 32(3):492-505 **Active Clinical Trials:** (1) Comparison of Effects of Telmisartan and Valsartan on Neointima Volume in Diabetes. ClinicalTrials.gov (ID:NCT00599885)	

QUALITATIVE RANKING	RESEARCH AREA	UPDATED RANKING
14	**Research Need:** Impact of the **dose response** (impact of medication dose or dosing interval) of ACE-I and ARBs on their effectiveness or harms in patients with stable IHD **Recently Published Research:** none **Active Clinical Trials:** none	
15	**Research Need:** The impact of ACE-I/ARB in patients with stable IHD on development of **non-angioedema adverse effects** (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia) **Recently Published Research:** (1) Short 12wk rct evaluating safety and tolerability of an olmesartan medoxomil-based regimen in 130 patients with stage 1 hypertension. Found no difference between olmesartan and placebo in safety and tolerability. Clin Drug Investig, 2010; 30(7):473-82 **Active Clinical Trials:** (1) ACEIs and ARBs Treatment in Diabetic Patients -Drug Interactions and Adverse Drug Effects. ClinicalTrials.gov (ID:NCT00437775). (2) Safety of Dual Blockage of Rennin-angiotensin System in Patients With Advanced Renal Insufficiency (SDBRAS). ClinicalTrials.gov (ID:NCT00630708). (3) Prevention of Diabetes and Hypertension (PHIDIAS). Randomize ~6000 pts to different medication and diet interventions (including ACEI and ARB arms); evaluate safety/tolerability as secondary outcomes. ClinicalTrials.gov (ID:NCT00456963).	
16	**Research Need:** The impact of ACE-I/ARB in patients with stable IHD on development of **angioedema** **Recently Published Research:** (1) one case control study proposing RR of 4.5 for ACE-I angioedema for patients on concurrent vildagliptin Hypertension, 2009; 54(3):516-23) **Active Clinical Trials:** none	

QUESTION: As we discussed on our September 3rd conference call, the EPC program is looking to determine how best to engage Stakeholders to help prioritize future research needs in comparative effectiveness reviews. Please provide in the space below any specific suggestions that you might have for how to make this process successful:

References

1. Coleman CI, Baker WL, Kluger J, et al. Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers Added to Standard Medical Therapy for Treating Stable Ischemic Heart Disease (Prepared by the University of Connecticut/Hartford Hospital Evidence-based Practice Center under Contract No. 290-2007-10067-I). Rockville, MD: Agency for Healthcare Research and Quality, October 2009. Available at: http://www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed September 7, 2010.

2. Baker WL, Coleman CI, Kluger J, et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors or angiotensin II-receptor blockers for ischemic heart disease. Ann Intern Med 2009;151(12):861–871.

3. Matchar DB, McCrory DC, Orlando LA, et al. Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Antagonists (ARBs) for Treating Essential Hypertension. Comparative Effectiveness Review No. 10 (Prepared by Duke Evidence-based Practice Center under Contract No. 290-02-0025). Rockville, MD: Agency for Healthcare Research and Quality, November 2007. Available at: http://www.effectivehealthcare.ahrq.gov/reports/final.cfm. Accessed September 10, 2010.

4. Matchar DB, McCrory DC, Orlando LA, et al. Systematic review: comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers for treating essential hypertension. Ann Intern Med 2008;148(1):16–29.

Appendix E. Results of Prioritization Exercises—ACEI/ARB Case Study

Results of Prioritization Exercise 1

Table D1. Importance of individual research areas (Prioritization Exercise 1, Likert scale)

Research area	Not at all important (1)	Somewhat unimportant (2)	Neutral (3)	Somewhat important (4)	Very important (5)	Average
Impact of **comorbidities** (such as hypertension, CHF with or without preserved LV function, diabetes, peripheral arterial disease, chronic kidney disease, prior coronary revascularization; single- vs. multivessel coronary artery disease) on ACE-I/ARB effectiveness or harms in patients with stable IHD	0.0% (0)	0.0% (0)	0.0% (0)	14.3% (1)	85.7% (6)	4.86
The impact of ACE-I/ARB in patients with stable IHD on progression of **renal insufficiency** or development of dialysis dependence	0.0% (0)	0.0% (0)	14.3% (1)	28.6% (2)	57.1% (4)	4.43
The impact of ACE-I/ARB in patients with stable IHD on **utilization and cost of therapy**	0.0% (0)	0.0% (0)	0.0% (0)	57.1% (4)	42.9% (3)	4.43
Impact of **demographic** differences (such as age, race, sex) on ACE-I/ARB effectiveness or harms in patients with stable IHD	0.0% (0)	0.0% (0)	0.0% (0)	71.4% (5)	28.6% (2)	4.29
Impact of **concurrent medications** (such as antiplatelet agents, lipid-lowering medications, other antihypertensives) on ACE-I/ARB effectiveness or harms in patients with stable IHD	0.0% (0)	0.0% (0)	14.3% (1)	42.9% (3)	42.9% (3)	4.29
The benefit of ACE-Is/ARBs relative to **alternative medication classes** (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD	0.0% (0)	0.0% (0)	14.3% (1)	42.9% (3)	42.9% (3)	4.29
Strategies to enhance greater **evidence-based use** of ACE-Is/ ARBs	0.0% (0)	0.0% (0)	14.3% (1)	42.9% (3)	42.9% (3)	4.29
The impact of ACE-I/ARB in patients with stable IHD on **cardiovascular outcomes** (such as cardiovascular death, non-fatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure control, measures of atherosclerosis, etc.)	14.3% (1)	0.0% (0)	0.0% (0)	14.3% (1)	71.4% (5)	4.29

Research area	Not at all important (1)	Somewhat unimportant (2)	Neutral (3)	Somewhat important (4)	Very important (5)	Average
The impact of ACE-I/ARB in patients with stable IHD on incidence of **new diagnoses** (such as diabetes, atrial fibrillation, CHF with or without preserved LV function)	0.0% (0)	0.0% (0)	14.3% (1)	42.9% (3)	42.9% (3)	4.29
Impact of g**enetic differences** (such as ACE or angiotensin II receptor gene polymorphisms) on ACE-I/ARB effectiveness or harms in patients with stable IHD	0.0% (0)	0.0% (0)	0.0% (0)	85.7% (6)	14.3% (1)	4.14
The impact of ACE-I/ARB **adherence** (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD	0.0% (0)	0.0% (0)	28.6% (2)	28.6% (2)	42.9% (3)	4.14
The impact of ACE-I/ARB in patients with stable IHD on patient **quality of life**	0.0% (0)	0.0% (0)	28.6% (2)	28.6% (2)	42.9% (3)	4.14
Impact of the **dose response** (impact of medication dose or dosing interval) of ACE-Is and ARBs on their effectiveness or harms in patients with stable IHD	0.0% (0)	0.0% (0)	28.6% (2)	57.1% (4)	14.3% (1)	3.86
Impact of **class effect** (impact of differences between specific agents within each class) of ACE-Is and ARBs on their effectiveness or harms in patients with stable IHD	0.0% (0)	14.3% (1)	14.3% (1)	42.9% (3)	28.6% (2)	3.86
The impact of ACE-I/ARB in patients with stable IHD on development of **non-angioedema adverse effects** (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)	0.0% (0)	0.0% (0)	14.3% (1)	85.7% (6)	0.0% (0)	3.86
The impact of ACE-I/ARB in patients with stable IHD on development of **angioedema**	0.0% (0)	0.0% (0)	28.6% (2)	71.4% (5)	0.0% (0)	3.71

ACE-I(s) = angiotensin-converting enzyme inhibitor(s); ARB(s) = angiotensin II receptor blocker(s)/antagonist(s); CHF = congestive heart failure; CVA = cerebrovascular accident; IHD = ischemic heart disease; LV = left ventricular; MI = myocardial infarction; PICO = population, interventions, comparators of interest, and outcomes

