

A First Look at the Volume and Cost of Comparative Effectiveness Research in the United States

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Executive Summary

While the health policy community debates the potential contributions of comparative effectiveness research to health care quality and costs, there is limited understanding of the current capacity for conducting comparative effectiveness research in the United States. This report is intended to help fill this gap by providing an environmental scan of the volume and the range of cost of recent comparative effectiveness research.

There is, of course, debate over the scope of this type of research.¹ For purposes of this project, we have defined comparative effectiveness research as, “Comparison of the *effectiveness* of the risks and benefits of two or more health care services or treatments used to treat a specific disease or condition (e.g. pharmaceuticals, medical devices, medical procedures, and other treatment modalities) in approximate real-world settings.” In this definition we have not included studies that only compare an intervention to placebo or usual care.

This review included three phases. The first phase consisted of a workshop with comparative effectiveness researchers that allowed us to identify a typology of studies and treatments that are the focus of comparative effectiveness studies. The second phase examined the volume of comparative effectiveness research by reviewing two databases of research studies: Clinicaltrials.gov and Health Services Research Projects in Progress (HSRProj). We also conducted a purposeful sample of interviews with research organizations and funders. As part of the interviews, individuals identified a subset of large trials they considered “comparative effectiveness studies”.

An important study limitation is that we were not able to cross reference all three data sources. As a result, the findings reported from the databases and interviews stand on their own and should

not be summed. In addition, we relied on funders and researchers to provide a range of cost estimates for conducting comparative effectiveness studies and insights into some of challenges researchers currently face in this area.

Study Highlights:

- Using Clinicaltrials.gov and HSRProj we identified 689 comparative effectiveness studies.
- Interviews with research funders or those who self-fund research projects identified 617 comparative effectiveness studies.
- The types of study designs used in comparative effectiveness research are broad-ranging. Within the interviews, observational studies (prospective cohort studies, registry studies, and database studies) comprise the largest group (54 percent), but research syntheses (reviews and modeling studies) (33 percent), and experimental head-to-head studies (13 percent) also represent a significant proportion of research activities. Among observational studies 23 percent are registry studies and the rest are based on other types of primary or secondary data.
- The general range of cost for head-to-head randomized trials was reported to be extremely broad, from \$400,000 to \$125 million. Within this range, many smaller trials have a range of cost on the order of \$2.5 million to \$5 million, while the cost of larger-scale trials clustered around \$15 million to \$20 million.
 - As part of this project we identified 17 trials that interviewees characterized as “comparative effectiveness research.” Virtually all of these studies are federally-sponsored trials.
- The cost of observational studies was also broad, from \$25,000 to \$38 million. Retrospective database studies tend to be less expensive and cost on the order

of \$100,000 to \$250,000, while large prospective cohort studies may cost several million dollars.

- Registry studies may cost between \$800,000 and \$6 million, with multi-year studies falling at the higher end of this range.
- Systematic reviews and modeling studies tend to be less expensive and have a far narrower range of cost, in great part because these studies are based on existing data. The range of cost for modeling studies may be \$75,000 to \$300,000, with a cluster in the range of \$100,000 to \$200,000 while systematic reviews cost a range of \$100,000 to \$500,000, with a cluster in the range of \$200,000 to \$350,000.
- Interviewees stressed the need to provide more training in the methods and conduct of comparative effectiveness research. They also emphasized the need to bring researchers together to discuss the relative roles of randomized controlled trials and observational studies within the area of comparative effectiveness research, given the degree to which training for clinical and observational research are currently separated.

It is important to emphasize that the estimates of volume and cost presented in this report are based on convenience samples and thus are not necessarily representative. It is impossible to know the universe of comparative effectiveness research given the limitations of the two databases that attempt to track ongoing research. However, our findings represent a first attempt to provide a structured, in-depth view of the current level of activity in the area of comparative effectiveness research.

Our findings suggest that there is a significant volume of comparative effectiveness research in the United States, but that there is a lack of coordination across, and even within funding organizations, making it difficult to visualize the whole. The interviews also

suggested a wide range of comparative effectiveness research costs by study design, and even within study design. These findings highlight the need to begin a policy discussion around the types of research designs that are most cost effective for the specific question being addressed and underscore the importance of developing a comparative effectiveness research agenda that is transparent and involves stakeholders with multiple methodological perspectives.

As conversations on comparative effectiveness research progress, there is a critical need to understand the value of different research designs and be able to track the production of research activities and how results are used, if at all. Only by improving understanding of the current research and coordinating future research activities can we ensure that comparative effectiveness research will realize its full potential and contribute meaningful information to improve health care in the United States.

Introduction

Comparative effectiveness research is viewed by many experts as a potentially powerful tool to improve health care quality (IOM, 2007) and a strategy to help reduce health care costs (CBO, 2007; Schoen, 2007). There are several components of comparative effectiveness research, including: 1) research production; 2) translation of research into clinical (and potentially coverage) recommendations; 3) policies to promote the use of evidence; and 4) assessment of research impact (areas 1-3) on cost and quality.

This study focuses on the first function, comparative effectiveness research production. Current production of comparative effectiveness research is not well understood, perhaps due to the relatively new use of the term, or as a result of fragmented funding streams. This study purports to determine whether there is a significant body of comparative effectiveness research underway so that policymakers interested in improving

Efficacy and Effectiveness

Efficacy research is generally thought of as looking at “what can work”; i.e., is a treatment safe and does it have a real effect? Effectiveness research, on the other hand, looks at what works “for whom and under what conditions.” Efficacy research also generally involves comparison of an active agent to a placebo, whereas effectiveness studies tend to make comparisons between a new treatment and standard practice, rather than a placebo.

outcomes can plan appropriate initiatives to bolster comparative effectiveness research in the United States. This study does not propose to assess the universe of comparative effectiveness research for improving health outcomes because this is not feasible with existing data sources, which are limited by the way research portfolios are collected and monitored.

This report intends to help fill this gap by reporting findings from an environmental scan of comparative effectiveness research. Specifically, the aims of the study are to:

- Identify a typology of comparative effectiveness research designs and list the types of treatments that are the subject of comparative effectiveness studies;
- Characterize the volume of research studies that address comparative effectiveness questions, and the types of treatments that are the focus of these studies;
- Provide a range of cost estimates for conducting comparative effectiveness studies by type of study design; and
- Elicit recommendations from funders and researchers on infrastructure support needed to improve the capacity to produce comparative effectiveness research.

Though many definitions of comparative effectiveness research have been developed,² this project relies on the following definition:

Comparison of the *effectiveness* of the risks and benefits of two or more health care services or treatments used

to treat a specific disease or condition (e.g. pharmaceuticals, medical devices, medical procedures and other treatment modalities) in approximate real-world settings.

