Confidential

Evaluation of AHRQ's Pharmaceutical Outcomes Portfolio

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1. Introduction

1.1. Overview of the Pharmaceutical Outcomes Portfolio

Medications are very frequently used for the treatment and prevention of numerous medical conditions. In 1999, 62% of the U.S. civilian non-institutionalized population had an outpatient drug expense and 2.1 billion prescriptions were purchased with an average of eight prescriptions per person (AHRQ, 2003). Outpatient prescription drug expenses accounted for almost 16% of health care spending, at $94.2 billion (AHRQ, 2003). In addition to the expenditures for medications, the cost of the morbidity and mortality associated with medications was estimated at $76.6 billion in 1995 (Johnson & Bootman, 1995)[1] and $177.7 billion in 2001 (Ernst & Grizzle, 2001)[2].

AHRQ's Pharmaceutical Outcomes Portfolio has consisted of support for grants through Requests for Applications (RFAs) and has expanded to include support for the Centers for Education and Research on Therapeutics (CERTs) program. [3] The overarching program goals of the Pharmaceutical Outcomes Portfolio are:

- *Understanding benefits and risks*. Expand our knowledge about the benefits and risks and outcomes of pharmacological therapies so that better decisions can be made about how and when to appropriately use pharmaceuticals to improve health.
- *Advancing optimal use in clinical practice*. Identify opportunities and strategies to increase the likelihood that patients will receive the right treatment at the right time from their health care providers across all practice settings.
- *Helping patients and consumers derive maximum benefit*. Identify and evaluate strategies for communicating the information that patients and consumers need to make decisions about the appropriate use of therapeutics, in consultation with their health care providers.
- *Informing policies*. Provide government agencies, managed care organizations, employers and other decision-makers with scientific evidence to inform their decisions and evaluate the policy implications of their decisions.
- *Supporting the extension of education and research*. Support multi-disciplinary efforts to educate health care providers, researchers and students about how to evaluate the optimal use of therapeutics and apply scientific evidence to practice.

Specific FY'04 Office of Management and Budget (OMB) Program Assessment Rating Tool (PART) review goals for the Pharmaceutical Outcomes Portfolio include:

- Reduce congestive heart failure re-admission rates during the first six months after initial admission by approximately 2% per year through 2014;

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1 Johnson, J.A. & Bootman, J.L. (1995). Drug-related morbidity and mortality: a cost of illness model. *Archives of Internal Medicine*, 155(18), 1949-56.

2 Ernst, F. R. & Grizzle, A. J. (2001). Drug-related morbidity and mortality: updating the cost-of-illness model. *Journal of the American Pharmaceutical Association*, 41(2), 192-199.

3 Referenced in RFTO 05R000075 "Evaluation of AHRQ's Pharmaceutical Outcomes Portfolio: Request for Task Order June 8, 2005; page 2.

- Decrease the inappropriate use of antibiotics in children by approximately 2.5% per year through 2014; and
- Reduce hospitalization for upper gastrointestinal by 2% per year through 2014.[1]

1.1.1. The CERTs Program

The CERTs program is a national initiative and network of centers funded under cooperative agreements by AHRQ "to conduct research and provide education that advances the optimal use of therapeutics (i.e. drugs, medical devices, and biological products)."[4]

> *The CERTs concept grew out of a recognition that physicians and other healthcare providers need information more information about prescription and non-prescription medications. Although some information is available through the pharmaceutical industry, continuing medical education programs, professional organizations, and peer-reviewed literature, comparative information about the risks and benefits of new and older agents and about drug interactions is limited.*
>
> *At the same time that medical products improve the lives of many patients, significant numbers of adverse events and inappropriate product use cause serious impairment to the health of others. Guidance on appropriate product use, prevention of errors and adverse effects, and cost-effective use of new and existing products is limited, indicating that health professionals need more complete information about the drugs and biologics they prescribe, the devices they use and what practices associated with their use need improvement. To address these issues, Congress authorized the CERTs demonstration program as part of the Food and Drug Administration Modernization Act of 1997. AHRQ was given responsibility for administration of the program. AHRQ awarded the first CERTs cooperative agreements in September 1999; the full CERTs program in December of that year was made part of the Healthcare Research and Quality Act of 1999 (Public Law 106-129).*
>
> *The goals for CERTs were such that AHRQ did not have adequate resources to achieve the goals of the legislation. In order to compensate, the program was designed to allow the program grantees to generate funds from other organizations. Additionally, AHRQ designed the program to allow for continued involvement of government program staff through the cooperative agreement mechanism.*
>
> *In September of 1999, four CERT research centers and a Coordinating Center were funded and three other centers were funded in 2000. Dr. Hugh Tilson was appointed as the Chairperson of the Steering Committee. The Steering Committee consists of representatives of the private sector, the government, and the grantee institutions. The Steering Committee meets two to four times per year.*[1]

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[4] Fact Sheet: Centers for Education and Research on Therapeutics. AHRQ Pub. No. 02-P025 Interim revision April 2004

The seven CERTs centers and their target areas are:

- University of Arizona (Arizona): drug interactions, women's health
- Duke University Medical Center (Duke): cardiovascular therapies
- HMO Research Network (HMO): managed care
- University of Pennsylvania School of Medicine (Penn): anti-infectives
- University of Alabama at Birmingham (UAB): therapies for musculoskeletal therapies
- University of North Carolina at Chapel Hill (UNC): pediatrics
- Vanderbilt University Medical Center (Vanderbilt): Medicaid, vulnerable populations

In April 2006 AHRQ announced the funding of four additional cooperative agreements with the following CERTs centers: Rutgers, the State University of New Jersey will focus on mental health; the University of Iowa will focus on the elderly; Baylor College of Medicine will focus on consumers and patients; and the Weill Medical College of Cornell University will focus on medical devices.

The Pharmaceutical Outcomes Portfolio consists of both individual grants (different types) and funding of the CERTs centers; however a higher proportion of the research is the result of the CERTs program. The AHRQ RFTO requested data collection methods focused on the CERTs program (i.e. appreciative inquiry and social network analysis. Consequently, the evaluation findings in this report place more emphasis on the CERTs program than on the individual grants.

1.2. Purpose and Objectives of the Evaluation

In September 2005, AHRQ contracted with Abt Associates to evaluate the AHRQ's Pharmaceutical Outcomes Portfolio for the years 2002 to 2005[5]. The purpose of this evaluation is to analyze the impact of AHRQ's Pharmaceutical Outcomes Portfolio (Portfolio) and to determine if the program is moving toward its goals as described in the RFTO and as clarified by the FY'04 Office of Management and Budget (OMB) Program Assessment Rating Tool (PART) review. The evaluation has six primary objectives:

A. Assess progress of the Portfolio towards meeting Agency and DHHS objectives in the past four years.
B. Assess impact of Portfolio research on state and federal health care policy making.
C. Assess adequacy of Portfolio progress reporting.
D. Assess contribution and role of the Duke Coordinating Center (CC), Steering Committee, program office, and other partners to the CERTs.
E. Identify strengths of the program and most successful or promising research, especially with respect to the PART goals.
F. Assess role of Portfolio relative to other AHRQ and DHHS priorities.

For each of the study objectives, study questions were devised to operationalize the evaluation objectives. Appendix 1 displays the study questions and the corresponding evaluation objectives. This evaluation examines the original seven CERTS research centers, the Coordinating Center and individual grantees for the period 2002 through 2005. We refer to this group collectively as the

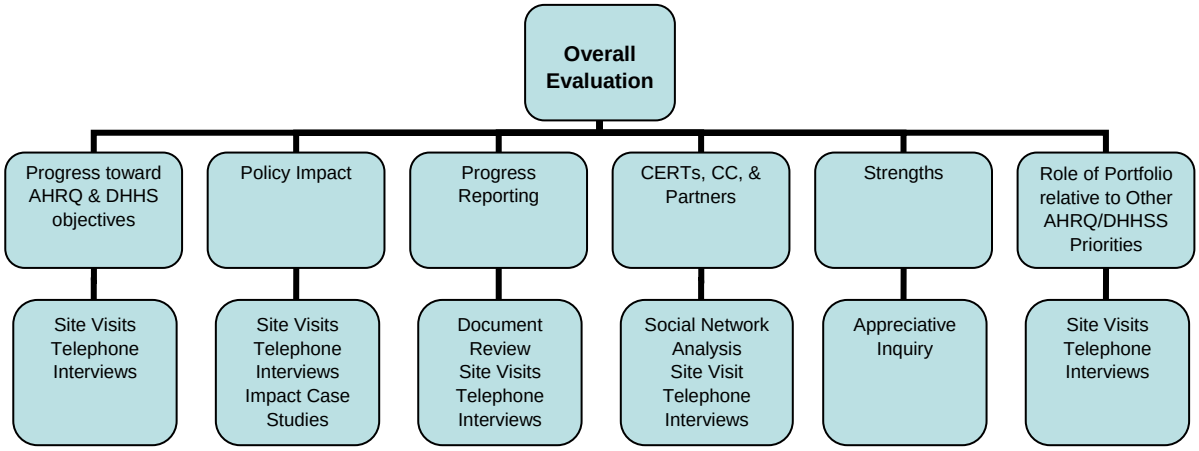
[5] The exact evaluation period varies somewhat; for example some individual research studies 'spill over' into 2006.