Table D2. Ranking of research priorities using average Likert scale score

Rank	Research area
1	Impact of **comorbidities** (such as hypertension, CHF with or without preserved LV function, diabetes, peripheral arterial disease, chronic kidney disease, prior coronary revascularization; single- vs. multi-vessel coronary artery disease) on ACE-I/ARB effectiveness or harms in patients with stable IHD
2	The impact of ACE-I/ARB in patients with stable IHD on progression of **renal insufficiency** or development of dialysis dependence
2	The impact of ACE-I/ARB in patients with stable IHD on **utilization and cost of therapy**
3	Impact of **demographic differences** (such as age, race, sex) on ACE-I/ARB effectiveness or harms in patients with stable IHD
3	Impact of **concurrent medications** (such as antiplatelet agents, lipid-lowering medications, other antihypertensives) on ACE-I/ARB effectiveness or harms in patients with stable IHD
3	The benefit of ACE-Is/ARBs relative to **alternative medication classes** (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD
3	Strategies to enhance greater **evidence-based use** of ACE-Is/ARBs
3	The impact of ACE-I/ARB in patients with stable IHD on **cardiovascular outcomes** (such as cardiovascular death, non-fatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure control, measures of atherosclerosis, etc.)
3	The impact of ACE-I/ARB in patients with stable IHD on incidence of **new diagnoses** (such as diabetes, atrial fibrillation, CHF with or without preserved LV function)
4	Impact of **genetic differences** (such as ACE or angiotensin II receptor gene polymorphisms) on ACE-I/ARB effectiveness or harms in patients with stable IHD
4	The impact of ACE-I/ARB **adherence** (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD
4	The impact of ACE-I/ARB in patients with stable IHD on patient **quality of life**
5	Impact of the **dose response** (impact of medication dose or dosing interval) of ACE-Is and ARBs on their effectiveness or harms in patients with stable IHD
5	Impact of **class effect** (impact of differences between specific agents within each class) of ACE-Is and ARBs on their effectiveness or harms in patients with stable IHD
5	The impact of ACE-I/ARB in patients with stable IHD on development of **non-angioedema adverse effects** (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)
6	The impact of ACE-I/ARB in patients with stable IHD on development of **angioedema**

ACE-I(s) = angiotensin-converting enzyme inhibitor(s); ARB(s) = angiotensin II receptor blocker(s)/antagonist(s); CHF = congestive heart failure; CVA = cerebrovascular accident; IHD = ischemic heart disease; LV = left ventricular; MI = myocardial infarction; PICO = population, interventions, comparators of interest, and outcomes

Table D3. Ranking of importance of research areas (Prioritization Exercise 1, top five ranking)

Research area	1	2	3	4	5	Average
The impact of ACE-I/ARB in patients with stable IHD on **cardiovascular outcomes** (such as cardiovascular death, nonfatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure control, measures of atherosclerosis, etc.)	75.0% (3)	25.0% (1)	0.0% (0)	0.0% (0)	0.0% (0)	4.75
The impact of ACE-I/ARB in patients with stable IHD on incidence of **new diagnoses** (such as diabetes, atrial fibrillation, CHF with or without preserved LV function)	0.0% (0)	75.0% (3)	25.0% (1)	0.0% (0)	0.0% (0)	3.75
The benefit of ACE-Is/ARBs relative to **alternative medication classes** (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD	50.0% (1)	0.0% (0)	0.0% (0)	50.0% (1)	0.0% (0)	3.5
Strategies to enhance greater **evidence-based use** of ACE-Is/ARBs	50.0% (2)	0.0% (0)	25.0% (1)	0.0% (0)	25.0% (1)	3.5
Impact of **demographic differences** (such as age, race, sex) on ACE-I/ARB effectiveness or harms in patients with stable IHD	0.0% (0)	50.0% (1)	0.0% (0)	50.0% (1)	0.0% (0)	3
The impact of ACE-I/ARB **adherence** (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD	25.0% (1)	25.0% (1)	0.0% (0)	25.0% (1)	25.0% (1)	3
The impact of ACE-I/ARB in patients with stable IHD on patient **quality of life**	0.0% (0)	0.0% (0)	100.0% (1)	0.0% (0)	0.0% (0)	3
Impact of **comorbidities** (such as hypertension, CHF with or without preserved LV function, diabetes, peripheral arterial disease, chronic kidney disease, prior coronary revascularization; single- vs. multivessel coronary artery disease) on ACE-I/ARB effectiveness or harms in patients with stable IHD	0.0% (0)	0.0% (0)	75.0% (3)	25.0% (1)	0.0% (0)	2.75
Impact of **class effect** (impact of differences between specific agents within each class) of ACE-Is and ARBs on their effectiveness or harms in patients with stable IHD	0.0% (0)	25.0% (1)	25.0% (1)	0.0% (0)	50.0% (2)	2.25
Impact of **genetic differences** (such as ACE or angiotensin II receptor gene polymorphisms) on ACE-I/ARB effectiveness or harms in patients with stable IHD	0.0% (0)	0.0% (0)	0.0% (0)	100.0% (1)	0.0% (0)	2
The impact of ACE-I/ARB in patients with stable IHD on **utilization and cost of therapy**	0.0% (0)	0.0% (0)	0.0% (0)	100.0% (1)	0.0% (0)	2
Impact of **concurrent medications** (such as antiplatelet agents, lipid-lowering medications, other antihypertensives) on ACE-I/ARB effectiveness or harms in patients with stable IHD	0.0% (0)	0.0% (0)	0.0% (0)	50.0% (1)	50.0% (1)	1.5

Research area	1	2	3	4	5	Average
The impact of ACE-I/ARB in patients with stable IHD on progression of **renal insufficiency** or development of dialysis dependence	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	100.0% (2)	1
Impact of the **dose response** (impact of medication dose or dosing interval) of ACE-Is and ARBs on their effectiveness or harms in patients with stable IHD	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0
The impact of ACE-I/ARB in patients with stable IHD on development of **angioedema**	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0
The impact of ACE-I/ARB in patients with stable IHD on development of **non-angioedema adverse effects** (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0

ACE-I(s) = angiotensin-converting enzyme inhibitor(s); ARB(s) = angiotensin II receptor blocker(s)/antagonist(s); CHF = congestive heart failure; CVA = cerebrovascular accident; IHD = ischemic heart disease; LV = left ventricular; MI = myocardial infarction; PICO = population, interventions, comparators of interest, and outcomes

Table D4. Ranking of research priorities using top five ranking score

Rank	Research area
1	The impact of ACE-I/ARB in patients with stable IHD on **cardiovascular outcomes** (such as cardiovascular death, nonfatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure control, measures of atherosclerosis, etc.)
2	The impact of ACE-I/ARB in patients with stable IHD on incidence of **new diagnoses** (such as diabetes, atrial fibrillation, CHF with or without preserved LV function)
3	The benefit of ACE-I/ARBs relative to **alternative medication classes** (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD
3	Strategies to enhance greater **evidence-based use** of ACE-Is/ARBs
4	Impact of **demographic differences** (such as age, race, sex) on ACE-I/ARB effectiveness or harms in patients with stable IHD
4	The impact of ACE-I/ARB **adherence** (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD
4	The impact of ACE-I/ARB in patients with stable IHD on patient **quality of life**
5	Impact of **comorbidities** (such as hypertension, CHF with or without preserved LV function, diabetes, peripheral arterial disease, chronic kidney disease, prior coronary revascularization; single- vs. multi-vessel coronary artery disease) on ACE-I/ARB effectiveness or harms in patients with stable IHD
6	Impact of **class effect** (impact of differences between specific agents within each class) of ACE-Is and ARBs on their effectiveness or harms in patients with stable IHD
7	Impact of **genetic differences** (such as ACE or angiotensin II receptor gene polymorphisms) on ACE-I/ARB effectiveness or harms in patients with stable IHD
7	The impact of ACE-I/ARB in patients with stable IHD on **utilization and cost of therapy**
8	Impact of **concurrent medications** (such as antiplatelet agents, lipid-lowering medications, other antihypertensives) on ACE-I/ARB effectiveness or harms in patients with stable IHD
9	The impact of ACE-I/ARB in patients with stable IHD on progression of **renal insufficiency** or development of dialysis dependence
10	Impact of the **dose response** (impact of medication dose or dosing interval) of ACE-Is and ARBs on their effectiveness or harms in patients with stable IHD
10	The impact of ACE-I/ARB in patients with stable IHD on development of **angioedema**
10	The impact of ACE-I/ARB in patients with stable IHD on development of **non-angioedema adverse effects** (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)