Excluded from this definition are studies of the comparative effectiveness of organizational and system level strategies to improve health outcomes. Research that is clearly “efficacy” research based on comparison of new treatment to a placebo is also outside this definition, although, as discussed below, the methodological overlap with trials sometimes makes it difficult to differentiate from effectiveness research. In this definition we also have not included studies that compare an intervention to placebo or usual care.

Finally, there are additional activities and cost of involving stakeholders in research agenda setting as well as prioritizing, coordinating, and disseminating research on comparative effectiveness research, all of which are not included in this report.³ These activities represent important investments that must be considered in the process of budgeting for comparative effectiveness research as external costs to the direct expense of research production.⁴

Methods

The project included three phases:

- 1) Developing a framework of study designs and topics;
- 2) Conducting a structured search of research projects listed in two databases, Clinicaltrials.gov and HSRProj,⁵ a database of health services research projects in progress;
- 3) Conducting in-person and telephone interviews with research funders or

researchers identified as conducting comparative effectiveness studies.

Framework

Our first step in assessing the volume and cost of comparative effectiveness research was to generate a framework of research designs that would allow us to categorize our findings. In December 2007 we convened a panel of research experts for this purpose (Appendix A).

Research Databases

Clinicaltrials.gov is the national registry of data on clinical trials. The database includes an extensive listing of randomized trials, as mandated by the FDA reporting process required for drug regulation and approval. Studies listed on Clinicaltrials.gov tend to be focused on establishing the efficacy of drugs and devices, rather than effectiveness. More than 53,000 study records are included in Clinicaltrials.gov and approximately 13,000 new studies are added to the database each year (Zarin, 2008).⁶ Theoretically, Clinicaltrials.gov provides a complete set of information on all clinical trials of drugs, biologics, and devices subject to FDA regulations (Zarin, 2008).

Three statutes compel registration on Clinicaltrials.gov.⁷ Since these policies only mandate reporting of trial results as part of the regulatory approval process, the vast majority of trials included in Clinicaltrials.gov are controlled experimental studies (85 percent), referred to as “interventional” studies. The remaining 15 percent are observational studies, for which reporting is not required, other than in cases where participation in a trial registry is required before study results can be published. Because it is not mandatory to report observational studies in Clinicaltrials.gov we do not know how many observational studies are not included in the database results presented here.

Using Clinicaltrials.gov an electronic search was conducted to look at phase III and phase IV interventional studies with the word “effectiveness” in the project

description. The search resulted in a list of 1,730 trials that were active between Jan. 1, 2007 and Feb. 29, 2008. Through a process of hand searching, studies explicitly identified as “efficacy” studies or studies with “placebo” controls were excluded, as were studies that did not include at least two active comparators.

A subset of phase III studies identified in Clinicaltrials.gov are included in this analysis because they have some of the characteristics of “effectiveness” studies and because many of our interviewees offered phase III trials as examples of “comparative effectiveness trials” (Appendix C). In all cases, the studies are head-to-head trials that appear to have some characteristics of effectiveness studies, such as broader inclusion criteria, a larger patient population that may capture adverse events, and inclusion of hard endpoints such as health outcomes. Nonetheless, because these types of studies are often conducted in settings with more internal controls, they tend toward the “efficacy” end of the research continuum. To help address this we have excluded all studies that explicitly list “efficacy” as an element of their study design.

HSRProj

Health Services Research Projects in Progress (HSRProj) is a database of health services research (HSR) projects that are ongoing and have not been completed.⁸ The field of HSR focuses on research questions related to health care access, cost, quality, and performance of health care systems. Some clinical research may be included in HSRProj if it is focused on effectiveness. HSRProj includes a variety of public⁹ and private organizations but only a limited number of projects funded by private or industry sources.

Comparative effectiveness research projects in HSR were identified by searching HSRProj for projects using the key words “comparison” or “effectiveness.” Projects were also identified by searching for each of the study types included in the study design typology developed during the focus group session. The database was also searched for

ongoing projects sponsored by organizations interviewed by AcademyHealth as part of this project. A hand search of project titles was then conducted to ensure appropriate selection of studies according to the definition of comparative effectiveness selected for this project.

Interviews

The interview phase of the project included in-person and telephone interviews with research funders and researchers who conduct comparative effectiveness research. The purpose of these interviews was three fold: first, to determine the number of comparative effectiveness research studies being funded or conducted by that organization; second, to assess the cost of conducting these studies by design type; and third, to identify issues currently faced by researchers conducting comparative effectiveness research, including infrastructure needs.

Participants were selected for interviews using the “snowball” sampling method. An initial sample of individuals funding and conducting comparative effectiveness research were contacted in response to recommendations by our focus group panel. Based on this initial sample a first round of interviews was scheduled with individuals who confirmed they were knowledgeable about comparative effectiveness research projects within their organization. These individuals were then asked about other key contacts we should interview.¹⁰ In total, 65 individuals were contacted for an interview. Ultimately, 35 individuals from 25 research funders and research organizations participated in the project,¹¹ including five government agencies; seven private sector funders; five contract research organizations (CROs); five university-based research centers; and three other specialty societies and research entities.¹²

All respondents were sent a project overview with a basic definition of comparative effectiveness research and a grid of study designs and research domains (Appendix B). Using this outline

we asked the respondents to share with us the number of studies and approximate cost of comparative effectiveness research studies they had initiated or planned to initiate in 2008. The interviews also sought to identify the types of treatments that are most commonly the focus of investment in comparative effectiveness research.

When estimates were provided by phone, these were summarized and sent back to interviewees for confirmation. Due to the proprietary nature of the estimates, the data is aggregated for all respondents. Once data from the interviews was aggregated, we summed the total number of studies by research type. Where interviewees reported a range of studies we used the lower bound estimate in our total count of ongoing projects.

A few limitations should be noted. The first is that while we initially requested that interviewees identify ongoing or planned studies in 2008, because the interviews were conducted in the first few months of 2008, many organizations are unable to predict their research efforts for the full year. These respondents extrapolated from studies conducted in 2007 to provide a representative number for 2008.

In addition it was not feasible to cross reference all three data sources since the studies identified in the interviews were reported in aggregate. To do so would have required that we identify project titles or detail on individual research projects. This was not possible because of the burden it would have caused our respondents.

Among the interviews there was also potential for overlap in the number of studies cited by funders and research organizations that received funding. For this reason we elected to present only the number of studies identified by research funders in order to avoid a potential double-count of comparative effectiveness research projects. This issue is less problematic for the two databases, which are complementary in theory. We did cross check the observational studies in Clinicaltrials.gov with HSRProj and did not find any instances in which projects were listed twice.

As a result of the potential for duplication between the data collected from the databases and interviews, the two should stand on their own and not be summed. They are presented as alternative sources.

Findings

Framework

In the first stage of the project the panel of experts discussed the challenges of identifying research studies that contribute to knowledge on the comparative effectiveness of treatments. They identified two primary dimensions, “comparison” and “effectiveness” (Figure 1), both of which can be conceptualized as continuums of research designs.