‘Portfolio”. The four CERTs whose funding began in 2006 are not part of this evaluation. In the balance of this report, we describe the methodology and findings of the evaluation.

2. Methods

The evaluation methods and data sources included: social network analysis (SNA), site visits and phone calls to CERTs and individual grantees, discussion with six different stakeholder groups, document review, case studies, and an appreciative inquiry (AI) exercise. Each of these sources is described below. The diverse data sources, methods, and stakeholder discussions enabled us to compare and verify independent sources of data ("triangulate") to strengthen the validity of the evaluation. The site visits and phone interviews provided information used for most of the evaluation objectives, while certain techniques such as SNA and AI were targeted to only one or two evaluation objectives. Exhibit 1 summarizes the relationship of each of these components to the overall evaluation:

Exhibit 1 Evaluation Components



2.1. Social Network Analysis

2.1.1. Purpose and Objectives

The organizational rationale of the CERTs program' 'centers mechanism' is to spread best practices within the framework of their partnerships, to coordinate resources (e.g. education, databases, administration), and to encourage inter- or cross-disciplinary work, with the goal of improving the understanding and use of pharmacological therapies. SNA labels such networks as "ego" networks, because they focus on understanding each of the egos (i.e. each individual CERT). We used SNA[6] to understand the relationships between organizations ("nodes") through visual representations of linkages between them (e.g. contacts and collaborations) and through quantitative network measures. Characterizing and mapping the structure of the overall network and the relationship of individual organizations or entities within it can help to understand CERTs collaborative processes. Our approach to social network analysis included the characterization of the relationships within and between the individual CERTs, the Coordinating Center, the Steering Committee, and other partnering organizations (i.e., government, non-profit, and for-profit entities).

[6] Wasserman, S. and Faust, K. Social Network Analysis: Methods and Applications, Cambridge University Press, Cambridge, England, 1994.

We defined the CERTs network as the Duke University Coordinating Center, the CERTs Steering Committee, the individual CERTs (Alabama, Arizona, Duke, Harvard, Penn, UNC, and Vanderbilt) and other CERTs stakeholders including government agencies and partnering organizations. We sampled each of the seven individual CERTs, the Coordinating Center, and the members of the Steering Committee. We used the UCINET 6 software package to draw sociograms (network graphs) and to calculate quantitative network measurements.

Based on discussions with the client, the analysis focused primarily on the CERT network as a whole and secondarily on the networks of each of the CERTs and the CERT Coordinating Center. The analysis of networks was guided by the following questions:

- What does the CERT Network look like?
- What is the shape of the individual CERTs network and how does that relate to their research focus?
- Who are the key entities within each of the CERTs' individual networks?
- What is the level of interdependence or independence of the different CERTs network actors from each other?

2.2. Site Visits and Discussions

We conducted discussions and site visits with six Portfolio stakeholder groups: CERTs investigators, Portfolio grantees, AHRQ representative, Steering Committee members, CERTs partners, and policymakers. Forty-eight individuals associated with the Portfolio were interviewed. Exhibit 2 shows the distribution of stakeholders by type.

Exhibit 2: Distribution of Stakeholder Discussions

Stakeholder Group	Respondents
CERTs or CC	38
Portfolio Grantees	4
AHRQ	1
Steering Committee	1
Partners	1
Policymakers	3
TOTAL	**48**

Steering Committee members interviewed were the chair, two outside policymakers, and the principal investigators (PI) of the CERTs research centers and the CC. We visited on site four of the CERTs research centers (Duke, HMO, Penn, and UNC) and the CERT Coordinating Center. The site visits included in-person semi-structured discussions with the principal investigators (PI), CERTs investigators, and staff at each center. We conducted telephone discussions with the CERT PIs and other investigators at the three other centers (Arizona, UAB, & Vanderbilt).

Exhibit 3 shows the distribution of respondents across the CERTs.

Exhibit 3: Respondents by CERT

CERTs	#	%
Arizona	4	10.5%
Duke	7	18.4%
HMO	4	10.5%
Penn	5	13.2%
UNC	8	21.1%
UAB	4	10.5%
Vanderbilt	2	5.3%
CC	4	10.5%
TOTAL	38	100.0%

In addition to the 48 individuals who were interviewed, several additional external respondents with no affiliation to the Portfolio were sought to discuss briefly their familiarity with the CERTs program and AHRQ's pharmaceutical work. Of those respondents, one was from a university-affiliated medical school pharmacy program and was familiar enough with the program to answer questions, and another was from a federal agency who indicated some knowledge (but ending a year and a half ago) of the program.

Purposive sampling was used to select respondents who were knowledgeable, involved participants in the work of their organizations. Different purposive sampling strategies and criteria were used for each of the six stakeholder groups. For all stakeholder groups except external respondents, we compiled a list of potential respondents in each group (e.g. CERTs investigators, Steering Committee members, Portfolio grantees) from administrative documents and public data sources (e.g. CERTs website). AHRQ's representative was selected based on degree of involvement with the CERTs program. For the CERTs discussions, PIs were always selected; other investigators were selected based on their perceived involvement with their CERT (based on websites, project and publication databases) supplemented by CERT staff recommendations when needed. Participation was also affected by the availability of individuals on the day(s) of the site visit. We selected Steering Committee chair and other stakeholders (except CERT PIs) based on their organizational affiliation to obtain representation from key stakeholder and potential end users of CERTs education and research initiatives.

Individual Portfolio grantees were selected based on the attributes of their grant research. The Portfolio applications included 22 grants, 8 of which were the CERTs applications which were excluded. Two grants awarded to CERTs investigators who had already been selected were excluded. Since the evaluation period was for 2002-2005, 4 grants not completed at the time of the evaluation were excluded. One grant was initiated and completed within the evaluation period and was selected; however the remaining grant time periods overlapped on either end of the evaluation time period (2002-2005) but were completed by the time of the interviews (Fall 2006). One investigator held 2 grants and was selected. The remaining respondents were selected based on whether their research focused on a topic relevant to the PART goals. Using this approach, we selected 4 grantees representing 5 Portfolio grants.

We identified Partners based on their connection to a CERT project that was selected as a case study. Policymakers were selected based on the organization they represented and its relevance as an end

user of the CERTs research. Two policy makers were also members of the CERT Steering Committee. Outside respondents not affiliated with the CERTs program were selected from a list of referrals from evaluation team member contacts.

2.3. Document Review

We collected and used relevant and available program and supporting documents: Investigator Annual Progress Reports to AHRQ; other administrative program documents and databases, and relevant documents external to the program. One important use of the document review was to provide background information on the research to facilitate the discussion process.

2.4. Impact Case Studies

2.4.1. Purpose and Objectives

We developed case studies to assess the impact of several key CERTs projects. A primary objective of the case studies was to assess the impact of Portfolio research on state and federal health care policy making by identifying and describing where Portfolio research findings had a substantive impact on policy. The evaluation study questions addressed at least in part by the impact case studies were:

1. What have been the program impacts?
2. Have outputs/outcomes had impacts on clinical practice, policies?
3. Do program outcomes/impacts reflect program goals and AHRQ/DHHS priorities?

A secondary objective of the case studies was to identify, if possible, the mechanisms that led CERTs' projects to have the impact that they did. Four impact case studies were chosen using criteria described below.

2.4.2. Case Study Selection

The goal of the case study selection process was to identify a subset of the most potentially relevant case studies from a list of 296 CERTs projects. From this subset a purposive sample of four case studies was selected based on input from the Abt research team, Dr. Sheila Weiss (Abt's consulting pharmacoepidemiologist), and AHRQ. The first phase of case study selection involved applying inclusion and exclusion criteria based on the proposed evaluation plan and timeframe of the evaluation. The second phase involved characterizing and coding the projects that met the inclusion and exclusion criteria based on relevant characteristics. The third phase was selecting with AHRQ the final 4 projects for development into the case studies. The various data sources that were used for case study selection and nomination were:

- CERTs project database from Coordinating Center
- CERTs publications and presentations
- Review of other CERTs documents (e.g. progress reports, strategic plans)
- Data obtained from discussions with CERTs investigators

Case studies were selected from the CERTs project database maintained and provided by the Coordinating Center received in January 2006. The database included 296 projects, to which the

inclusion criteria were applied. The project had to be a "core" CERTs project (i.e. funded at least in part by an AHRQ CERTs grant or supported at least in part by the administrative core funded by an AHRQ CERTs grant)[7] in the Coordinating Center database and marked completed [8] in the Coordinating Center database as of January 2006. From the original list, 127 projects qualified. We applied the following exclusion criteria: From the original list, 127 projects qualified. We applied the following exclusion criteria:

- The project had associated publications published outside the period 2002-2005.[9]
- The project was completed[10] outside the evaluation period 2002 to 2005.
- The date of the project was unclear from the database, but was mentioned in the 2001-2002 Annual Report.
- The project was a feasibility study, workshop, think tank, or involved committee participation.
- There was no associated publication, and the project was not identified as having an impact by colleagues within own or other CERTs.

The 68 projects remaining after the application of these criteria were coded and classified as follows:[11]

- CERT(s) and CERTs investigator(s) involved
- Output types (e.g. research publication, curriculum, guideline)
- Level of Impact (Tunis and Stryer classification scheme)[12]
- Highest Location of Impact (national > regional > local)
- PART Goals addressed
- AHRQ Pharmaceutical Outcomes Portfolio goals addressed
- CERT program aims addressed
- Stakeholder groups impacted (e.g. professional society, government agency)
- Acknowledgement and description of the project's impact from the CERTs investigators
- Additional characteristics of the project that support its impact or can further guide selection and nomination of case studies

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7 This description of a CERTs project was provided by the CERTs Coordinating Center

8 A project wa considered completed when the analysis is done and the results are being presented or a manuscript is being written or published. Completion was determined by the CERT.