ACE-I(s) = angiotensin-converting enzyme inhibitor(s); ARB(s) = angiotensin II receptor blocker(s)/antagonist(s); CHF = congestive heart failure; CVA = cerebrovascular accident; IHD = ischemic heart disease; LV = left ventricular; MI = myocardial infarction; PICO = population, interventions, comparators of interest, and outcomes

Results of Prioritization Exercise 2

Table D5. Research area ranking and summary statistics after Prioritization Exercise 2

	E: Evidence-based use	J: New diagnoses	A: Comorbidities	K: Quality of life	B: Demographic differences	F: Adherence	I: Alternative medication	L: Cardiovascular outcomes	M: Utilization and cost	N: Renal insufficiency	C: Concurrent medications	D: Genetic differences	H: Class effect	G: Dose response	O: Non-angioedema adverse effects	P: Angioedema
Stakeholder 1	16	2	4	7	12	9	6	5	13	3	10	11	1	8	14	15
Stakeholder 2	1	8	12	5	4	7	2	15	6	10	11	3	16	9	14	13
Stakeholder 3	4	5	9	3	7	2	6	1	10	14	8	11	12	13	16	15
Stakeholder 4	16	2	3	6	7	13	11	1	15	5	4	8	12	14	9	10
Stakeholder 5	5	3	1	13	4	6	8	2	12	11	7	15	9	10	14	16
Stakeholder 6	2	3	11	10	7	1	13	8	5	9	12	16	14	15	4	6
Stakeholder 7	1	15	5	4	6	2	8	13	3	14	9	11	7	10	12	16
Stakeholder 8	1	9	5	6	8	15	7	16	3	2	11	4	13	12	10	14
SUMMARY																
Rank	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Average score	5.8	5.9	6.3	6.8	6.9	6.9	7.6	7.6	8.4	8.5	9.0	9.9	10.5	11.4	11.6	13.1
Minimum score	1	2	1	3	4	1	2	1	3	2	4	3	1	8	4	6
Maximum score	16	15	12	13	12	15	13	16	15	14	12	16	16	15	16	16
SD	6.50	4.55	3.96	3.28	2.53	5.22	3.34	6.32	4.72	4.69	2.62	4.67	4.75	2.50	3.85	3.48
Variance	42.21	20.70	15.64	10.79	6.41	27.27	11.13	39.98	22.27	22.00	6.86	21.84	22.57	6.27	14.84	12.13
Median score	3	4	5	6	7	6.5	7.5	6.5	8	9.5	9.5	11	12	11	13	14.5
1st quartile	1	2.75	3.75	4.75	5.5	2	6	1.75	4.5	4.5	7.75	7	8.5	9.75	9.75	12.25
3rd quartile	7.75	8.25	9.5	7.75	7.25	10	8.75	13.5	12.25	11.75	11	12	13.25	13.25	14	15.25

SD = standard deviation

Table D6. Ranking of 16 research areas after Prioritization Exercise 2

Ranking	Research area
1	Strategies to enhance greater **evidence-based use** of ACE-Is/ARBs
2	The impact of ACE-I/ARB in patients with stable IHD on incidence of **new diagnoses** (such as diabetes, atrial fibrillation, CHF with or without preserved LV function)
3	Impact of **comorbidities** (such as hypertension, CHF with or without preserved LV function, diabetes, peripheral arterial disease, chronic kidney disease, prior coronary revascularization; single- vs. multi-vessel coronary artery disease) on ACE-I/ARB effectiveness or harms in patients with stable IHD
4	The impact of ACE-I/ARB in patients with stable IHD on patient **quality of life**
5	Impact of **demographic differences** (such as age, race, sex) on ACE-I/ARB effectiveness or harms in patients with stable IHD
6	The impact of ACE-I/ARB **adherence** (including differential adherence within and between medication classes) on their effectiveness or harms in patients with stable IHD
7	The benefit of ACE-Is/ARBs relative to **alternative medication** classes (calcium channel blocker, diuretic, or beta-blocker) with respect to their effectiveness or harms in patients with stable IHD
8	The impact of ACE-I/ARB in patients with stable IHD on **cardiovascular outcomes** (such as cardiovascular death, non-fatal MI, CVA, hospitalization for CHF, and surrogates such as blood pressure control, measures of atherosclerosis, etc.)
9	The impact of ACE-I/ARB in patients with stable IHD on **utilization and cost** of therapy
10	The impact of ACE-I/ARB in patients with stable IHD on progression of **renal insufficiency** or development of dialysis dependence
11	Impact of **concurrent medications** (such as antiplatelet agents, lipid-lowering medications, other antihypertensives) on ACE-I/ARB effectiveness or harms in patients with stable IHD
12	Impact of **genetic differences** (such as ACE or angiotensin II receptor gene polymorphisms) on ACE-I/ARB effectiveness or harms in patients with stable IHD
13	Impact of **class effec**t (impact of differences between specific agents within each class) of ACE-Is and ARBs on their effectiveness or harms in patients with stable IHD
14	Impact of the **dose response** (impact of medication dose or dosing interval) of ACE-Is and ARBs on their effectiveness or harms in patients with stable IHD
15	The impact of ACE-I/ARB in patients with stable IHD on development of **non-angioedema adverse effects** (such as hypotensive symptoms, cough, syncope, diarrhea, renal insufficiency, hyperkalemia)
16	The impact of ACE-I/ARB in patients with stable IHD on development of **angioedema**

ACE-I(s) = angiotensin-converting enzyme inhibitor(s); ARB(s) = angiotensin II receptor blocker(s)/antagonist(s); CHF = congestive heart failure; CVA = cerebrovascular accident; IHD = ischemic heart disease; LV = left ventricular; MI = myocardial infarction; PICO = population, interventions, comparators of interest, and outcomes

Prioritization Exercise 3 Results

Table D7. Research area ranking and summary statistics after Prioritization Exercise 3