The first dimension of comparative effectiveness research is the degree of comparison for the treatment of interest, ranging from comparison of a placebo (or usual care) to direct comparison of two treatments. The second dimension addresses the degree of control over the study setting and ranges from *efficacy* studies that

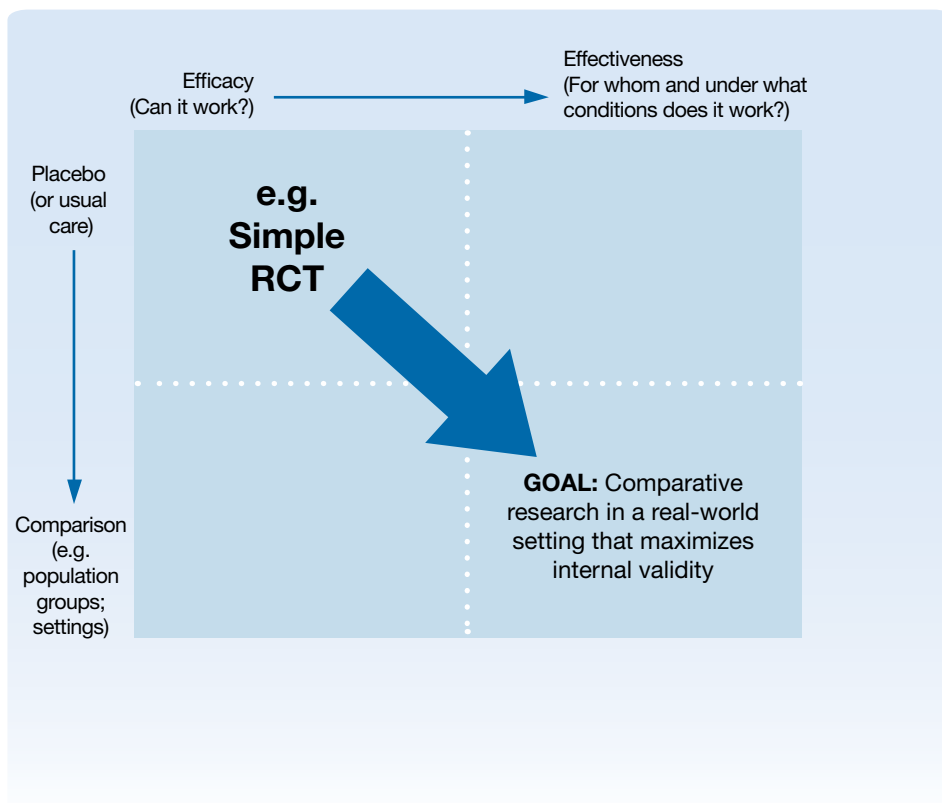
are conducted under highly controlled circumstances to evaluate the question, “Can it work?,” to *effectiveness* studies that address, “For whom and under what conditions does it work?”

The expert group also identified key research study designs and types of treatments that may be studied in comparative effectiveness research. Based on this meeting and in consultation with several additional experts in comparative effectiveness research, a grid of study designs and types of treatments that are the subject of comparative effectiveness studies was developed. This framework (Appendix B) was used to facilitate interviews with research funders.

Overall, there was general agreement that there are three primary research categories¹³ applicable to comparative effectiveness research:

- Head-to-head trials;
- Observational studies; and
- Syntheses and modeling.¹⁴

Figure 1: Two Dimensions of Comparative Effectiveness Research: Degrees of Comparison and Experimental Control



Volume of Comparative effectiveness research

Clinicaltrials.gov

We identified 689 comparative effectiveness studies in Clinicaltrials.gov and HSRProj. Among these, 578 ongoing comparative effectiveness trials are “interventional trials”.

Among the interventional trials listed in Clinicaltrials.gov, the vast majority (97 percent) are phase III trials that compare two or more treatments “head-to-head”, have real-world elements of their study design, and do not explicitly include “efficacy” in their description of the study design. Only 19 studies are phase IV post-marketing studies that compare multiple treatments. In addition 38 studies were identified as “observational studies” (Figure 2), of which one appeared to be a registry study.

Research portfolios tend to focus on treatments that are of interest to the sponsoring organization. Large organizations are more likely to have a balanced portfolio across treatments,

with pharmaceuticals a major focus of ongoing research activities. Biological agents, devices, behavioral interventions and invasive procedures were mentioned, though with lesser frequency.

Among the interventional research studies, the majority of trials are focused on drugs and radiological therapy. Nearly 90 percent of studies identified in Clinicaltrials.gov compare the effectiveness of one or more drugs with some type of procedure. Chemotherapy regimens are by far the most common treatments listed in the group of studies identified in Clinicaltrials.gov. More than half of the trials specifically mention cancer treatment in the study description. Small proportions of the studies are focused solely on comparison of pharmaceuticals or procedures. An extremely small group is focused on behavioral therapies or a mix of behavioral therapies and prescription drugs or on devices and other treatments. Among the phase IV trials only, the majority of studies focus on prescription drugs.

Most other observational studies focus on drugs and procedures. A handful of studies also examine population characteristics. These studies range from prospective research assessing the progression of diseases over time to economic impact assessments.

HSRProj

We identified 73 comparative effectiveness research projects in HSRProj. The process of hand searching project titles revealed that most studies were observational research with primary or secondary data collection. Six studies were specifically identifiable as “registry” studies. Three studies were evidence synthesis or systematic reviews.

Interviews

As shown in Figure 2, our interviews with funders identified more than 600 comparative effectiveness studies. Among funders and those who self-fund comparative effectiveness research, observational studies (e.g. prospective cohort studies, registry studies, and database

Figure 2: Volume of Comparative Effectiveness Research*

Sources	Head-to-Head Trials with Elements of Real-world Setting		OBSERVATIONAL STUDIES		Syntheses (Simulation/ Modeling or Systematic Review)
			Registry Studies	All Other Observational Studies (Primary and Secondary Data)	
Interviews with funders or those who self-fund	81		78	256	202
Clinicaltrials.gov	Phase III	Phase IV	1	37	0
	559	19			
HSRProj	0 ¹⁵		6	64	3
Total in Databases	578		7	101	3

* Comparative effectiveness research reported by interviewees likely has some overlap with the databases. The two databases do not appear to have overlap.

studies) (54 percent) comprise the largest group. Research syntheses (reviews and modeling studies) (33 percent), and experimental head-to-head studies (13 percent) also represent a significant proportion of research activities. Among observational studies 23 percent are registry studies and the rest are based on other types of primary or secondary data. Among the trials identified by the interviews, the majority are conducted at a small number of research organizations. They tend to include features of efficacy trials such as restricted inclusion criteria and use of standard operating procedures (SOP) in order to ensure the internal validity of study findings. A relatively small group of studies (approximately 45) were identified as “pragmatic” trials. This is not entirely surprising due to the some of the current impediments to conducting pragmatic trials (Luce, 2008). Please see further discussion on p. 8

We asked respondents to note what proportion of their work focused on specific types of treatments such as prescription drugs, biologicals, invasive therapies, and other types of treatments. Overall, research portfolios tend to be concentrated on specific types of treatments by the focus of the

organization. Pharmaceuticals were a major focus of ongoing research activities, though interviewees were also very likely to report research on biological agents, devices, behavioral interventions and invasive procedures as areas of comparative effectiveness research. Within large organizations that have substantial research portfolios in comparative effectiveness research, respondents were more likely to report that their research is balanced across the variety of treatments included in the list (Appendix B).