9 If a manuscript was published on-line within the timeframe it was included.

10 The completion dates of projects were determined from 1) the dates provided in the database or 2) associated publication dates within the range

11 Based on primarily on discussion data

12 The Impact of Studies funded under the Outcomes of Outcomes Pharmaceutical Research. AHRQ. October 2001. This is the perceived level of impact determined based on the information available. Level of impact: Level 1: Impact on knowledge base, future research; Level 2: Impact on policies and change agents; Level 3: Impact on clinical practice; Level 4: Impact on patient outcomes.

Sarah Shoemaker (pharmacist and researcher) and Sheila Weiss (consultant pharmacoepidemiologist and researcher) reviewed these projects using the following criteria:

- The project meets greater than 1 AHRQ Portfolio goal
- The project meets at least one of the CERTs aims
- The project is valuable research that changed policy or practice (a Level 2 or 3 impact[13])
- The impact of the project is already known (e.g. change in guidelines, policies)

The seven nominated case studies were provided to AHRQ along with the characteristics of the case studies (described above). We targeted a subset of four of the seven representing diversity across:

- CERTs involved
- Output types (e.g., curricula, reports/publications, tools)
- Perceived impact (i.e. level of impact)
- Location of impact (e.g. national, state)
- Publicized and unpublicized impacts
- CERTs, Outcomes Portfolio, AHRQ, and PART goals addressed

The following 4 cases were selected to provide examples of CERT research findings, the impact of those findings, and to identify potential mechanisms of impact: FDA Black Box warning by Dr. Wagner at the HMO CERT; QT Prolongation study by Nancy Allen-LaPointe at Duke; Tensions in Antibiotic Prescribing by Dr. Metlay at Penn; and Rickets, Vitamin D, and AAP Guidelines work of Dr. Davenport and Calikoglu at UNC.

2.5. Appreciative Inquiry

2.5.1. Purpose

The purpose of the overall evaluation was to analyze the impact of AHRQ's Pharmaceutical Outcomes Portfolio and to determine if the program has been moving toward its goals. While traditional evaluation techniques can identify problems and, when appropriately designed, areas of strength, "Appreciative Inquiry," the technique used for this portion of the evaluation is literally designed to focus on identifying those aspects of the program's foundation that have promise for the future. In addition, this technique can help encourage favorable organizational change among Portfolio stakeholders.

Appreciative Inquiry is a qualitative research technique centered on the belief that organizations have an infinite capacity to learn, innovate and create, and that they are much more likely to change in a positive and meaningful way if they explore all the things that are "right" within their organization as opposed to "wrong." AI encourages organizations to focus on possibilities rather than problems. It focuses on what is best in organizations[14] and has been used in healthcare.[15] We used AI to support

[13] Per the Tunis and Stryer criteria for Levels of Impact.

[14] Preskill, H. and Coughlan, A. Using Appreciative Inquiry in Evaluation, Number 100, Winter, 2003, Jossey Bass, San Francisco.

the evaluation of AHRQ's Pharmaceutical Outcomes Portfolio while encouraging positive organizational change by providing a structured format for AHRQ and CERTs respondents to articulate and build upon their personal, professional and organizational strengths. This methodology was designed to encourage creative thinking that would lead to ideas, solutions and ultimately a plan to further strengthen the Portfolio. The AI "workshop" was designed to answer the following research questions: (1) What do various stakeholders view as the most successful processes and outcomes of the CERTs, and (2) How can this information be used to maximize, leverage, or build upon success in the future?

2.6. Data Collection

Data collection and analysis techniques varied for each method. In this section we summarize how data we collected and analyzed data.

2.6.1. SNA Data Collection and Analysis

The analysis of the CERTs network was based on data available from internal planning or management documents (e.g., meeting minutes, memos, and progress reports), publication lists, and the data collected from the discussions and site visits. This allowed us to describe the CERTs network and assess potential mechanisms through which the network might be maintained and expanded. We defined the boundaries of the study population through official documentation and the application of participation criteria and the collation and review of CERTs publication data. The second data collection phase involved the CERTs network members, including the Coordinating Center, Steering Committee and partners mentioned above. This discussion phase aimed to verify previously collected data, to ascertain the relationships between different actors (an organization, agency, group, or individual (e.g. Steering Committee chair) in the network, and to assess processes and practices. Through the analysis of discussion-based and publication-based data, we characterized the entire CERTs network with respect to its productivity, collaboration, cohesiveness, and organization practices and processes. As part of the network analysis a "collaboration network" was created.

The CERT Coordinating Center is the primary network of analysis within this study and encompasses the entire CERT network structure. The ego (individual organizational networks of the particular CERTs) are subsets of the primary network. Data collection centered around interview questions of key CERT personnel regarding the presence, nature, and type of relation individual CERTs had with other CERTs, the Coordinating Center, other agencies (e.g. FDA, NIH), and any other entities with which the CERT collaborate. Each relationship depicted in the SNA diagrams within this analysis was validated by a triangulated data collection methodology with more than one key staff person at each CERT interviewed, through content analysis of CERT reports and documentation, and through follow-up interviews with CERT and agency personnel. Each node is labeled with the abbreviation for the entity's name or appropriate acronym. We used several measures to depict each network, including size of the network, number of ties, average distance, density, degree centralization, closeness, betweeness, and keyplayers within the network. These measures are described briefly in the analysis section and in more depth in Volume 2 Attachment 2). Relational and organizational data collected during discussions and the publication data were indexed in Excel files and then formatted

[15] See, for example, the healthcare section http://appreciativeinquiry.case.edu/practice/organization.cfm?sector=21 of the website 'Appreciative Inquiry Commons'.

for import into the UCINET 6 software package16 to calculate the measures described above and to draw sociograms (network graphs).

2.6.2. Site and Telephone Interview Data Collection

We developed guides to structure discussions with each stakeholder group. Individual discussions varied in content. The majority of respondents participated in only one discussion; however, a few CERT individuals were re-contacted because their research was selected as a case study. Abt staff and consultants with expertise in pharmacoepidemiology and patient safety, discussion techniques, appreciative inquiry, and qualitative research design developed the discussion guides. Data gathered through review of administrative documents (e.g. applications, progress reports) provided by AHRQ were used for background information on the CERTs, the investigators, and their research prior to the discussions. We developed sample questions to address each of the areas identified for data collection, and we tailored the questions for each group of respondents. After the discussion guide was drafted, the Project Officer provided input and the guide was finalized. Additionally, Abt conducted an initial site visit to the HMO Research Network CERT as a "live" data collection activity and as a pilot.

We addressed respondent questions and emphasized the need for candid contributions by respondents. Respondents were assured that the information they provided would be used without name, specific job title or by any identifier, with the exception of data provided for case studies.[17] Open-ended questions phrased in objective language were often used to encourage candor and openness at the start of a discussion. The language used in questions and the sequence of topics in the discussion guides did not imply any particular viewpoint. Probes and follow-up questions were used to obtain examples and evidence behind responses that might be initially articulated in generalizations. The primary Abt staff member who conducted the discussions is a PharmD, which facilitated dialogue about the research topics in therapeutics. Two Abt staff members conducted the on-site discussions. One led the discussion and the other took notes. Telephone discussions were conducted by one Abt staff member, recorded when respondents granted permission, and transcribed by another Abt staff member. The study approach and discussion guides were reviewed and approved by Abt's Institutional Review Board.

Discussion notes were coded using the NVivo software package to annotate and organize the information produced through the tasks outlined above. Each discussion was formatted as required for use with the software and coded. Coded reports list all text for relevant codes to facilitate the analysis, interpretation, and summary of the findings relevant to each topic. The coding reports generated from NVivo were often used as one data element that was triangulated with data from other sources. The analysis included looking at similarities and contrasts among the different stakeholder group perspectives, the context in which perspectives were offered, and review of program documents. The analysis included summaries of the findings for each objective and research question. When appropriate, across and within stakeholder level findings were distinguished.

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16 Borgatti,S., Everett, M. and Freeman, L., Ucinet for Windows: Software foe Social Network Analysis (Analytic Technologies, Inc., Harvard, MA, 2002).

17 Except for respondents (researchers) selected for the Case Studies. These respondents were asked if they would be comfortable with their name being openly attributed to their research that was being featured. A few seemed uncomfortable, so the discussion leader offered to have them review the write-up before final submission of the report.

Once common and different perspectives and themes were identified, quotes were selected to best illustrate a perspective or theme. Additionally, respondent quotes were selected based on cogency and appropriate illustration of the finding(s) being described, rather than as representative of all respondents' perspectives. The respondents' statements are represented by use of quotation marks when the statement is less than 40 words and represented by italics and indented when the statement is more than 40 words. Additionally, the statements contain the essential content provided by the respondent, but the language was edited to facilitate conveying the point. Lastly, he respondent who made a statement or the stakeholder group he/she represents is referenced either in the introduction of the statement or in parentheses following the statement. Depending on the nature and content of the statement the reference was masked at different levels. For example, if the content of the statement was particularly critical the reference was to a CERT investigator rather than to the "Name of CERT" investigator to further ensure confidentiality. We use summary terms such as "a few" and do not usually report specific numbers because the nature of the interviews generally did not include yes/no questions; each stakeholder group was asked slightly different questions, so it would be difficult to directly quantify such responses.