	E: Evidence-based use	F: Adherence	A: Comorbidities	K: Quality of life	B: Demographic differences	J: New diagnoses	I: Alternative medication	M: Utilization and cost	L: Cardiovascular outcomes	C: Concurrent medications	N: Renal insufficiency	D: Genetic differences	G: Dose response	H: Class effect	O: Non-angioedema adverse effects	P: Angioedema
Stakeholder 1	12	6	2	3	5	1	7	13	4	11	8	14	10	9	15	16
Stakeholder 2	1	6	7	4	2	8	9	3	10	11	12	5	14	13	15	16
Stakeholder 3	1	3	6	2	8	4	7	9	5	12	10	11	14	13	16	15
Stakeholder 4	1	7	2	3	5	4	6	10	9	8	11	12	14	13	15	16
Stakeholder 5	1	4	3	6	5	2	8	10	7	9	11	12	13	14	15	16
Stakeholder 6	1	2	9	3	8	10	6	4	7	5	11	16	12	15	14	13
Stakeholder 7	1	2	4	7	5	6	9	3	10	8	11	13	12	14	15	16
Stakeholder 8	2	4	3	11	5	1	6	12	7	16	8	10	14	13	9	15
Stakeholder 9	1	5	4	2	3	14	10	9	16	8	15	11	6	12	13	7
SUMMARY																
Rank	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Original Rank	***1***	***6***	***3***	***4***	***5***	***2***	***7***	***9***	***8***	***11***	***10***	***12***	***14***	***13***	***15***	***16***
Average score	2.3	4.3	4.4	4.6	5.1	5.6	7.6	8.1	8.3	9.8	10.8	11.6	12.1	12.9	14.1	14.4
Minimum score	1	2	2	2	2	1	6	3	4	5	8	5	6	9	9	7
Maximum score	12	7	9	11	8	14	10	13	16	16	15	16	14	15	16	16
SD	3.64	1.80	2.40	2.96	1.96	4.42	1.51	3.82	3.54	3.15	2.11	3.05	2.67	1.69	2.09	2.96
Variance	13.25	3.25	5.78	8.78	3.86	19.53	2.28	14.61	12.50	9.94	4.44	9.28	7.11	2.86	4.36	8.78
Median score	1	4	4	3	5	4	7	9	7	9	11	12	13	13	15	16
1st quartile	1	3	3	3	5	2	6	4	7	8	10	11	12	13	14	15
3rd quartile	1	6	6	6	5	8	9	10	10	11	11	13	14	14	15	16

SD = standard deviation

Appendix F. Detailed Description of Uterine Fibroids Model

MODEL STRUCTURE

States: The model is a Markov state-transition model, which starts after performance of one of the three procedures of interest—myomectomy, uterine artery embolization (UAE), or MRI-guided focused ultrasound (FUS). Health states include:

- Immediate postprocedure, no complications
- Immediate postprocedure, complications
    - Both of these states can transition into improved, persistent, or recurrent symptoms
- Improved symptoms
    - Women who desire pregnancy can transition into Attempting Pregnancy, or into Recurrent Symptoms. We assume that only women experiencing improved symptoms will attempt pregnancy.
- Persistent symptoms
- Recurrent symptoms
    - We assume all of these women eventually transition into the Retreatment state.
- Attempting Pregnancy
    - These women either become pregnant, seek infertility treatment after an age-dependent period of time without conception, or develop recurrent symptoms.
- Pregnant
    - These women can experience a miscarriage, deliver a preterm infant, or deliver a term infant.
- Retreatment
- Miscarriage
- Preterm delivery
- Term delivery
- Infertile
    - For the purposes of this modeling exercise, the above five states are "absorbing" states—we do not continue to model events after these occur. Although doing so would be of great interest, incorporating them would have added even more complexity to an already complex model, especially given the methodologic issues involved with modeling events such as preterm birth which affect more than one individual.

We did not include mortality, either from other causes or from the procedure itself. All-cause mortality is quite low in this age group. Reliable estimates for mortality associated with individual procedures are difficult to obtain from readily available sources—there are no count data on in-hospital deaths for myomectomy or UAE for women 15–44 within HCUP, and estimates based on hysterectomy are likely to overestimate mortality risk, especially if all-indication rates are used.

We did not include long-term complications from any of the procedures, because of both a relative paucity of long-term data and a desire to focus on other understudied aspects of treatment.

We also did not include menopause, or any potential effects of treatment on ovarian function. We believe this is an area of great importance and one for which models may useful; however, the further complexity of modeling ovarian function and its effects on fibroid symptoms, menopausal symptoms, and fertility, as well as the potential effects of different treatments on ovarian function, was beyond the scope of this project.

Cycle length: We used 1-week cycle lengths. This length allowed us to more precisely model short-term postprocedure outcomes (although days would obviously be preferable), and, more importantly, made it much easier to model time-dependent reproductive outcomes, which are usually reported in either weeks or cycles of approximately 4 weeks duration.

Time horizon: We modeled a 3-year time horizon, primarily because of limited data on outcomes beyond 3 years. Exploring the impact of possible longer-term differences in treatment outcomes is an important next step.

Discount: We discounted costs and quality-adjusted life expectancy at a 3 percent annual rate, varied from 0–5 percent in sensitivity analysis.

Software: The model was built and run in TreeAge Pro 2009 (Williamstown, MA: TreeAge, Inc). Microsoft Excel was used for deriving conditional probabilities from published cumulative probability data.

PATIENT DEMOGRAPHICS

Racial distribution: In the base case, we assumed that 48 percent of the population would be African-American, consistent with the baseline patient demographics in the FIBROID UAE registry.[1] Because 85–95 percent of patients in those studies that report racial/ethnic distributions are either African-American or white, and because racial differences in pregnancy outcomes are most well-characterized for African-Americans versus whites, we did not separately model either age or reproductive outcomes for other ethnic groups.

Interest in pregnancy: At the baseline visit in the FIBROID registry, approximately 25 percent of women expressed a desire to retain the potential for future childbearing, with 9 percent expressing definite plans within the next 2 years. Because there are no published data on racial differences among women seeking fibroid treatment who wish to attempt pregnancy after treatment, we assumed equal proportions among racial groups (although the higher parity among African-American women suggests that this is worthy of further exploration).

Data on age distribution among women desiring the potential for pregnancy versus those who don't are not readily available, although it seems likely that these women would be younger. We describe our methods for our age distribution assumptions for this subgroup in the next section.

Age: Among women presenting with fibroids, African-American women are consistently younger than white women for any given procedure; for example, mean age of African-American women in the FIBROID registry was 42.5 years, versus 44.5 for white women. Women undergoing myomectomy are also younger than women undergoing UAE (38.2 vs. 43.9 in one prospective series[2]); this is at least partially due to current guidelines considering desire for pregnancy a relative contraindication for UAE. The published age distribution of women undergoing focused ultrasound is comparable to that of women undergoing UAE, again in part because the majority of these studies excluded women planning further childbearing. Studies that report summary statistics for age typically report means and standard deviations; for the purposes of this model, we assume normal distributions for each age group, although other distributions are also plausible (for example, a left skew for women wanting pregnancy and a right skew for women who definitely have completed childbearing).

Taking the above into account, we modeled age as follows:

- We restricted the age range from 25–44 years, to (a) incorporate the group with realistic probabilities of pregnancy, and (b) to reduce the potential interaction of natural perimenopausal changes with treatment effects on outcomes. This is clearly an area for further model development.
- We assumed a mean age of 40.0 years to better reflect women who would be potential candidates for any of the procedures.
- We assumed a 2-year difference in mean age between African-American and white women (39.0 and 41.0).
- Given that 25 percent of women desire future pregnancy, the mean age of this group among African-American women would be 34.5 years, and among white women 36.5 years.
- Mean age for the 75 percent of African-American women not desiring pregnancy would be 39.5 years, and 41.5 years for white women not desiring pregnancy.
- In order to obtain an age distribution which would reflect our restricted range of 25–44, we performed simulations and varied the standard deviations. A SD of 2.5 resulted in over 99 percent of the youngest group (African-American women desiring pregnancy) with an age 25 and older, and over 90 percent of the oldest group (white women not desiring pregnancy) with an age less than 45.

Uterine anatomy: There are fairly consistent data that the number, size, and location of fibroids can affect the likelihood of different outcomes. Due to resource constraints, we did not incorporate baseline uterine anatomy into the model, but this would be an interesting next step.

Other patient characteristics: We did not include other patient characteristics that have been reported to affect outcomes, such as BMI or history of previous surgery.

REPRODUCTIVE OUTCOMES

Time after procedure: There is a lack of consensus on recommended times after myomectomy for attempting conception, as well as a lack of data for myomectomy, UAE, or FUS on the

distribution of time after procedure before women attempt pregnancy. Based on our clinical experience and reviewing several Internet chat boards for women with fibroids, we believe most clinicians would recommend 3–6 months; we therefore assumed a mean time of 5 months, with a standard deviation of 1 month.