Cost of Comparative Effectiveness Research

The summary below provides an illustration of the general magnitude of the investment in comparative effectiveness research (Figure 3). Neither Clinicaltrials.gov nor HSRProj publish funding amounts, therefore interviews with funders and researchers are the sole source of these data.

As Figure 3 shows, the general range of cost for head-to-head randomized trials is extremely broad, from \$400,000 to \$125 million.¹⁶ This is reflective of the high cost of conducting effectiveness trials, which generally involve large numbers of enrollees, coordination of multiple sites, and long time

horizons to collect data. Within randomized trials, however, there were two commonly cited cost groupings from \$2.5 million to \$5 million for smaller studies, and \$15 million to \$20 million for large trials. While there continues to be debate over the extent to which some of the large trials that have been conducted are truly comparative effectiveness research, there is agreement that the costs can be very high. Of the 17 studies identified during our as trials that are “comparative effectiveness research” these range in cost from \$2.2 million to \$300 million (see Appendix C).

The cost of observational studies is also broad, due to the range of study types included in this group. Observational studies may range from as little as \$25,000 to as much as \$38 million. Studies at the high end of this range of cost are generally large cohort studies conducted over a long period of time. These studies are not randomized but otherwise may have the same study design characteristics that drive the high cost of randomized controlled trials (large number of enrollees, multiple sites, long duration). Large prospective cohort studies may cost several million dollars and registry studies may cost between \$800,000 and \$6 million, with most multi-year studies falling at the higher end of this range. One rule of thumb

Figure 3: Cost of Comparative Effectiveness Research

	Head to Head Trials with elements of real-world setting	OBSERVATIONAL STUDIES		Syntheses (Simulation/ Modeling or Systematic Review)
		Registry Studies	All Other Observational Studies (Primary and Secondary Data)	
Range of Cost Per Study	\$400k-125m	\$800k-5m	\$25k-38m	Modeling: \$75k-300k Systematic Review: \$30k-500k
Approximate Cost of a Typical Study	\$2.5-5m for smaller studies; \$15-20m for larger studies	\$2m-4m*	\$100k-250k for small studies, less than 2 years; \$1.5m-3m for larger, lengthier studies	Modeling: \$100k-200k Systematic Review: \$200k-350k

* One rule of thumb used by some interviewees was \$1.5m per year.

PRAGMATIC TRIALS

According to Tunis et al., the primary features of a pragmatic trial are that they:

- 1) Select clinically relevant alternative interventions to compare;
- 2) Include a diverse population of study participants;
- 3) Recruit participants from heterogeneous practice settings; and
- 4) Collect data on a broad range of health outcomes (Tunis, 2003).

To date, however, pragmatic trials have not been widely implemented. Luce and colleagues provide an informative case study of two pragmatic trials that have been conducted as public-private partnerships with manufacturers during the mid-nineties (Luce, 2008). The authors cite several barriers to implementing pragmatic trials, including the high cost and long length of time for pragmatic trials to be completed; the risk of producing evidence that may not support marketing objectives, and the limited demand for high-quality effectiveness data (Tunis, 2003). Despite the potential utility of pragmatic trials outlined by Luce and colleagues, the authors suggest that minimal FDA guidance on conducting pragmatic studies as phase IIIb trials before the drug is approved for sale is a major limitation to adopting pragmatic designs. Perhaps for this reason, Luce and colleagues say they have only identified a total of three private partnerships that conduct pragmatic trials.

mentioned by a few interviewees is that large multi-site registries may cost approximately \$1.5 million per year, though some cost substantially less. Retrospective database studies tend to be less expensive and cluster around \$100,000 to \$250,000.

Like retrospective database studies, systematic reviews and modeling studies tend to be less expensive and narrower range of cost, in part because these studies are based on existing data. The cost for modeling studies ranged from \$75,000 to \$300,000, with many clustered between \$100,000 and \$200,000. It is important to note, however, that this may not include the cost of procuring data. Systematic reviews may cost from \$100,000 to \$500,000, with many clustered between \$200,000 to \$350,000.

Infrastructure needs

Two additional themes were identified over the course of the interviews: the need for additional training in the methods and conduct of comparative effectiveness research, and the need to bring researchers together to discuss the relative contributions of randomized controlled trials and observational studies in comparative effectiveness research.

With regard to existing research capacity, most of our interviewees said that they have additional capacity to expand their current research activities in comparative effectiveness research. A few of our interviewees noted that they believe they have the capacity to expand their activities “two or three fold” without major new investments in personnel or training. Above this level, however, there may be difficulties finding appropriately trained researchers to conduct comparative effectiveness research.

Despite the availability of some additional capacity to conduct comparative effectiveness research, some of the interviewees noted that they have had difficulty finding adequately trained researchers to conduct comparative effectiveness research. The problem is exacerbated by what many view as a fundamental philosophical difference between researchers who are academically trained in observational research, and those who are trained on the job to conduct clinical trials. Several respondents noted that these differences likely arise because the majority of researchers are trained in either observational study methods or randomized trials, but rarely both.

Depending on an individual researcher’s training background, they may have a limited awareness of the unique contributions of randomized trials and observational studies.

Though there is great interest in developing new models for conducting randomized controlled trials, there is also an array of new analytic techniques that are now used to enable researchers to draw valid inferences from observational data. Despite these new advances and because few individuals are trained in both approaches, it takes time for innovations to reach academic centers that tend to focus on particular study designs and techniques. A lack of awareness of the contributions of observational research was mentioned on several occasions as the primary reason that study sections and peer review panels struggle to evaluate proposals and articles on comparative effectiveness studies.

Despite some disagreement about the benefits of various observational study designs, most individuals interviewed as part of this study felt that randomized controlled trials, observational studies (including registry studies, prospective cohort studies, and quasi-experiments), and syntheses (modeling studies and systematic reviews) are complimentary strategies to generate useful information to improve the evidence base for health care. Furthermore, many participants agreed that as comparative effectiveness research evolves it will be critical to develop a balanced research portfolio that builds on the strengths of each study type.

Discussion

Our study revealed more than 600 comparative effectiveness studies ongoing in 2008 in the United States. This is more than commonly assumed by policymakers who are debating the merits of a new entity focused on comparative effectiveness research.