2.6.3. Data Collection and Analysis of Documents

Documents that were reviewed and used to inform data collection and analysis included those shown in Appendix 3. Prior to interviews, Abt staff carefully reviewed documents. Where appropriate, extracted data were used to supplement the background information on the CERTs and Portfolio grants. The annual and cumulative progress reports provided quantitative data on program outcomes (e.g. number of publications, number of presentations) as well as qualitative data (e.g. organizational structure, what the researchers consider to be the most important outcomes and impacts). We extracted much of this data from the progress reports to construct (1) An updated list of Portfolio publications, presentations, and other research outputs; (2) Descriptions of research findings and outcomes; (3) A compilation of educational trainings, courses, or curricula development funded (e.g. CME, medical school courses, and patient education websites); and (4) A list of CERTs respondents. The databases were used as one source of information about the Portfolio's productivity. We collected data on educational activities ranging from single trainings to web-based modules to address fulfillment of the educational mission.

We also quantified publications[18], books/book chapters, lectures/presentations and performed bibliometric analyses on reported publication information using standard measures of scientific productivity. Bibliometric analysis included basic counts of publications by CERTs, by year, publication type (e.g., journal article, abstract, conference proceeding) and whether a journal was high impact,[19] indicated by impact factor (IF). A journal's impact factor is based on two elements "the numerator, which is the number of citations in the current year to any items published in a journal in the previous 2 years, and the denominator, which is the number of substantive articles (source items) published in the same 2 years."18

[18] A publication list was compiled from the Coordinating Center database of publications and from updates requested of each CERT. We did not distinguish the source of funding for a publication (i.e. core versus leveraged) due to lack of ready access to such data.

[19] Garfield, E. (2006). History and meaning of the journal impact factor. Commentary. JAMA.

We compiled a breakdown of funding by source and percent of total funding from the information provided by each CERT. To evaluate the utility and effectiveness of investigator progress reporting to AHRQ as a management tool for the Portfolio, we reviewed and coded these reports for content relevant to the research objectives and questions. Common formats and information across CERTs were noted as well as inconsistencies. The site visits and discussions offered data to externally validate and/or update the data extracted from the progress reports. Evidence that addressed the following research questions was extracted from the progress reports and coded: (1) What have been the research outputs? (2) What have been the educational outputs? (3) What have been the program impacts? (4) Is investigator progress reporting complete, accurate, and timely? Is it adequate to assess inputs/outputs/outcomes/impacts?

When we report findings and when statements were pulled directly from Portfolio documents (e.g. progress reports, annual reports) the reference is provided. For example, if an output of the Arizona CERT was provided in their progress report for 2003-2004, then the finding is referenced as AZ PR 03-04, to indicated Arizona progress report (PR) for the year 2003-2004. Another example, AR Y5 indicates the annual report for year 5. The excerpts taken from Portfolio documents, research abstracts, or articles are referenced in this way. The citations for respondent statements are similar but italicized and indented if longer than 40 words.

The publication list was compiled from the Coordinating Center publication data file in addition to the updates to the list provided directly by each center and were coded for type of publication and characterized by CERT and evaluation year (2002-2005). The presentations list was compiled from the CERT website www.certs.hhs.gov. We compiled the educational outputs from the various document sources referenced above in addition to the individual CERTs websites and descriptions provided in the discussions and site visits.

2.6.4. Impact Case Study Data Collection and Analysis

The case studies relied primarily on data collected through the discussion and documentation review data sources described above. These data sources identified candidate case studies and supplied more in-depth information regarding the cases. Additional telephone discussions were conducted with the PIs to obtain further details of the case, the findings, and background on how it was able to achieve the impact. Discussions were also conducted with members of the target audience for the case study outputs, such as policymakers (CMS, FDA, NIH), clinical directors, or partners. As appropriate, discussions were conducted via telephone and took place soon after the case studies were selected. In addition to the data collected through discussions and documentation, information was gathered from a literature and media search of a topic citation to lend support to the case studies. For each case study an Internet search was conducted to identify the publication(s) of the case study, pick-up by web sites, discussions conducted with the PI, and other relevant publicly available information. The next stage involved integrating the data. For each case, a timeline of events (publications, reports, and related statements from discussions) was constructed. Given the small quantity of cases and the diversity of topics and impacts, it was difficult to identify common mechanisms of impact, so we describe mechanisms that arose in each of the case studies.

Appreciative Inquiry Data Collection and Analysis

Data were collected by a facilitator with a discussion guide during a CERT Steering Committee Meeting. Some of the questions for the workshop were derived from the discussion data component of the overall evaluation; those discussions were conducted with key CERTs stakeholders. In

addition to the AI workshop, Abt Associates also incorporated AI questions into the discussion guide used in the discussions with key stakeholders at the CERTs. Similar to the AI workshop, these questions were designed to uncover the CERTs' greatest strengths and successes to-date. Volume 2 Attachment 12 contains the discussion guide used in the exercise.

2.7. Limitations of the Methods

2.7.1. Interviews and Site Visits

We selected a sample of Portfolio researchers for either site visits or telephone interviews. Five of 8 CERTs (including the Coordinating Center) were visited, while researchers from the other CERTs were contacted by phone. Researchers who were willing and able to participate in discussions may be different from researchers who were not, and information collected in person may have differed from information collected by telephone. However, we did speak with a relatively large number of researchers chosen carefully to represent a variety of perspectives. Our use of the publicly available websites and CERTs resources to obtain additional information about their projects helped provided information about CERTS not visited. Furthermore, we used the broader program data gained from administrative data review and previous evaluations to frame the discussions.

2.7.2. Document Review

A wide variety of documents were abstracted, and abstraction was constrained only by the availability, completeness, and accuracy of the documents. The most important methodological challenge in using administrative data such as progress reports was the internal and external validity. Examples of threats to internal validity include inaccurate or incomplete citations in a publications list. Threats to external validity included missing citations or citations not truly attributable to the program. If the available documents were systematically more likely to include certain types of information (e.g. publications from earlier program years), this might have introduced bias.

2.7.3. Impact Case Studies

While we hoped to learn a great deal about the impact of the cases we chose, that understanding may be difficult to generalize and the studies selected may not always be the best examples. While we selected a variety of cases, these cases are not necessarily representative of the impacts of all CERTs products. Furthermore, the validity of the mechanisms we identified was entirely dependent on the availability of relevant data. Finally, the endpoints of the impact case studies for the purposes of this evaluation were intermediate with respect to the ultimate outcome of the therapeutic under study. Instead of measuring changes in medical practice or improvement in patient survival (the ultimate outcome), we assessed a necessary step in the process – the impact of CERTs research as a proxy for the ultimate outcome.

2.7.4. Social Network Analysis

Social network analysis can only represent the data used to create the network diagrams or measures and can tell us only a limited amount about why the network has formed as it has. In addition, the social network analysis is a snapshot in time and may not adequately address the dynamic nature of the network. Thus, changes in the collaborative nature of colleagues or centers after data collection could not be represented in this analysis. Similarly, leaves from work, the shifting workload of the

academic calendar, and the yearly funding or fiscal cycle may all affect how people recall their current social relationships and as such might be reflected in the quantity/quality of the relationships reported. These effects were partly mitigated through careful construction of the discussion guide and through secondary analysis of CERTs materials to validate reported relationships.

2.7.5. Appreciative Inquiry Exercise

The most important design limitation to this exercise within the study is that the discussion facilitated by Abt was a one-time data collection event. Ideally, appreciative inquiry is conducted as a multi-stage process, but resource constraints required that it be condensed in this case.

3. Findings

3.1. The CERTs Network: Understanding Structure, Communication & Relationships

3.1.1. The Network Structure of the CERT Community

As described above, we employed Social Network Analysis (SNA) to address the following questions:

- What does the CERT Network look like?
- What is the shape of the individual CERTs network and how does that shape relate to the CERTs' research focus?
- Who are the key entities within each of the CERT's individual networks?
- What is the level of interdependence or independence of the different CERTs network actors (an organization, agency, group, or individual such as the Steering Committee chair) from each other?

In this section we examine the networks of the individual CERTs as well as the CERT Coordinating Center. The findings are presented as sociograms and network measures for each of the individual CERTs and Coordinating Center. We discuss each of the individual CERTs before presenting the overall CERT structure surrounding the Coordinating Center. Although SNA measures are presented in a table, these measures will be described individually due to the difficulties in comparing individual organizational or ego networks with different sizes and structures directly against one another. We will present general trends and patterns of the total network of our sample. Additionally, the SNA analysis provides diagrams that illustrate the relationships CERTs have with their partners and the CERT network as a whole. They do not illustrate the intensity, frequency or nature of those relationships, but are measures of the absence or presence of a relationship.

3.1.2. HMO Research Network CERT

The HMO CERT was established in 2000 and is a Health Maintenance Organization Research Network (HMORN) through which several HMOs work together and share data to improve health outcomes and program performance. Volume 2 Attachment 1 depicts the sociogram (each node in the sociograms represents an actor) of the HMO CERT ego network (SNA labels such networks as "ego" networks, because they focus on understanding each of the individual CERTs (i.e. "egos").