Time to attempt pregnancy before seeking infertility care: We assumed women under the age of 35 would seek infertility care after 12 months without a pregnancy, while women 35 and older would seek care after 6 months, based on current guidelines from the American Society for Reproductive Medicine.

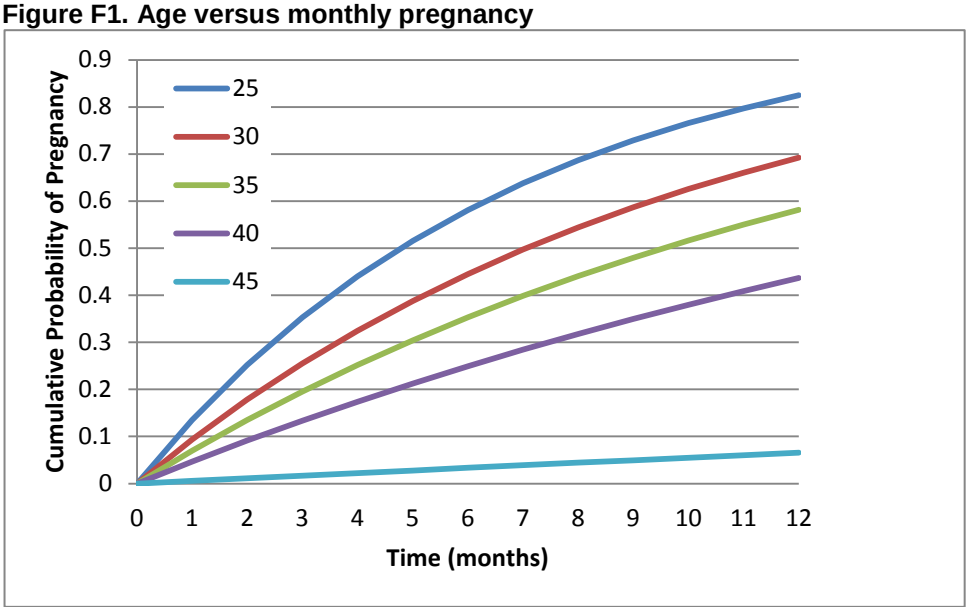
Pregnancy rates: Fertility is highly dependent on maternal age. Because data on relative age-specific fertility rates between African-American and white women are lacking, we modeled only age dependency for fertility.

We took data from several sources—studies of couples undergoing donor insemination for azoospermia[3,4] and 2008 data from CDC on cycle-specific pregnancy rates after undergoing assisted reproductive technology (ART) with fresh embryos from nondonor eggs (http://www.cdc.gov/art/ARTReports.htm). Because the CDC data reflect couples undergoing ART, we reduced the age-specific rates across all ages to result in cycle specific rates which, when converted to 12-month cumulative rates, resulted in values similar to that observed in the other studies for younger women (a reduction of approximately two-thirds).

We plotted age versus monthly pregnancy in Excel, and generated curves to fit the observed data (Figure F1). For both the insemination data and adjusted CDC data, the fitted curves had R^2 values above 0.99. Because the decline in fecundity is especially rapid after age 35, we used these formulae to generate age-specific pregnancy probabilities rather than tables coded to an individual year. Because the estimated 12-month rate in older women was substantially higher in the adjusted ART data than in the insemination studies, we used the more conservative estimates.

Conception can only occur when intercourse takes place during a 6-day window ending at ovulation.[5] Because the cycle length in the model is 1 week, we assumed a 28-day cycle, and that the probability of pregnancy would be 0 for weeks 1, 3, and 4, and the age-specific fertility rate during week 2.

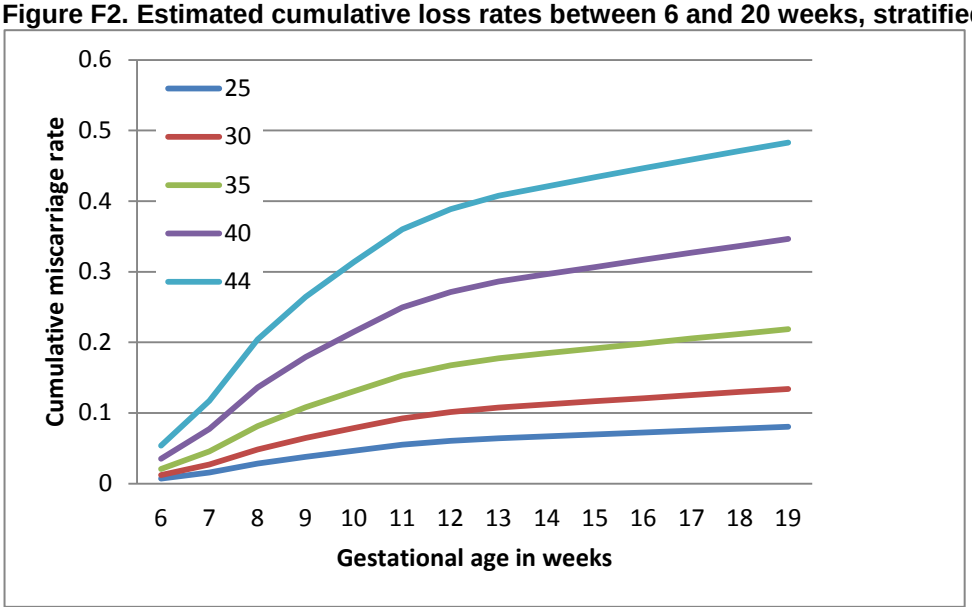
Figure F1. Age versus monthly pregnancy



Spontaneous abortion rates: Spontaneous abortion rates are also highly dependent on maternal age (as with pregnancy rates, we assumed that age-specific rates would be similar for African-American and white women). We derived age-specific spontaneous miscarriage rates for clinical pregnancies (pregnancy detected at 5-6 weeks gestation) for weeks 6 through 20 from two sources. First, we used gestational age-specific loss rates from a large prospective cohort study of women attempting to get pregnant[6] to generate conditional probabilities of spontaneous abortion for each week. We then adjusted these weekly rates to fit age-specific cumulative loss rates from a population-based study.[7] As with the fecundity data, we fitted an equation to the observed data to generate age-specific estimates in 1-year increments.

Figure F2 shows the estimated cumulative loss rates between 6 and 20 weeks, stratified by maternal age, for ages 25, 30, 35, 40, and 44.

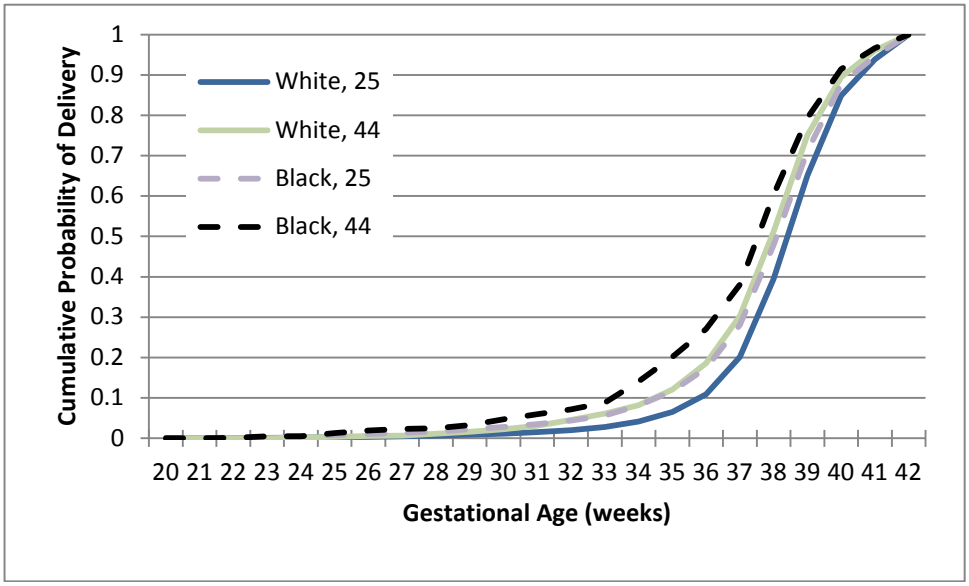
Figure F2. Estimated cumulative loss rates between 6 and 20 weeks, stratified by maternal age



Gestational age-specific delivery rates: We used the most recently available (2006) birth certificate data from the National Center for Health Statistics (http://www.cdc.gov/nchs/data_access/vitalstats/VitalStats_Births.htm) to generate tables of number of deliveries between 20 and 42 weeks, stratified by best estimated gestational age (in weeks), maternal age (in years), and racial group (African-American vs. white). Because the standard of care in the United States is to deliver all ongoing pregnancies between 42–43 weeks because of an increased risk of stillbirth, we included the small number of deliveries estimated as beyond 42 weeks in the 42-week total.