It is likely that our estimates of the volume of comparative effectiveness research represent a lower-bound of ongoing studies. Due to the limited scope of this project, it was not possible to survey all of the major pharmaceutical companies, contract

TRAINING AND CAREER DEVELOPMENT SUPPORT FOR COMPARATIVE EFFECTIVENESS RESEARCH

Formal training in comparative effectiveness research is emerging as this area of investigation and funding grows. AHRQ supports research trainees working with AHRQ's EPCs and as part of the DEClIDE Network. However, there are few formal programs that train individuals in the specific approaches discussed. In the interviews respondents mentioned two particular post-doctoral training programs they felt were designed to teach researchers how to conduct effectiveness research. The first is the Duke Clinical Research Institute (DCRI), which offers a fellows program for fellows and junior faculty. Fellows studying clinical research may take additional coursework and receive a Masters of Trial Services degree in clinical research as part of the Duke Clinical Research Training Program. The second is the Clinical Research Training (CREST) Program at Boston University. The CREST program trains researchers in aspects of clinical research design including clinical epidemiology, health services research, bio-behavioral research and translational research. Both the DCRI and CREST programs have a strong emphasis on clinical research of randomized experimental study designs and methods of conducting observational studies.

There are also some emerging sources of support for young researchers interested in developing a career in comparative effectiveness research. The NIH funds K30 awards are available to support career development of clinical investigators and new modes of training in theories and research methods necessary to educate independent clinical researchers. The program's goal is to produce researchers who are knowledgeable about the issues associated with conducting sound clinical research. These programs include patient-oriented research on epidemiologic and behavioral studies, and outcomes or health services research (NIH, 2006).

As of January 2006, the Office of Extramural Affairs lists 51 curriculum awards funded through the K30 mechanism. In November 2007, AHRQ released a Special Emphasis Notice for Career Development (K) Grants focused on Comparative effectiveness research (AHRQ, 2007). Four career awards are slated to support development of generation and translation of scientific evidence by enhancing understanding and development of methods used to conduct comparative clinical effectiveness.

research organizations, or academic institutions that may be conducting comparative effectiveness research. Arguably, we have also used a reasonably restrictive definition of comparative effectiveness research. Expanding the definition to incorporate studies on process of care or systems-level research would increase the number of ongoing studies.

Nevertheless, it is clear that comparative effectiveness research represents a small proportion of current health research. The studies we identified in Clinicaltrials.gov and HSRProj represent five percent or less of the new studies added to these sources each year.

Our findings further demonstrate that there is a substantial range in cost of comparative

effectiveness studies, as might be expected due to the wide range of study questions and designs that comprise this area of research. The number of data collection sites included in a study; the number of patients and duration of study follow-up; and whether the cost of medication or personnel are included in reported cost estimates are the factors mostly likely to influence cost.

The data show there is a magnitude of cost difference between research syntheses and large head-to-head trials. And while the general rule of thumb is that head-to-head trials cost more than observational studies, this is not always the case. To the extent that observational studies, including registry studies and large prospective cohort studies, incorporate study characteristics such as

collection of new data, longer timeframes with multiple follow-up period, and data on clinical endpoints from multiple institutions, these studies will be costly. Potentially at the same level of expense as some head-to-head trials.

The database sources suggest cancer treatment is far and away the most common treatment that is the focus of comparative research in clinical trials. Though it was not possible to quantify the magnitude of research activity focused on specific treatment types overall, the interviews suggest that researchers are conducting comparative effectiveness research on a broad array of treatments, including behavioral therapy and a range of surgical or minimally-invasive therapies.

The study revealed that tracking comparative effectiveness research is no easy matter. Existing databases have serious limitations and within organizations that fund and/or conduct comparative effectiveness research there is no consistent way to track research by study design. Poor coordination is a central challenge to identifying comparative effectiveness research. In the context of the database analysis, the format of study records and limited ability to search for studies by method pose limitations to identifying studies by design type. In particular, study abstracts in HSRProj are not all formatted to reflect key methods, so it was not always possible to reliably identify studies by study design. In the interviews, funders and researchers also noted the difficulty tracking of research by study design since research portfolios tend to be organized by topic or research group. For this reason it was difficult for some participants to extract relevant studies to meet our definition of comparative effectiveness.

Some interviewees commented that they believed it was not possible to conduct a census of ongoing comparative effectiveness research activities across the public and private sector due to the number of unique institutions conducting research and the breadth of research activities that may be considered comparative effectiveness research. The proprietary nature of some lines of

research was also listed as an impediment to fully assessing comparative effectiveness portfolios.¹⁷ The project acknowledges that at present it is not possible to conduct a full accounting of comparative effectiveness research in the United States, but also demonstrates that even with a relatively modest review, there is a sizable volume of comparative effectiveness research.

Definitional boundaries in comparative effectiveness research are extremely challenging to resolve. While it is reasonably straightforward to identify head-to-head, or comparative studies, there are differences of opinion regarding which types of treatments should be considered within the scope of comparative effectiveness research. We stressed during interviews that studies looking at adherence and process of care are not part of our definition of comparative effectiveness research; however, some interviewees felt strongly that these studies should be included due to the interaction between treatments and process of care, which they felt were both important aspects of comparative effectiveness.

Conservative management, in particular, blurs the lines of process of care. Some argue that certain types of care management should not be included in comparative effectiveness

research, while others contend that process measures are central to care delivery and effectiveness research. In the analysis of studies in Clinicaltrials.gov and HSRProj we sought to exclude studies focused on process of care. In HSRProj, for example, we elected to exclude 30 studies that were identified in the initial search because they focused on managerial or process of care issues. Since the field of HSR is more likely to focus on research questions related to health systems delivery, this is not particularly surprising. However, we excluded these studies to maintain a consistent definition throughout the project.

A related definitional issue is the challenge of drawing a line between efficacy and effectiveness research. As discussed, there are multiple criteria used to identify effectiveness studies, each on a continuum (Gartlehner, 2006). In the process of conducting interviews we attempted to clarify these distinctions and ensure that all included studies are effectiveness studies. However, since the interview data are self-reported, there was no way to ensure all studies conformed to our definition. In searching Clinicaltrials.gov for comparative effectiveness research, we separated studies by their phase of development in order to illustrate differences between phase III pre-approval

studies, which include efficacy studies that have elements of effectiveness research, phase IV post-marketing surveillance studies, and observational studies, most of which are effectiveness research.