The HMO CERT sociogram is unusual because it displays a portion of the underlying macro (global) structure of the total CERT network on the left of the diagram. Although the main focus of the ego network is to describe the structure surrounding individual CERTs, the overall connection of the broader CERTs program networks' relationship to each individual CERT is also important. The HMO CERT is an illustration of this broader relationship. Exhibit 5 displays the HMO CERT and other CERT network results.

Exhibit 5: CERT Social Network Analysis Measures

METRIC	HMO	DUKE	UNC	VANDERBILT	ARIZONA	PENN	ALABAMA	UNC	CC
CERT Founding Date	2000	1999	1999	1999	1999	2000	2000	1999	1999
Primary Research Area	HMO data	Cardio-vascular	Pediatric	Medicaid and VA data	Drug-drug Interactions and Women's Health	Anti-infectives	Musculo-Skeletal Disorders	Pediatric	
Size of Network	52	22	34	15	26	51	39	34	16
Number of Ties	15	27	20	8	12	22	22	20	82
Average Distance	2.11	1.82	2.00	2.03	1.95	2.55	1.97	2.00	1.58
Density	0.57%	5.84%	1.78%	3.81%	1.85%	24.44%	1.48%	1.78%	34.17%
Mean Degree Centrality	4.03	100.00	94.44	14.62	6.34	18.52	6.34	94.44	41.92
Mean Closeness	48.04	100.00	94.44	50.70	51.38	42.19	51.38	94.44	65.41
Betweeness	1.95	86.58	91.16	6.05	2.50	8.68	2.50	91.16	3.87
Keyplayers	AHRQ	CERT-CC	CERT-CC	CERT-CC	CERT-CC	CERT-CC	AHRQ	CERT-CC	CERT-Penn
	CERT-CC	AHRQ		CERT-CC	AHRQ	PCPPP	CERT-CC	AHRQ	AHRQ

Following is a brief description of the meaning of the measures in the table:

- **Network Size** The number of unique ordered pairs of actors within the network.
- **Number of Ties:** Count of the number of relationships in the network.
- **Average Distance** Average number of relations in the shortest possible connection from one actor to another.
- **Density:** The higher the density of a network, the more connected the actors.
- **Degree Centrality**: Measure of the ego actors' position within the network by counting the total number of direct connections of that actor.
- **Closeness**: Measure for networks that are fully connected and examines the "shortness" of the direct connections of the actor to other actors in the network.
- **Betweeness**: Measure of an actor's ability to be a bridge or 'go between' for other pairs of actors by being an intermediary connecting that relationship.
- **KeyPlayer:** identifies key members of the network.

Citations for these measures and more comprehensive definitions are provided in Appendix 2. As mentioned in the Methods section, these measures (except for size and number of ties) cannot be directly compared against one another due to varying network sizes and characteristics. We describe the results for each CERT and use them to understand differences in their networks.

The HMO CERT sociogram shows a fairly large network of 52 actors, one of the two largest networks in this study, with three distinct groupings. The first large group is on the right side of the figure and is the local community network in which the HMO CERT has approximately 39 actors with whom they are connected as research partners. These partners include such entities as Kaiser Permanente, University of Massachusetts, and Harvard Medical School. This core group represents 75% of the actors within the network; the majority of the relations are densely located within the HMO CERTs community research network.

The middle group comprises actors that are not only associated with the HMO CERT but also those that have connections with the CERT Coordinating Center. The final grouping on the left, as

discussed above, displays the macro structure of the total CERT network and encompasses the other CERT partners, the CERT Steering Committee, and AHRQ. The HMO CERT is unique in that its research partners are mostly health plans. The other CERTs do not have access to the breadth of data that the HMO CERT has within its network, so some of the CERTs appear to have relationships with the other CERTs primarily through data sharing. The HMO CERT's existence prior to becoming a CERT may have affected its network size. Its age may have allowed time for the network to increase its size and number of connections. The HMO CERT has a direct connection to the CERT Steering Committee, CERT Coordinating Center, and AHRQ as well as additional access to connections and resources.

Although the HMO CERT has the largest network in terms of its number of actors, it has a relatively low number of ties. Although this is a large network, there are relatively few connections per actor, suggesting that the network has opportunities for developing further relationships among its actors. The average distance within this network is slightly greater than 2, suggesting that information and resource flows have to go through on average two actors to get to the target actor. This again suggests that there are opportunities for further connections within the network. The 0.57% density within the network is very low, suggesting that the actors within the network are not be highly connected and are unevenly distributed throughout the network. For example, there are clusters of actors that appear to be close together, with connections not evenly spread across the network. The density is low, with few interconnections among actors. (The low density may be an artifact of data collection. We did not go to each connection and ask who they were connected to, because these are ego networks, the focus being on that ego network perspective.) The low density level indicates that, within this network, information and resource flow may be slowed.

There may be opportunities to create further connections among actors. The mean degree centrality is slightly over 4, which suggests that most actors within the network have few connections to other actors, which again relates to the sparse and less dense nature of the network. The closeness measure of the HMO CERT is slightly over 48, suggesting that the CERT itself is the only highly connected actor within the network compared to the other actors in the HMO CERT network. The betweeness measure of 1.95 for the HMO CERT is the lowest among all CERTs in the study sample. This could be because of the limited relationships or collaborations the HMO CERT has with the other CERTs beyond data sharing, although it may also be an artifact of the data collection process, in that the HMO CERT was the pilot site visit and they do not have a website describing partners and key players the way other CERTs did. The HMO CERT generally appears to play a liaison role between its research partners and the CERTs network as a whole and does not appear to mitigate many other relationships between the actors in the network.

Finally, the key players within this network were identified as AHRQ and the CERT Coordinating Center. This indicates that these two actors have a great deal of communication with the CERT and connects the HMO CERT with the larger CERT network and program resources. Most of the CERTs research partners are unique to the HMO CERT and are not shared among the CERT program's general preferred partners. Based on their pre-CERT existence as a network, the HMO CERT may be more active in its own research network than with other CERTS. The SNA suggests that the HMO CERT has established its own identity and research niche within the CERTs broader network, which is not surprising given this CERT's origins. The HMO CERT probably is the closest to Penn in terms of having a strong community network of partners, but it does appear as strong in that regard.

3.1.3. Duke CERT

The Duke CERT was established in 1999 and was one of the original CERTs. This CERT's main research focus is on cardiovascular therapeutics. Volume 2 Attachment 2 depicts the sociogram of the Duke CERT ego network. As can be seen in the figure, the Duke CERTs network has a star shape structure with one main group and is of medium size with 22 actors within the network. The Duke CERT is surrounded by a relatively small community research network of approximately 9 actors representing just 41% of the actors in the network, but has a very strong university connection. The Duke CERT, located in the North Carolina research triangle, is near the Coordinating Center and UNC CERT. The Duke CERT also has relationships with the Alabama, HMO and UNC CERTs. Additionally, the Duke CERT investigators expressed interest in identifying opportunities to collaborate with two of the new CERTs (Iowa and Cornell).

Examining the Duke CERT network data, we see that the overall size of the network is 22 actors, with 27 ties. Although the Duke CERT is a smaller network than the HMO CERT, it has a larger number of ties indicating the network may be relatively more connected. The average distance within this network is 1.82, thus information and resource flows have to go through on average a fewer than two actors to get to the target actor. Although this network is more connected, there is still opportunity for further connections within the network. The density within the network is low at 5.84%, suggesting that the actors within the network are not highly connected but are concentrated around the CERT. Again, this lower level of density indicates that within this network, information and resource flow could be slowed. Yet, there may be opportunities to create further connections between actors. The mean degree centrality and closeness within the network is 100, which indicates that the CERT is in the center position, the focal node, and highly connected. The betweeness measure of 86.58 indicates that the CERT plays a bridging role between its community network and the broader CERTs community. This role is further illustrated through the star shape of the network as seen in the Duke CERT sociogram. A star network can indicate that there are shorter distances between partners as compared to the HMO CERT, for example. The network (more than the metrics, because they do not vary significantly) suggests that it is easy for Duke to work with its partners. The Duke network also suggests that there are further opportunities to make connections or further develop partnerships.

Finally, the key players within this network were identified as the CERT Coordinating Center and AHRQ. Similar to the HMO CERT, this suggests that these two actors have a great deal of communication with the CERT and connects the CERT with the larger CERT network and program resources. The Duke CERT appears to have relatively few research partners, but interacts with many other CERTs. This could be due to its proximity to the Coordinating Center and desire to reach out to other new CERTs, or due to the nature of its research, which can cross into the research areas of other CERTS.

3.1.4. University of North Carolina CERT

The UNC CERT was established in 1999, one of the first four CERTs. This CERTs main research focus is on pediatric therapeutics in contrast to the other CERTs focus primarily on therapeutics in the adult population. Volume 2 Attachment 3 depicts the sociogram of the UNC CERT ego network. As can be seen in the figure, the UNC CERT exhibits a star shaped network similar to the Duke CERT with one main group and is a larger size with 34 actors within the network. The UNC CERT is surrounded by a community research network of approximately 23 actors representing 68% of the

actors in the network. The UNC CERT is close to the Duke CERT and Coordinating Center and has a strong university connection and connection with its partners in North Carolina, in part with the research triangle. The UNC CERT network illustrates relationships with the Alabama, Arizona, Duke, HMO, Penn, and Vanderbilt CERTs. Discussions with investigators, though, acknowledge the difficulty of collaborating on projects, given their focus on pediatrics. The relationships with other CERTs revealed in the UNC CERT analysis suggest only sharing of advice or methodological discussions because the perception of collaboration and actual level of collaboration were not revealed in the data.