We then used these tables to generate the conditional probability of delivery for each week of pregnancy, again stratified by maternal age and race (Figure F3).

Figure F3. Conditional probability of delivery per week of pregnancy, stratified by maternal age and race



NOTE: We did not further stratify delivery probability by parity, primarily because the available literature did not provide sufficient detail to include parity and age and race without making further assumptions. Women seeking fibroid treatment who are considering childbearing are more likely to be nulliparous or have low parity. Because nulliparous women are at higher risk for a variety of adverse outcomes (including preterm birth), accounting for differences in parity would further refine the model's ability to estimate adverse reproductive outcomes. We also did not include other pregnancy outcomes that have been associated with fibroids or fibroid treatments.

Impact of fibroids on reproductive outcomes: Two recent meta-analyses found significant effects of fibroids on clinical pregnancy rates, spontaneous abortion rates, and preterm birth rates, with some variation in risk depending on fibroid location.[8,9] For the purposes of the model, we used the estimates from each review that included all fibroids rather than site-specific risks—future refinement of the model could stratify risk by fibroid location at baseline (Table F1).

Table F1. Effects of fibroids on clinical pregnancy, spontaneous abortion, and preterm birth rates

Outcome	OR	95% CI	Reference
Clinical pregnancy	0.85	0.734, 0.983	[8]
Spontaneous abortion	1.68	1.37, 2.05	[8]
Preterm birth	1.5	1.3, 1.7	[9]

OR = odds ratio; CI = confidence interval

Modeling the impact of fibroids and fibroid treatments on these outcomes is difficult for a variety of reasons beyond the methodological issues involved in the primary studies themselves. From the standpoint of appropriate parameter derivation, the primary issue is that overall

population event rates represent the weighted average of the rates in people with a given risk factor and in those without the risk factor. Given the overall event rate, the relative risk associated with a given factor, and the prevalence of the factor in the population, the individual rates can be easily derived. If this correction is not done, simply multiplying the population rate by the relative risk associated with the risk factor will result in an overestimation of both the overall risk and the risk in people with the risk factor. Another issue is that the available data, both in individual studies and systematic reviews, are summarized as relative risks or odds ratios; for the purposes of our model, which uses time-dependent conditional probabilities, hazard ratios would be more appropriate.

In the case of reproductive outcomes associated with fibroids, some of the overall population rates are likely due to fibroids, but data on the prevalence of asymptomatic fibroids in the appropriate populations are lacking, particularly in the general population of women seeking to achieve pregnancy. For the impact of fibroids on fertility, we assumed no impact on overall age-specific fecundity in the base case, but varied the relative risk to 0.85 (i.e., a 15% reduction in age-specific cycle fecundity). We used the observed prevalence of fibroids in a large prospective study of early pregnancy[10] as the assumed population prevalence; however, if fibroids do adversely affect the probability of a detectable clinical pregnancy, than the observed prevalence in women in early pregnancy will be lower than in the overall population of women trying to conceive.

We used the prevalence of fibroids reported in Laughlin et al.[10] and adjusted the weekly probability of spontaneous abortion and delivery under 37 weeks accordingly, using the summary relative risks reported by Klatsky et al.[9]

TREATMENT OUTCOMES

Short-term complications: Because we modeled costs and return to work separately for patients with and without complications, we focused solely on major short-term complications. The largest series with detailed reporting was the FIBROID registry,[11] with a major complication rate of 0.66 percent. We modeled the probability of major complications with the other procedures as relative risks, using 2.0 in the base case for myomectomy,[2] and 0.01 for FUS (assumption).

Long-term complications: We did not model post-discharge complications, either within the "typical" recovery time or over the course of the simulation. Although differential complications rates will have some impact on both costs and quality-of-life outcomes, most studies did not report data in great detail. Because the impact of periprocedural complications, including ones within the first 30–45 days of the procedure, would translate into differences in the distribution of costs and return to activity, we varied short-term complication rates, which have the effect of increasing the overall mean periprocedural costs and time lost from usual activities, as a surrogate.

Relief of symptoms: Following other recent cost-effectiveness analyses of fibroid treatments, we used retreatment as a surrogate marker for recurrent symptoms. We identified studies that reported at least 24-month data on cumulative retreatment rates (Table F2).

Table F2. Studies reporting at least 24-month data on cumulative retreatment rates

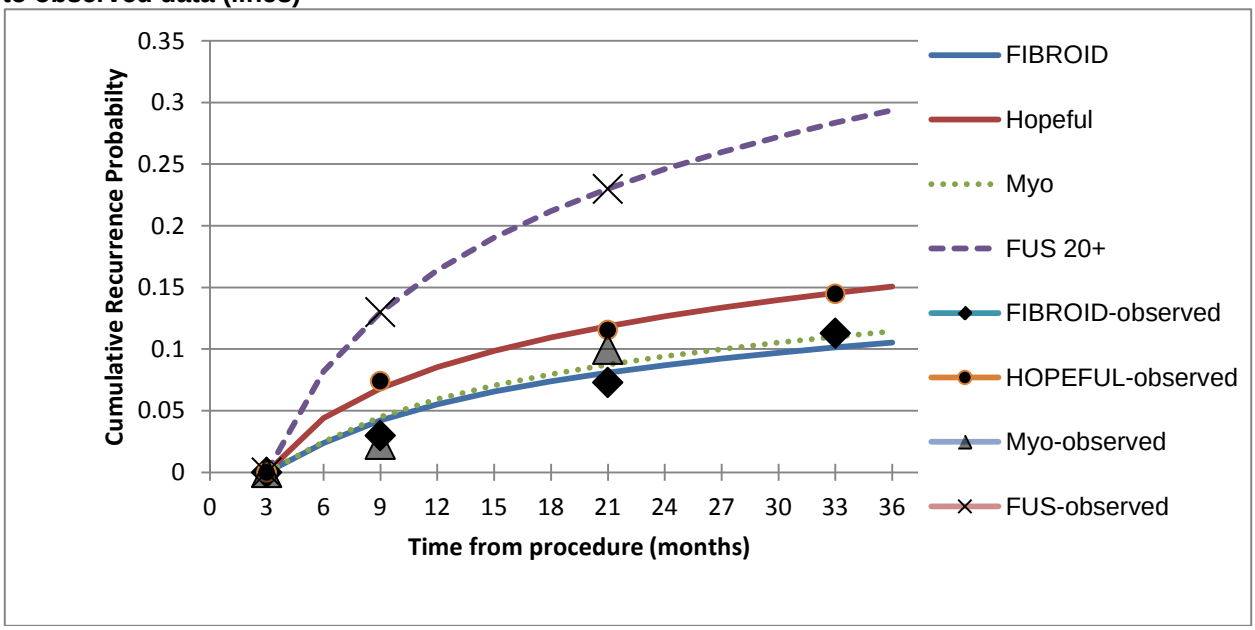
Time	UAE				Myomectomy		FUS[12]		
	EMMY[13]	FIBROID[14]	HOPEFUL[15]	REST[16]	Hanafi[17]	Subramanian[18]	All Subjects	% nonperfused	
								<20	20+
3	0.075								
6	0.102	0.025				0.083	0.031	0.04	0.02
9	0.129								
12	0.172	0.055	0.074	0.094	0.01	0.106	0.236	0.3	0.15
15	0.231								
18	0.263								
21	0.279								
24	0.295	0.098	0.116	0.198	0.03	0.183	0.336	0.4	0.25
27	0.311								
30									
33									
36	0.329	0.138	0.145		0.1				