The limited degree of coordination among comparative effectiveness studies, coupled with the definitional challenges that have been identified are both critical issues that hinder the ability to accurately assess the state of current research, identify gaps in knowledge, and set new research priorities for the future. The findings in this study illustrate that the budget for a national research agenda on comparative effectiveness research will depend greatly on the study designs determined to meet comparative effectiveness research objectives. For this reason it is crucial that the process of developing a comparative effectiveness research agenda is transparent and involve stakeholders with multiple methodological perspectives. Only by improving understanding of current research and coordinating future research activities can we ensure that comparative effectiveness research will realize its full potential and contribute meaningful information to improve health and health care in the United States. ■

About AcademyHealth

AcademyHealth represents a broad community of people and organizations with an interest in and commitment to using health services research to improve health care. We promote interaction across the health research and policy arenas by bringing together a broad spectrum of players to share their perspectives, learn from each other, and strengthen their working relationships. Together with our members, AcademyHealth is dedicated to improving the knowledge base of health care decision-making by supporting the professional development of those who conduct and use health services research, advocating for the tools and funding necessary to do this important work, and helping to translate HSR findings into policy and practice.

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Sources

1. Agency for Healthcare Research and Quality (AHRQ). "Special Emphasis Notice: AHRQ Announces Interest in Career Development (K) Grants focused on Comparative effectiveness research." <http://grants.nih.gov/grants/guide/notice-files/NOT-HS-08-003.html>. November 21, 2007.
2. Agency for Healthcare Research and Quality (AHRQ). "About the Effective Health Care Program." <http://effectivehealthcare.ahrq.gov/aboutUscfm?abouttype=program#SG>.
3. Agency for Healthcare Research and Quality (AHRQ). "AHRQ Launches New "Effective Health Care Program" To Compare Medical Treatments and Help Put Proven Treatments into Practice." www.ahrq.gov/news/press/pr2005/effectivepr.htm.
4. Avalere Health. 2008. *Patient and Clinician Participation in Research Agenda Setting/ Lessons for Future Application*. www.avalerehealth.net/research/docs/Patient_Clinician_Research_Participation_White_Paper.pdf.
5. Boston University. "Boston University Clinical Research Training (CREST) Program." www.bumc.bu.edu/Dept/Content.aspx?DepartmentID=353&PageID=5352.
6. *Clinicaltrials.gov*. "About Clinicaltrials.gov." <http://Clinicaltrials.gov/ct2/info/about>. April 3, 2008.
7. Congressional Budget Office. 2007. *Research on the Comparative Effectiveness of Medical Treatments*. Publication No.2975.
8. Congressional Research Service. 2007. *Comparative Clinical Effectiveness and Cost-Effectiveness Research: background, History, and Overview*. Order Code RL34208.
9. Food and Drug Administration. "Patient Participation in FDA Regulatory Issues." www.fda.gov/oashi/patrep/pindex.html.
10. Gartlehner, G. and R.A. Hansen, "A Simple and Valid Tool for Distinguishing Efficacy from Effectiveness Studies." *Journal of Clinical Epidemiology*, Vol. 59, No. 10, 2006, pp. 1040-8.
11. Gliklich, R.E. and Dreyer N.A., eds. April 2007. *Registries for Evaluating Patient Outcomes: A User's Guide (Prepared by Outcome DEcIDE Center [Outcome Sciences, Inc. dba Outcome] under contract No. HHSA29020050035ITOI)*. AHRQ Publication No. 07-EHC001-1. Rockville, MD. Agency for Health care Research and Quality (AHRQ).
12. Institute of Medicine. 2007. *Learning What Works Best: The Nations Need for Evidence on Comparative Effectiveness in Health Care*. www.iom.edu/ebm-effectiveness.
13. Last, J. ed. 1983. *A Dictionary of Epidemiology*. New York: Oxford University Press.
14. Luce, B. et al. "Can Managed Care Organizations Partner with Manufacturers for Comparative Effectiveness Research?" *American Journal of Managed Care*, Vol. 14, No. 3, 2008, pp. 149-156.
15. National Cancer Institute Care Outcomes Research and Surveillance Consortium. <http://healthservices.cancer.gov/cancers/>. 2007.
16. National Institute for Clinical Excellence (NICE). "Summary Budget Statement 31 July, 2004." <http://www.nice.org.uk/niceMedia/pdf/boardmeeting/brdsep04item12.pdf>.
17. National Institutes of Health. "K30 Clinical Research Curriculum Award." <http://grants.nih.gov/training/k30.htm?sort=inst#list>. January 17, 2006.
18. Schoen, C. et al. December 2007. *Bending the Curve: Options for Achieving Savings and Improving Value in U.S. Health Spending*. The Commonwealth Fund.
19. Shadish, W. et al. 2002. *Experimental and Quasi-Experimental Designs for Generalized Causal Inference*. Boston, NY: Houghton Mifflin Company.
20. Tunis S.R. et al. "Practical Clinical Trials: Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy," *Journal of the American Medical Association*, Vol. 290, No. 12, September 24, 2003, pp. 1624-1632.
21. Zarin, D. and T. Tse, "Moving Toward Transparency of Clinical Trials." *Science*. Vol. 319, March 7, 2008, pp. 1340-2.