The UNC CERT network data shows that the overall size of the network is fairly large with 34 actors and 20 ties. The average distance within this network is 2, indicating that information and resource flows have to go through on average two actors to get to the target actor. Although this network is connected, there is still opportunity for further connections within the network. The density within the network is low at 1.78%, suggesting that the actors within the network are not highly connected but are concentrated around the CERT. Again, this lower level of density suggests that within this network, information and resource flow would be slow. The star shape network suggests proximity between partners and the CERT. There are opportunities to create further connections between actors. The mean degree centrality and closeness within the network is 94.4, which indicates that the CERT is in the center position, the focal node, and highly connected. The betweeness measure of 91.16 suggests that the CERT plays a bridging role between its community network and the broader CERTs community, which is further illustrated through the star shape of the network.

The key players within this network were identified as the CERT Coordinating Center and AHRQ. Similar to the HMO CERT, this suggests that these two actors have a great deal of communication with the CERT and suggests a connection between the CERT with the larger CERT network and program resources. The UNC CERTs has many research partners and interacts with many other CERTs. This could be due to its proximity to the Coordinating Center and reaching out to other CERTs.

3.1.5. Vanderbilt CERT

The Vanderbilt CERT was established in 1999 and was one of the first CERTs. This CERT's main research focus is on therapeutics in the Medicaid and VA populations. Volume 2 Attachment 4 depicts the sociogram of the Vanderbilt CERT ego network. Its research focus on data from VA and Medicaid populations likely explains the structure of its network; the Vanderbilt CERT has a very unusual "double star" network structure with a focused star network on the left side of government agencies with the CERT Coordinating Center and the Steering Committee at its center. On the right side of the sociogram is the CERTs community research network with the Vanderbilt CERT at its core. The increased interaction among federal government agencies may be due to their research focus and government agencies' interest in the outcomes of their work. As can be seen in Attachment 4, the Vanderbilt CERTs is relatively small with 15 actors and is surrounded by a community network of approximately 12 actors representing 80% of the actors in the network. Those actors within the CERTs community network represent many government agencies, including such entities as the State of Tennessee Health Department and the Veterans Administration. The Vanderbilt CERT is a very sparse network and appears to interact only with the HMO CERT.

The Vanderbilt CERTs network data shows the overall size of the network (15 actors), with 8 ties. This is a relatively small, sparse, and relatively unconnected network. The average distance within

this network is 2.03; information and resource flows have to go through on average approximately two actors to get to the target actor. The density within the network is low at 3.81%, so the actors within the network do not appear highly connected. Again, this lower level of density suggests that within this network, information and resource flow would be slowed, but that there would be opportunities to create further connections between actors. The mean degree centrality is 14.62 and closeness within the network is 50.7. These measures are consistent with the double star structure of the network in which connections and core structure is shared among the CERT and the Coordinating Center. The betweeness measure of 6.05 suggests that the CERT plays a very limited liaison role in connecting other actors within the network.

The key players within this network were identified as the CERT Coordinating Center and the CERT Steering Committee. This suggests that these two actors have a great deal of communication with the CERT and connect the CERT with the larger CERT network and program resources. The double star structure and the metrics of the network point to the collaboration of the CERT with many more government entities as compared to other CERTs. Those government entities appear to be interdependent and have connections with one another. The Vanderbilt CERT is unusual in terms of how sparse its network of partners appears compared to others. Again, the intensity of relationships was not evident from the data. The interviews indicated that the Vanderbilt investigators collaborate extensively with TennCare and VA. In summary, these analyses suggest that the Vanderbilt CERT may focus more on its own research than on working with the other CERTs and that it has room to expand its network of partners.

3.1.6. Arizona CERT

The Arizona CERT was initially funded in 1999 at Georgetown under the direction of the same principal investigator. This CERTs main research focus is on prescription drug safety. Volume 2 Attachment 5 depicts the sociogram of the Arizona CERT ego network. As can be seen in the figure, the Arizona CERTs network has a distinct star shape structure with one main group and is of medium size with 26 actors within the network. The Arizona CERT is surrounded by a community network of approximately 15 actors representing 58% of the actors (26) in the network. The Arizona CERT maintains a methadone registry, focuses on drug safety and women's health and consequently collaborates with such partners as healthcare providers, pharmacies, and government agencies that benefit from this work. The Arizona CERT has relationships with the Penn, Duke, and HMO CERTs.

The Arizona CERT network data show a medium-sized overall network of 26 actors, with 12 ties --- a structure and density similar to the Vanderbilt CERT. The average distance within this network is 1.95, so information and resource flows have to go through on average approximately 2 actors to get to the target actor. The density within the network is low at 1.85%. The actors within the network do not appear to be highly connected based on the structure and its measures, but are concentrated around the CERT. This lower level of density suggests that within this network, information and resource flow may be slowed getting to the entire network. The mean degree centrality is 6.34 and the closeness measure is 50.38, which suggests that there are, on average, few direct connections among the actors. The CERTs focal role is mitigated by its strong connection to the CERT Coordinating Center and Steering Committee. The betweeness measure of 2.50 is very low and suggests that the CERT does not appear to play a strong bridging role between its community research network and the broader CERTS community.

The key players within this network were identified as the CERT Coordinating Center and AHRQ. Similar to the HMO CERT, this suggests that these two actors have a great deal of communication with the CERT and connect the CERT with the larger CERT network and program resources. The structure and connections of this CERT to a broader or larger network may be due to the nature of its research which lends itself to the connections this CERT makes within its network. It appears that this CERT is still developing resources and creating relationships.

3.1.7. PENN CERT

The PENN CERT was established in 2000 and its main research focus is anti-infectives. Volume 2 Attachment 6 depicts the sociogram of the PENN CERT ego network. As can be seen in the figure, the PENN CERTs network has a strong double star shape structure. The PENN CERT has a very large and strong community research network of 29 nodes out of the total size of 51, representing 58% of the network and is its own integrated micro network structure of the CERT network. The PENN CERT community research network is on the right side of the sociogram, is encapsulated by the label of Penn CERTs Public and Private Partnerships (PCPPP), and is highly evolved and dense. As a Coordinating Center member said, "*Penn has a clear leadership structure with a large number of co-investigators who are receiving some support from AHRQ and are leveraging many other partnerships.*"

On the left side of the sociogram is the second star and the main CERT ego configuration. This is also a dense and connected structure. Within that configuration is one of the key CERTs community partners (the Leonard Davis Institute) that conducts policy research and briefings that incorporate the research of the CERT. This is a powerful resource to the CERT; it allows for information regarding the CERTs research to flow into the broader community and increase the PENN CERT's opportunities for additional collaborative connections and for garnering resources outside of the CERT program. The PENN CERT also has relationships with the Duke and HMO CERTs. The Penn CERT is such a large community network that it resembles 2 networks - a very large and strong network of partners and the CERTs network. This suggests that the Penn CERT has been successful developing and leveraging partners. Additionally, there is very limited overlap of Penn's partners with the CERTs program partners, which suggests the availability of even further collaboration opportunities for the Penn CERT.

The overall size of the network is 51 actors, with 22 ties. The average distance within this network is 2.55. This is the largest average distance among the study sample networks; it is based on the dense structure in which the CERT is embedded which suggest that the CERT is as involved in its own community structure as in the CERT program and which places it in more of a liaison position for the broader network. The density within the network is low at 24.44%, thus the actors within the network are somewhat connected but are more highly linked and concentrated around the PENN CERT. The mean degree centrality is 18.52 and the closeness measure is 42.19, which suggest that there are on average many direct connections among the actors and that the CERT is a liaison between its strong community partners and the broader CERT network. The betweeness measure of 8.68 is relatively low and suggests that the CERT plays a bridging role between its community research network and the broader CERTs community, but apparently not a strong one.

Finally, the key players within this network were identified as the CERT Coordinating Center and PCPPP. This appears to correlate with the strong community research network that the Penn CERT has created and is embedded within.

3.1.8. Alabama CERT

The Alabama CERT was established in 2000 and its main research focus is on musculoskeletal disorders therapeutics. Volume 2 Attachment 7 depicts the sociogram of the Alabama CERT ego network. As can be seen in the figure, the Alabama CERTs network has a very distinct star shape structure. The Alabama CERT is a relatively large network of 39 actors with 30 actors within its community research network, representing 77% of the network. The Alabama CERTs community network is relatively connected and dense. Alabama appears to have relationships with four other CERTS, Arizona, Duke, HMO, and PENN and appears similar to Arizona, Duke, and UNC in terms of having some partners in their network. If their network wanted to work with the CERTs program partners, it is linked to that larger network. Additionally, the Alabama CERT appears to have opportunities and room to expand its network.

The overall size of the network is 39 actors with 22 ties. The average distance within this network is 1.97; information and resource flows have to go through on average fewer than two actors to get to the target actor. The density within the network is very low at 1.48%; thus, the actors within the network are sparsely connected. The mean degree centrality is 6.34 and the closeness measure is 51.38, which suggests that there are on average few direct connections among the actors and that the CERT appears to be in a liaison role between its community partners and the broader CERT network. The betweeness measure of 2.50 is low and suggests that the CERT does not readily play a bridging role between its community research network and the broader CERTS community. The key players within this network were identified as AHRQ and the CERT Coordinating Center.