EMMY = EMbolization versus hysterectoMY trial; FIBROID = FIBROID registry; FUS = MRI-guided focused ultrasound; HOPEFUL = Hysterectomy Or Percutaneous Embolisation for Uterine Leiomyomata study; REST = Randomised Study of Embolisation and Surgical Treatment for Uterine Fibroids; UAE = uterine artery embolization

Persistent symptoms: We assumed that all retreatments in the first 6 months after the initial treatment represented persistent symptoms. We used the rates from Subramanian for myomectomy, and Stewart et al for FUS. In the case of FUS, we used the rates for higher treatment volumes to reflect current clinical practice. Because the EMMY trial rates were substantially higher than any of the others for longer term outcomes, we elected to use the 6 month rate from the FIBROID registry as the base case. We used the lowest reported rate (UAE) as the reference, and modeled rates for myomectomy and FUS as relative rates.

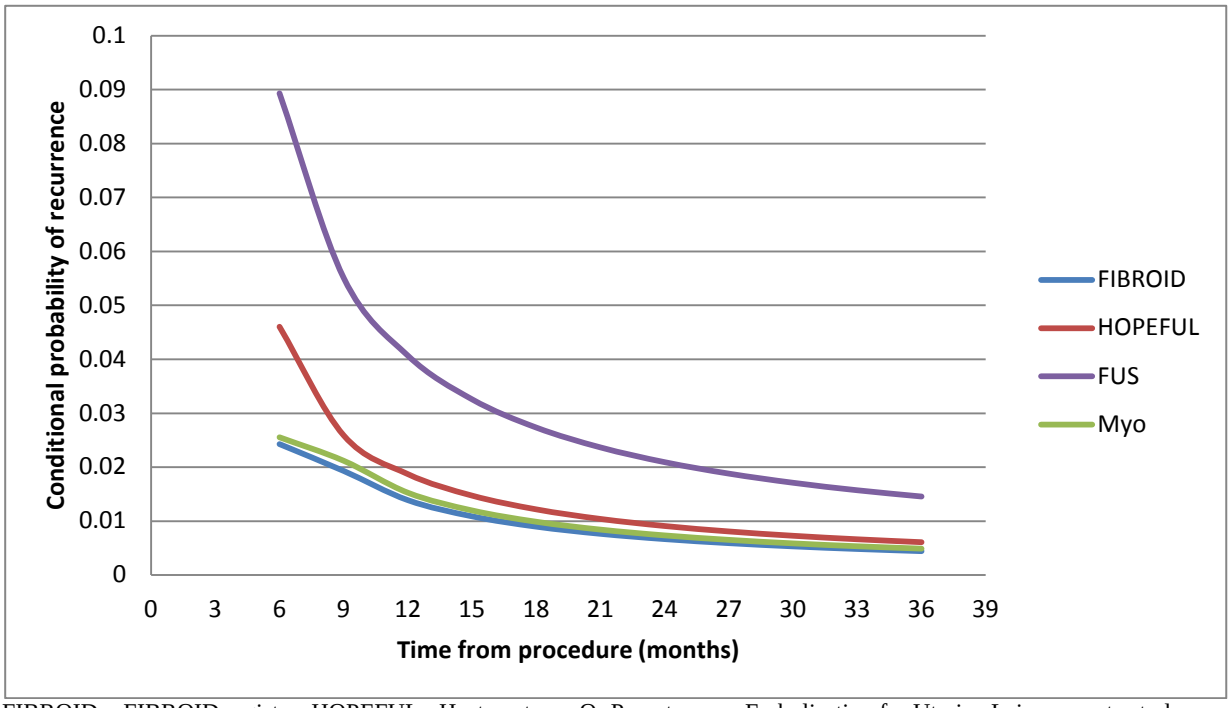
Recurrent Symptoms: We recalculated the cumulative retreatment rates after removing those who "persisted" within 6 months from the at-risk pool. We also assumed that symptoms would recur on average 3 months prior to retreatment. We used the U.S.-based FIBROID and UK-based HOPEFUL studies for deriving rates for UAE, and the Subramanian and Stewart studies for myomectomy and FUS (Figure F4). After plotting the observed rates, curves were fitted to the cumulative probabilities, all with R^2 values above 0.99. These functions were then used to calculate conditional probabilities (Figure F5).

Figure F4. Recalculated cumulative probabilities of recurrence after removal of "persistent" cases and assumption of recurrence occurring 3 months prior to retreatment (symbols) and fitted curves to observed data (lines)



FIBROID = FIBROID registry; HOPEFUL= Hysterectomy Or Percutaneous Embolisation for Uterine Leiomyomata study; , Myo = Subramanian; FUS = Stewart

Figure F5. Plot of conditional probabilities of recurrence derived from fitted cumulative probability curves



FIBROID = FIBROID registry; HOPEFUL= Hysterectomy Or Percutaneous Embolisation for Uterine Leiomyomata study; , Myo = Subramanian; FUS = Stewart

On the basis of these studies, recurrence risk fits a proportional hazards model, which is especially helpful for modeling comparative effectiveness, since the relative effectiveness of a given treatment can be modeled using hazard ratios. We chose the FIBROID registry data as the reference (and modeled the variability in observed recurrence rates using hazard ratios), and varied hazard ratios for myomectomy and FUS across a wide range, from 0.85 to 3.0. In the base case, we used a HR of 1.1 for myomectomy and 3.0 for FUS.

NOTE: We did not incorporate the potential effect of patient characteristics on recurrence rates. In particular, age is consistently a predictor of recurrence risk for UAE, and likely for other treatments as well. Incorporating age-specific effects is an important next step, but requires additional data (such as specific parameters from survival analyses from primary studies).

Impact on reproductive function: There are no large-scale data on comparative impact of different treatments on reproductive function. We therefore modeled the potential impact of each treatment by adjusting the relative risk associated with fibroids on fertility, miscarriage, and preterm birth. A fully effective treatment would reduce this relative risk to 1.0 (so that the rate would be equivalent to women of the same age and racial group without fibroids); we included the possibility of treatments reducing fertility or increasing the risk of miscarriage or preterm birth.

COSTS

Procedure costs: Using the Nationwide Inpatient Sample from the Healthcare Cost and Utilization Project, we identified hospital admissions in 2008 with diagnoses of uterine fibroids (ICD-9 218.0-218.9) and procedure codes for myomectomy (ICD-9 68.29) or uterine artery embolization (ICD-9 99.29). The estimated mean and median charge data from HCUP were converted to costs assuming a 0.6 cost/charge ratio. These were then inflated to 2010 data using the medical care component of the Consumer Price Index (www.bls.gov).

Using the adjusted mean and medians, we generated lognormal distributions for hospital costs and generated a distribution using 10,000 simulations. We assumed that the right tail represented patients with periprocedural complications. We generated separate estimates for uncomplicated and complicated procedures as follows:

- For uncomplicated procedures, we took the interquartile range from the overall lognormal distribution and calculated the mean and standard deviation.
- For complicated procedures, we took the upper quartile, calculated mean and medians, and generated a new lognormal distribution.