Endnotes

- 1 Some favor inclusion of studies that evaluate changes at the systems-level or due to changes in processes of care, while others view prescription drugs as the primary object of analysis.
- 2 In a recent report from the Congressional Budget Office (CBO), the authors state that comparative effectiveness is “simply a rigorous evaluation of the impact of different treatment options that are available for treating a given medical condition for a particular set of patients” (CBO, 2007). An earlier report by the Congressional Research Service (CRS) makes an additional distinction that comparative effectiveness is “one form of health technology assessment” (CRS, 2007).
- 3 Examples of activities designed to prioritize and coordinate research activities include the NCI’s comparative effectiveness research Cancer Control Planet (<http://cancercontrolplanet.cancer.gov/>), which serves as a community resource to help public health professionals design, implement and evaluate comparative effectiveness research-control efforts. Within AHRQ, the prioritization and research coordination efforts for comparative effectiveness studies are undertaken as part of the Effective Health Care Program. Translation and dissemination of comparative effectiveness research findings is handled by John M. Eisenberg Clinical Decisions and Communications Science Center, which aims to translate research findings to a variety of stakeholder audiences (AHRQ, 2005). No budget information is readily available for The Eisenberg Center activities.
- 4 Examples of stakeholder involvement programs include two programs at the Food and Drug Administration focused on involving patient stakeholders, the Patient Representative Program and the comparative effectiveness research Drug Development Patient Consultant Program (FDA, 2006; Avalere Health, 2008). Other examples of stakeholder involvement programs include the National Institute for Occupational Safety and Health (NIOSH)-National Occupational Research Agenda (NORA) program, the American Thoracic Society (ATS) Public Advisory Roundtable (PAR), and the NIH Director’s Council of Public Representatives (COPR). These efforts can represent a sizeable investment in order to assure stakeholder involvement among the potentially diverse group of end-users. For example, the COPR is estimated to cost approximately \$350,000 per year (Avalere Health, 2008). From an international perspective, the National Institute for Health and Clinical Excellence (NICE) allocates approximately four percent of their annual budget (approximately \$775,000) in NICE’s Citizen’s Council and for their “patient involvement unit” (NICE, 2004).
- 5 HSRProj may be accessed at: www.nlm.nih.gov/hsrproj/
- 6 The Clinicaltrials.gov definitions of interventional and observational trials are as follows: “Interventional trials determine whether experimental treatments or new ways of using known therapies are safe and effective under controlled environments. Observational trials address health issues in large groups of people or populations in natural settings.”
- 7 First, section 113 of the FDA’s Modernization Act (FDAMA 113) mandates registration of trials testing the effectiveness of drugs treating a serious or life-threatening disease or condition (Zarin, 2008). Second, the FDA Amendments Act (FDAAA 801) mandates registration of a set of controlled clinical investigations in phase II and above of drugs, biologics, and devices subject to regulation by the FDA (Zarin, 2008). The third is a requirement imposed by the International Committee of Medical Journal Editors (ICMJE) and the World Health Organization (WHO) that trials must be registered in order to be considered for publication (Laine, 2007). ICMJE require trials whose primary purpose is to affect clinical practice (“clinically directive” trials) to be registered in a registry that is electronically searchable and accessible to the public at no charge before enrollment of the first patient. Clinicaltrials.gov is the largest of five registries that satisfy ICMJE trial registration requirements.
- 8 HSRProj is a joint effort of AcademyHealth and the Cecil G. Sheps Center for Health Services research and is funded by the National Library of Medicine. HSRProj includes a variety of public and private organizations in the database, but it has less of a focus on private or industry groups. For a list of organizations participating in HSRProj see: <http://www.nlm.nih.gov/nichsr/hsrpsas.html>
- 9 Relevant NIH records are identified through monthly searches of CRISP, a database of funded NIH projects. These records are then processed and uploaded to the HSRProj database every quarter.
- 10 Early in the interview process our respondents acknowledged the difficulty of conducting a fully representative sample of interviews due to the number of divisions within individual organizations that conduct research, and the number of projects in each division. As a result, we continued to identify participants to the point that a reasonable degree of saturation was reached – both in terms of the content of responses and referees.
- 11 Though our initial group of respondents were all identified as sponsors of comparative effectiveness research, it was often necessary to speak with multiple individuals to find the appropriate person or group responsible for comparative effectiveness research within the organization’s portfolio. For this reason the response rate among individuals is lower than might be expected for a series of key informant interviews.
- 12 We identified 13 organizations that specifically said they did not received funding for their comparative effectiveness research from external sources. This is the sample that was determined to fund or self-fund comparative effectiveness research.
- 13 Though there are many specific study designs (e.g. pre-test post-test study design), our experts felt that the three categories of study types represent the appropriate degree of granularity when asking funders about their research portfolios. During the interviews we attempted to identify research by more specific type, asking questions about pragmatic trials, registry and modeling studies, and systematic reviews.
- 14 Observational research studies include a variety of research designs but are principally defined by the absence of experimentation or random assignment (Shadish, 2002). In the context of comparative effectiveness research, cohort studies and registry studies are generally thought of as the most common study types. Prospective cohort studies follow a defined group of individuals over time, often before and after an exposure of interest, to assess their experience or outcomes (Last, 1983) while retrospective cohort studies frequently use existing databases (e.g. medical claims, vital health records, or survey records) to evaluate the experience of a group at a point or period in time.

Registry studies are often thought of as a particular type of cohort study based on patient registry data. Patient registries are organized systems using observational study

methods to collect patient data in a uniform way. These data are then used to evaluate specific outcomes for a population of interest (Gliklich, 2007).

15 A search was conducted to identify project abstracts or titles including the terms “effectiveness” and “trial”. Eighty-seven projects were identified, but none of the effectiveness studies that incorporated trial data fit our definition of comparative effectiveness because they were not comparative; were focused on cost-effectiveness; or were sub-components of a trial focused specifically on process of care measures.

16 These data are generally consistent with estimates provided by the Congressional Budget Office (CBO). With regard to randomized trials, the report notes that the “total costs for conducting an extensive trial can exceed \$100 million over the course of the study, although many trials are less expensive and some may cost only a few million dollars.” The report also suggests that the annual cost of maintaining a typical registry may be on the order of “several million dollars.” Finally, the CBO estimates that a single systematic review may cost a “few hundred thousand dollars” (CBO, 2007).

17 Some respondents had significant difficulty summarizing their comparative effectiveness research portfolios. This is due to four factors: 1) Large research organizations often have multiple research divisions, which may not coordinate research activities. As a result no one individual can summarize all ongoing research projects; 2) within large research divisions there may be hundreds of ongoing projects, a small subset of which are focused on comparative effectiveness research questions; 3) comparative effectiveness research is both relatively new and research projects are difficult to define as “comparative effectiveness research”; and 4) research studies are not generally classified by study design;

Appendix A: Comparative Effectiveness Research Focus Group Participants

Individuals with an asterisk after their names were unable to attend, but offered their guidance in the process of developing the methods framework.

Naomi Aronson, Ph.D.
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Appendix B: Grid of Comparative Effectiveness Research Study Designs and Types of Treatment

		Study Designs		
		Head-to-head trials with a usual comparator in a real-world setting (e.g. ALLHAT)	Observational study using a large, broadly representative dataset may include existing registries or creation of new registries	Systematic review / Comparative Effectiveness Review (CER) or modeling study - Emphasis is on synthesizing data from various sources
Types of Treatment	Behavioral Therapy			
	Biological Therapy			
	Conservative Management (a defined protocol for usual source of care)			
	Devices			
	Diagnostic Testing			
	Genetic Testing			
	Invasive procedure (e.g. surgery), including minimally-invasive procedures			
	Other Outpatient Services			
	Pharmaceuticals			
	Physical Therapy			
	Screening			
	Watchful Waiting			

Appendix C: Comparative Effectiveness Research – Trials

The following table is a list of 17 randomized controlled trials that have been referenced in the course of our interviews as “comparative effectiveness studies.” However, among research funders and researchers included in our interviews, there is significant disagreement as to whether the studies listed below are truly comparative effectiveness studies. This definitional issue will be important to resolve as discussion of comparative effectiveness research evolves. All of these studies have been completed with the exception of the CATT and Daily Dialysis trials, which are currently on going. The daily dialysis trial is scheduled to be completed in 2009.