3.1.9. The CERTs Coordinating Center

In the original CERTs plan, as devised by AHRQ in conjunction with the CERT Steering Committee and its partners, the CERTs Coordinating Center was to have the role of liaison between the CERTs themselves and AHRQ, the Steering Committee, preferred partners, and other government agencies. In the sociogram in Volume 2 Attachment 8, the Coordinating Center appears to be functioning as it was envisioned in the original CERTs plan, acting as the bridge between the CERTs and the other actors within the program. The Coordinating Center is the focal node in this network, dispersing information from AHRQ and the Steering Committee to the CERTs as well as bringing together outside partners with the CERTs based on research needs and interests. This appears to be both an efficient and effective way to manage the macro CERTs network to avoid duplication of effort and resources to spread information and create collaborative connections.

Looking at the Coordinating Center network measures, the size of the network is relatively small at the macro level, but is highly connected with 16 actors and 82 ties. The average distance within this network is 1.58, so information and resource flows have to go through on average fewer than two actors to get to the target actor. The density within the network is relatively low at 34.17%; the actors within the network appear to be connected most directly to the Coordinating Center. The mean degree centrality is 41.92, the closeness measure is 65.41, and the betweeness measure of 3.87 point to the liaison role the Coordinating Center plays between the CERTs, AHRQ, the CERT Steering Committee, and other partners.

The key players within this network were identified as the Penn CERT and AHRQ. It is not surprising that AHRQ is noted as a key actor within the Coordinating Center's network, but the Penn CERT role is surprising. This is likely due to the fact that the Penn CERT has a large and strong

community network and many partners, and that it connects the Coordinating Center to an even larger network and as such plays a prominent role in the network as a whole. The PENN CERT is unusual in that its preferred partners are considered key players within the network. This is because PENN has a very large community network and appears to have strategically initiated and maintained these connections.

The keyplayer algorithm is a metric designed to locate the main actors within the network diagram which (1) if removed, would fragment the network or, (2) whose position in the network indicates an opportunity to expand the network. In most of the CERTs network diagrams; the Coordinating Center appears to be a vital actor within the networks whose removal would separate the CERT from the macro CERTs network. This confirms the vital role that the Coordinating Center appears to play in connecting the CERTs to each other and to the broader network, providing further evidence that the Coordinating Center is functioning as originally designed. Respondents had only positive comments about the Coordinating Center, and the SNA results support those statements that the CC is fulfilling its role and is viewed as a partner in the network. The Coordinating Center appears to be functioning as a liaison between the CERTs, AHRQ, and the SC and to bring partners to the CERTs when possible.

In many of the CERTs AHRQ is also seen as a second key player within the CERT network. This suggests (hypothetically, of course, given AHRQ's unique role) that if AHRQ were removed from the network, it would become more fragmented. This SNA finding confirms the direct contact that AHRQ has with the individual CERTs. As noted in interviews, the role of the Coordinating Center appears to be changing and evolving into the (future) potential network structure depicted in the sociogram show in Volume 2 Attachment 9. AHRQ may be starting to have more contact and information sharing directly with the CERTs, bypassing the Coordinating Center. This evolving structure may not be the most efficient and may reduce opportunities for collaboration.

The CERTs preferred partners are those connections that appear to be garnered and maintained by the CERTs Coordinating Center. For the sake of clarity within the CERT network diagram, these partners have been signified as PP, but are shown in full within the Preferred Partner diagram. See Volume 2 Attachment 10.

The collaboration network diagram provides a graphic illustration of the extent of collaboration across all authors associated with the CERTs publications. All of the CERT PIs are located within the dense, center of the diagram illustrating collaboration with many other authors; however, because of the lack of attributes about each author (1000 authors), further inference about co-authorship is not possible to assess. See Volume 2 Attachment 11.

3.1.10. Social Network Analysis Implications

The CERT ego networks are diagrams of each particular CERTs network, taken from the perspective of the individual organization. These ego networks are representations of the relationships in which the CERTs view themselves, and therefore do not display any broader connections of those CERT partners with one another or any additional actors. SNA frequently collects data on ego networks of only those organizations directly involved within a program or particular structure. In those cases, as was done here, data are collected from representatives of those organizations to establish their ego network. As noted previously, within the ego network diagrams, each node or circle represents an individual actor and each line represents a connection or relationship to that actor. The displayed

relationship is merely dichotomous in that the nature and value of that relationship is not represented. Rather, if any connection exists --- good, bad, collaborative to consultative, it is displayed within the ego network diagram. The scope and nature of this study did not allow for the understanding of the quantity, quality, nor nature of these relationships to be fully realized. Future research could look to incorporate these facets of each connection within the ego network by further questioning the value and nature of each relationship within the CERT itself, and by follow-up with each of the CERTs partners to inquire as to their perspective of that relationship and to solicit information about their individual networks. This would provide for more complete network data.

Although the CERTs ego networks are snapshots of the relationships of the CERT from their own perspective, it is important to understand that their network is affected by not only their actions and those of their partners, but also by the broader, macro CERT network. Each relationship within a network takes time and resources to maintain. Each individual CERT has various mandates to fulfill while also being expected to leverage funding to complete its work. With finite resources, it may be difficult to maintain relationships, let alone have the ability to strategically initiate connections for future work. Thus, geographic location and previously established ties become vital to each CERT. Proximity to a partner decreases the time and resources needed to maintain a relationship, and as such, CERTs that are geographically close are more apt to collaborate or provide resources to one another whether it is in the form of advice, assistance on a project, or information on potential partners. The Penn CERT appears to be truly different in structure from the other CERTs. This CERT may be an ideal CERT to emulate if developing partnerships and leveraging resources is a primary aim of a CERT. The HMO research network appears to be a near second in part because of its advantage of having a strong network already formed prior to becoming a CERT.

The relationships of individual members of each CERT can be vital in expanding the CERTs network under the conditions of finite resources. If a principal investigator within a CERT has worked with an individual or organization prior to being involved in the CERT, that relationship can be accessed in the future without the same level of resources as would be needed to initiate and maintain a new connection. Access and trust have already been established with that potential partner that mitigates costs and geographic proximity. Thus, an actor who has a history with a CERT or member of the CERT will be more likely to work with that CERT despite potential geographical limitations. In this situation, the Coordinating Center would play a vital role in maintaining past relationships of the CERT partners to decrease the individual resource costs to each CERT and to provide for future opportunities with the CERTS and those partners. The Coordinating Center currently appears to be succeeding at maintaining these linkages and bringing together CERTs with those partners who have similar interests or particular needs. If the Coordinating Centers role as the liaison between AHRQ, the CERT Steering Committee, and the CERTS is diminished or diluted through more direct contact with each CERT, the cost to each CERT to maintain relationships and create new connections may increase.

Additionally, the burden of the information processing that the Coordinating Center currently undertakes might be shifted to the individual CERTs as well, as there could be duplication in effort in providing information from both AHRQ and the Coordinating Center. It appears that AHRQ is leaning towards having more direct contact with the CERTs. This potential new configuration of the CERTs network is displayed in the Coordinating Center future diagram. In is important to keep in mind that not only are the CERTs network diagrams drawn from the CERTs perspective, but that is often how an ego views their network. Most egos within their network are concerned with their own actors and connections and often to not have an understanding or appreciation of the overall network

in which they are embedded. This focus and specialization can cause the network to be less dense and connected. The Coordinating Center would therefore become even more vital to maintaining coordination and communication among and between the CERTs so that the network does not become fragmented.

Network analysis techniques can help foster better communication channels and practices by identifying social constructs within the system that facilitate diffusion. It may be useful to further study the Penn CERTs structure, which as described above, appears different from the other CERTs in the SNA and which seems to facilitate the development of partnerships and leveraging of resources.

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3.2. Portfolio Outputs and Dissemination

The CERTs program strives to increase awareness of the risks and appropriate uses of therapeutics. It values making available CERT information to relevant audiences.[20] The understanding of the process

[20] CERTs Values: Communication retrieved from http://www.certs.hhs.gov/about_certs/values.html

of diffusion of research into practice is a complex process.[21] Awareness is "when potential users learn about the products, tools, or findings and gain some understanding about how they work."[22] As described by Rogers, diffusion is "a passive process by which an innovation is communicated through channels over time in a social system[23] and "dissemination involves a more active, tailored process of communication, with a goal of persuading users to adopt the innovation."[40] In this section we begin with a description of Portfolio research outputs and conclude with an overview of Portfolio dissemination initiatives.

3.2.1. Research Outputs

The research outputs of the Portfolio include publications, presentations, conferences, workshops, proceedings, committee roles, and testimony to federal agencies. [24] Descriptive statistics describing such outputs of the CERTs and individual grants are provided below, and some additional outputs are also described (e.g. registries).