We did not identify similar population-based data for focused ultrasound. To estimate costs, we took the mean cost from a previously cost-effectiveness analysis, which were derived from the Medstat database (REF) and inflated it to 2010 dollars. The estimated costs used in this study for myomectomy and UAE were somewhat lower than those derived from HCUP data, likely reflecting a somewhat different patient population (privately insured patients) with a different overall spectrum of disease and comorbidities. Since the populations undergoing UAE and focused ultrasound to date are more similar than the populations undergoing either procedure to those undergoing myomectomy, we adjusted the reported Medstat costs for focused ultrasound by the same ratio as that used in the previous analysis. We assumed that the ratio of median to mean costs would be similar to that observed for myomectomy and UAE (approximately 0.85), and used a similar approach to generate estimates for complicated and uncomplicated cases (Table F3).

Table F3. Estimated costs for fibroid treatment with myomectomy, UAE, and focused ultrasound

	Myomectomy				UAE				Focused ultrasound			
Medstat cost estimate*	$10,5461				$12,688				$8,028			
HCUP cost estimate*	Mean		Median		Mean		Median		Mean		Median	
	$14,775		$12,885		$15,375		$13,091		NA		NA	
Derived cost estimates*	No comp	Comp	No comp	Comp	No comp	Comp	No comp	Comp	No comp	Comp	No comp	Comp
	13043	**25699**	**12737**	**23410**	**13359**	**28025**	**13072**	**25149**	**9917**	**20805**	**9713**	**18542**

HCUP = Healthcare Cost and Utilization Project; NA = not applicable; UAE = UAE = uterine artery embolization
*2010 USD

There is no ideal data set for estimating costs associated with fibroids, because of differences in patient characteristics which could affect outcome, different coverage levels, and different sites

of care (for example, the Nationwide Inpatient Sample does not capture procedures performed on an outpatient basis).

Productivity costs: Data on estimated annual incomes by age and race for women were obtained from the 2009 Annual Social and Economic Supplement to the Current Population Survey (www.census.gov) and reflect 2008 data; these were inflated to 2010 values using the Employment Cost Index (www.bls.gov) (Table F4). Age- and race-specific wages were modeled as lognormal distributions. Annual wages were converted to daily values for estimating the impact of treatment and symptoms on productivity.

Table F4. Estimated annual incomes for women by age and race

Age	White		African-American	
	Mean	Median	Mean	Median
25-29	$27,853	$25,138	$24,216	$20,564
30-34	$32,019	$26,645	$29,007	$24,971
35-39	$36,281	$27,413	$32,651	$28,735
40-44	$35,424	$27,161	$31,598	$26,112

We derived recovery times as follows:

- Data on mean and median lengths of stay for myomectomy and UAE were obtained from HCUP. Using an approach similar to the one we took for deriving costs for uncomplicated and complicated cases, we generated distributions for length of stay.
- Some data on mean times for return to work and return to usual activities are available for myomectomy and UAE,[2] and for FUS,[19] although there are no data on the distribution of these times (although the data on FUS are strongly suggestive of a non-normal distribution). For simplicity, we used a normal distribution with a small standard deviation (1–2 days), under the assumption that most of the variability in time to return to work or usual activities after the procedure would be driven by complications and length of hospital stay (Table F5).

Table F5. Recovery times for myomectomy, UAE, and FUS

	Myomectomy		UAE		FUS	
LOS (days) (HCUP)	Mean	Median	Mean	Median	Mean	Median
	2.4	2.0	1.4	1.0	--	--
Return to usual activities or work (days)	14.6 (usual activities) 9.9 (work) [2]	--	44.4 (usual activities) 37.0 (work)[2]	--	1.2 ± 2.3 (usual activities) 0.8 ± 0.5 (work)[19]	
Derived added time after hospital discharge before return to usual activities	12.0 ± 1.0 days		43.0 ± 2.0 days		0	

FUS = MRI-guided focused ultrasound; HCUP = Healthcare Cost and Utilization Project; LOS = length of stay; UAE = uterine artery embolization

Productivity losses were modeled based on assumptions about missing work; we did not model decreases in productivity in symptomatic women who were able to be present at work.

Retreatment costs: We used the overall mean and median costs (which include both complicated and uncomplicated cases) for UAE, myomectomy, and FUS for retreatment costs, modeled as lognormal distributions. We also included the possibility of hysterectomy as a retreatment, and used mean and median charges, converted to costs using a 0.6 cost/charge ratio and inflated to 2010 USD, from the 2008 Nationwide Inpatient Sample. We did include varying costs based on a possible higher risk of complications in repeat procedures, although this would be straightforward to include.

Pregnancy-related costs: We did not include the costs of routine prenatal care, management of miscarriage or preterm labor, or fertility evaluation. We did include the mean costs of a preterm infant, inflated to 2010 USD[20] ($61,209). The model also has the capability of more precisely estimating the impact of preterm birth by using gestational age-specific morbidity and mortality rates.

We did not include several other potentially relevant costs, including:

- Transportation and child care costs
- Costs for office visits, prescription or over-the-counter medications, and supplies (such as sanitary products) for patients with persistent or recurrent symptoms

UTILITIES

Utilities, which are used to weight the duration of time spent in a given health state according to that state's relative impact on quality of life, range from 0 (death) to 1.0 (perfect health). Utilities used in previous studies are quite variable (Table F6).

Table F6. Utilities used in previous studies

STATE	STUDY			
	Kuppermann[21]	Hirst[15]	Zowall [22]	O'Sullivan [23]
Symptomatic fibroids	0.80 ± 0.01 (bleeding) 0.88 ± 0.01 (pressure)	0.705	--	0.67
Recovery from procedure	--	--	0.757 (myo) 0.783 (UAE) 0.783 (FUS)	
Symptom relief	--	0.825	0.802	0.76
Sources for utility value	Primary data collection using time tradeoff among symptomatic patients	Derived from SF-36 scores in REST trial	Derived from previous CEA of endometrial ablation	Unpublished data—unclear whether from utility scores or derived from other scale

As with many of the other parameters, we elected to model utilities as relative functions, using absolute changes. We used 0.70 as the baseline utility for symptomatic fibroids, and assumed that persistent and recurrent symptoms would have the same utility. We assumed that improved symptoms would lead to a mean increase of 0.12 in utility scores, with a standard deviation of 0.01 (although utilities are rarely normally distributed, we elected to model them as a normal distribution in the absence of any reliable data for using alternative distributions). Utilities during recovery are 60 percent (myomectomy) and 80 percent (UAE, FUS) of the final improved utility.

There are almost no data on utilities relevant to reproductive outcomes. The data that are available suggest that infertility is likely to have a lower value among nulliparous women than other outcomes. For example, in a study in U.K. women awaiting in vitro fertilization, the only outcome with a lower utility score using the standard gamble than continued infertility was an infant death followed by permanent infertility; 85 percent rated having a child with a permanent physical impairment equal or worse than infertility, 94 percent rated a child with a permanent cognitive impairment equal or worse, and 96 percent rated a child with permanent visual impairment equal or worse.[24] Median (IQR) score for infertility was 0.815 (0.712–0.977), with scores for physical, cognitive, or visual impairment, or preterm birth (the proximate cause of the impairments) as 0.94–0.97. This is consistent with U.S. studies of infertility patients,[25] as well as parental utility scores for other infant/childhood outcomes.[26,27] In another U.S. study of utilities for states relevant to pelvic inflammatory disease, infertility had a mean score of 0.84 with a median of 1 and IQR of 0.81-1 among 150 women with no history of PID, 65 percent of whom desired or planned to get pregnant in the future.

Based on these results, we assumed that women attempting pregnancy would maintain the "Improved Symptoms" utility of 0.12, with no change with a pregnancy resulting in a live birth. A diagnosis of infertility would result in a 0.06 reduction in utility, with the range varied from 0.06 to 0.12 (i.e., infertility equivalent to symptomatic fibroids).

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