Title	Sponsor(s)	Description	Population Subset(s) of Interest	Number of Participants	Study Duration in Months (Years)	Total Cost
Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial	National Heart, Lung, and Blood Institute (NHLBI)	A clinical study to test three treatment approaches (intensive lowering of blood sugar levels compared to a more standard blood sugar treatment; intensive lowering of blood pressure compared to standard blood pressure treatment; and treatment of blood lipids by a fibrate plus a statin compared to a statin alone) to determine the best ways to decrease the high rate of major CVD events among people with type 2 diabetes who are at especially high risk of CVD.	NA	10,251	48-96 (4-8) per patient	about \$300 million
Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)	National Heart Lung and Blood Institute (NHLBI)	A practice based clinical trial with two components: To determine whether newer antihypertensive agents, such as ACE inhibitors, calcium blockers, and alpha blockers, reduce incidence of coronary heart disease (CHD) in high-risk hypertensives when compared to long established, inexpensive diuretics; To determine whether reduction of serum cholesterol with pravastatin, an HMG-CoA reductase inhibitor (lipid lowering component), reduces total mortality in moderately hypercholesterolemic older hypertensives	African American	42,418	106 (8)	\$83,170,059
Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)	National Institute of Mental Health (NIMH)	Compared the effectiveness, side-effects and cost-effectiveness of older antipsychotic medication (Perphenazine) to newer medications such as Clozapine, Risperidone, Olanzapine and Quetiapine to treat schizophrenia and Alzheimer's Disease.	NA	Schizophrenia: 1460; Alzheimer's Disease: 450	33 (2.75); Schizophrenia: 24; Alzheimer's Disease: 9	\$67 million
Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial	Department of Veteran Affairs (VA)	A randomized controlled trial comparing PCI plus intensive medical therapy and intensive medical therapy alone in reducing all cause mortality or nonfatal MI in patients with documented myocardial ischemia who meet an AHA task force Class I indication for PCI.	NA	2,287	(7)	\$35 million
Comparison of AMD Treatments Trials (CATT): Lucentis - Avastin Trial	National Eye Institute (NEI)	A study to compare the relative safety and effectiveness of Lucentis (ranibizumab) and a low-cost alternative, Avastin (bevacizumab) currently used to treat advanced age-related macular degeneration (AMD).	aged 50+	1,200	24 (2) per patient	Trial is ongoing; costs not yet available

Appendix C: Comparative Effectiveness Research – Trials (Continued)

Title	Sponsor(s)	Description	Population Subset(s) of Interest	Number of Participants	Study Duration in Months (Years)	Total Cost
Daily Dialysis	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	An RCT to compare the conventional Hemodialysis, 3 days per week with daily HD, 6 days per week to determine composite of mortality with the change over 12 months in left ventricular mass, and to determine a composite of mortality with the change over 12 months in the SF-36 RAND physical health composite (PHC) quality of life scale.	NA	250	12 (1) per patient	\$3.2 million FY2008, \$0.5 million FY2009
Diabetes Control and Complication Trial (DCCT)	National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	A Clinical Study that compared the effects of two treatment regimens—standard therapy and intensive control—on the complications of diabetes.	NA	1,441	(10)	\$169 million FY 1982-1995
Diabetes Prevention Program (DPP) Clinical Trial	National Institute of Diabetes and Digestive and Kidney Disease (NIDDK)	Compared the effectiveness of intensive lifestyle change (goal of 7% weight loss; 150 minutes physical activity/week) with treatment with Metformin to slow development of type 2 diabetes in high-risk patients with impaired glucose tolerance.	55% Caucasian, 20% African American, 16% Hispanic, 5% American Indian, 4% Asian American	3,234	(3)	\$176 million FY 1994-2002

Appendix C: Comparative Effectiveness Research – Trials (Continued)

Title	Sponsor(s)	Description	Population Subset(s) of Interest	Number of Participants	Study Duration in Months (Years)	Total Cost
Medical Therapy for Prostatic Symptoms (MTOPS)	National Institutes of Health (NIH)	A study that tested whether the oral drugs finasteride (Proscar®) and doxazosin (Cardura®), alone or together, could further delay or prevent further prostate growth in men with Benign Prostatic Hyperplasia (BPH).	men	3,047	(10)	\$57 million
National Emphysema Treatment Trial (NETT)	National Heart, Lung, and Blood Institute (NHLBI), the Center for Medicare & Medicaid Service (CMS), Agency for Healthcare Research and Quality (AHRQ)	A study to determine the role, safety, and effectiveness of bilateral lung volume reduction surgery (LVRS) in the treatment of emphysema and to develop criteria for identifying patients who are likely to benefit from the procedure.	NA	1,218	60 (5)	\$35 million
NINDS t-PA Stroke Study Group	National Institute of Neurological Disorders and Stroke (NINDS)	To test the potential benefit of t-PA when administered within 3 hours of stroke onset.	NA	624	30 (5)	\$2.2 million
Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study	National Institute of Mental Health (NIMH)	A trial to determine the effectiveness of different treatments for people with Major Depressive Disorder (MDD) who have not responded to initial treatment with an antidepressant	18-75 years; broad range of ethnic and socio-economic groups	4,041; 2,876 “evaluable”	(7)	\$35 million
STEP a.k.a. HVTN 502 and Merck V520-023 (HIV vaccine trial)	Merck & Co., Inc. and the HIV Vaccine Trials Network	An HIV vaccine clinical trial among high-risk candidates (discontinued)	NA	3,000	33 (2.75)	

Appendix C: Comparative Effectiveness Research – Trials (Continued)

Title	Sponsor(s)	Description	Population Subset(s) of Interest	Number of Participants	Study Duration in Months (Years)	Total Cost
Study of Tamoxifen and Raloxifene (STAR)	National Cancer Institute (NCI)	A clinical trial designed compare the effectiveness of raloxifene with the drug tamoxifen in reducing the incidence of breast cancer in postmenopausal women who are at increased risk of the disease.	Women, 93.4% Caucasian	19,747	(10)	\$88 million
Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)	National Heart, Lung, and Blood Institute (NHLB), Medtronic, Inc., and Wyeth-Ayerst Laboratories	Identified therapy that will significantly reduce death rates in patients with CHF resulting from ischemic cardiomyopathy or nonischemic dilated cardiomyopathy by assessing the consequences of three treatments (ICD arm, drug arm (amiodarone), and the control group) as measured by their cost-effectiveness and maintenance of physical, emotional, and social well-being.	NA	2,521	73 (6); 30 (2.5) minimum follow up per patient	Nearly \$12 million
Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)	National Institute of Mental Health (NIMH)	Study aiming to determine which treatments, or combinations of treatments (mood-stabilizing medications, antidepressants, atypical antipsychotics, monoamine oxidase inhibitors, and psychosocial interventions), are most effective for treating episodes of depression and mania and for preventing recurrent episodes.	Almost anyone 15+, including those with more than one mental disorder	4,361	(up to 5 per patient)	\$26.8 million
Treatment for Adolescents with Depression Study (TADS)	National Institute of Mental Health (NIMH)	A study examining the short- and long-term effectiveness of an antidepressant medication and psychotherapy alone and in combination for treating depression in adolescents ages 12 to 17.	NA	439	21 (1.75) per patient	\$17 million

**All studies have been completed with the exception of the CATT and Daily Dialysis trials, which are currently on going. The daily dialysis trial is scheduled to be completed in 2009.