CERTs Publications

The CERTs program had 383 publications. The breakdown of the publications by individual CERT was: Vanderbilt (177); Penn (55); UNC (55); HMO Research Network (41); UAB (24); Duke (19); and Arizona (12). Of the seven CERTs Vanderbilt University had the most (177) publications, while Arizona had the fewest (12) publications. The number of publications produced by four of the seven CERTs rose during the period 2002 through 2005: HMO Research Network, UAB, Penn, and Vanderbilt. Of these the HMO Research Network displayed the most marked increase, rising from five publications in 2002 to nineteen in 2005. The Vanderbilt University CERT also saw a substantial increase in publications, rising from thirty-nine publications in 2002 to fifty-three publications in 2005. The UNC CERT publication volume rose from thirteen publications in 2002 to fifteen publications in 2005. Two CERTs had fewer publications over the four-year period. The Duke University CERT displayed a marked decrease in its number of publications between 2002 and 2005, with its publications dropping from five in 2002 to three in 2005 after rising to seven in 2003. The Arizona CERT saw a small decrease in its number of publications, dropping from four publications in 2002 to three publications in 2005 (Exhibit 6).

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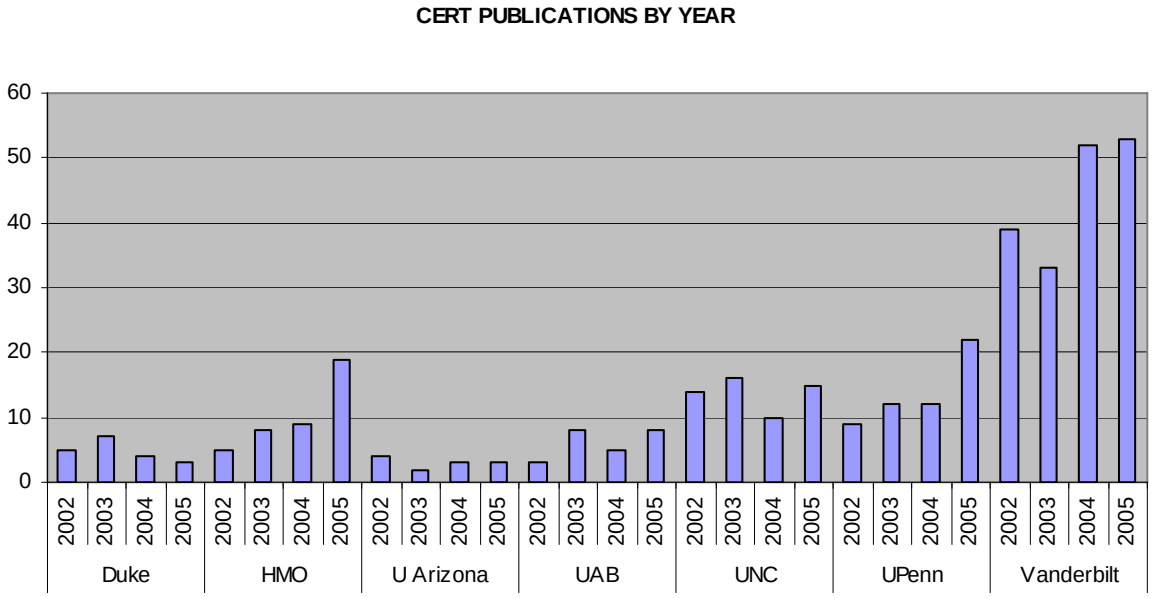
21 AHRQ Evidence Report/Technology Assessment No. 79. Diffusion and Dissemination of Evidence-based Cancer Control Interventions: Summary.

22 Carpenter D, Nieva V, Albaghal T, & Sorra J. Development of a Planning Tool to Guide Research Dissemination. Advances in Patient Safety: Vol. 4 Retrieved from http://www.ahrq.gov/downloads/pub/advances/vol4/Carpenter.pdf

23 Rogers, E, Diffusion of Innovations as referenced in Carpenter et al.

24 The research outputs may also include educational outputs if the publication or presentation is focused on an educational topic, however it was not feasible to discern these outputs for publications and presentations.

Exhibit 6 Count of Publications



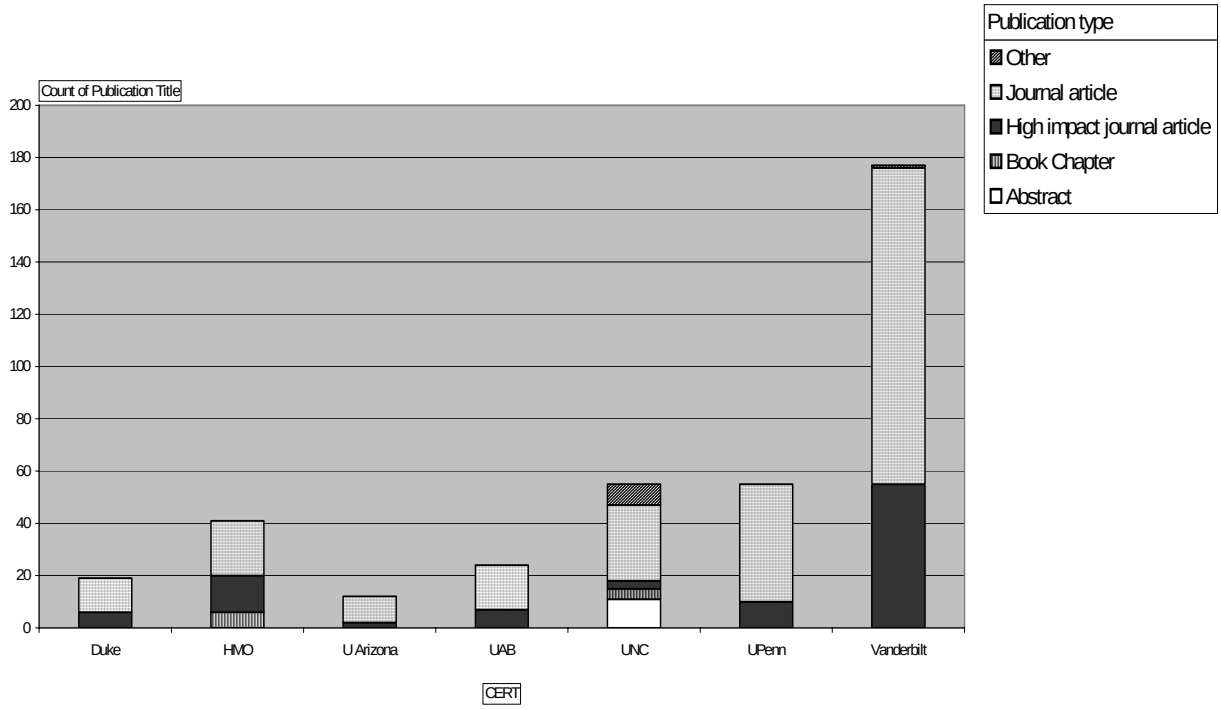
Publication counts represent only one measure of CERT output. Several factors likely impact the quantity of publications a CERT produced over the study period. For example, the first four CERTs that were funded (Duke, UNC, Vanderbilt, and Arizona) have had more time to develop a critical mass of research, data, and investigators. Additionally the nature of a CERTs specialty seems to impact the quantity of publications as well. For example, the Arizona CERT appears to have focused on education and the creation of an inter-disciplinary team, which may explain the smaller number of publications compared to other CERTs. The research foci of the CERTs may also influence publication counts, with some types of studies taking longer to complete and submit to journals than others. The number of investigators at each CERT may correlate with the quantity of publications, however that information was not consistently available from the individual CERTs.

As expected at primarily academic research institutions, the majority of the publications produced by each CERT were journal articles. Of the seven CERTs, the Vanderbilt, Penn, UAB, UNC, Arizona, and Duke CERTs publication lists were comprised entirely of journal articles. The UNC CERT publications were the most heterogeneous, with a publication list comprised of journal articles, abstracts, and book chapters (and items coded "other").[25]

Of the seven CERTs, the Vanderbilt University CERT published the greatest number (177) of articles, and 55 (31%) of these appeared in high impact journals. The HMO Research Network published the greatest percentage of its journal articles in high impact journals. 40% of thirty-five articles were coded as high impact. The remaining high impact percentage totals are as follows: Vanderbilt (31%); Penn (18%); UNC (9 %); UAB (29%); Arizona (17%); HMO Research Network (40%); and Duke (32%). Exhibit 7 shows the number of publications for each CERT by publication type --- journal article, high impact journal article, book chapter, and abstract.

[25] This category includes magazine articles, encyclopedia entries, and symposium publications.

Exhibit 7: Number of Publications by CERT by Type of Publication



CERTs Projects

The CERTs Coordinating Center maintains a database of the projects and publications of the CERTs program and individual centers. An entry in the database is defined as a project if it is a "core" CERTs project, i.e. funded at least in part by an AHRQ CERTs grant or supported at least in part by the administrative core funded by an AHRQ CERTs grant.[26] As of January 2006, the CERTs had 288 projects consisting of completed (127), ongoing (137), proposed (21), and discontinued (3) projects. Exhibit 8 shows the distribution across the CERTs of the 264 completed and ongoing projects.

Exhibit 8: Total Projects by CERT

CERT	Total	Percent
Coordinating Center	4	1.5%
Duke University Medical Center	43	16.3%
HMO Research Network	32	12.1%
University of Alabama at Birmingham	27	10.2%
University of Arizona Health Sciences Center	20	7.6%
University of North Carolina at Chapel Hill	28	10.6%
University of Pennsylvania School of Medicine	78	29.5%
Vanderbilt University Medical Center	32	12.1%
TOTAL	264	100.0%

[26] Per the CERT Coordinating Center

Of the projects that were ongoing or completed, the Penn CERT had the most projects and the Arizona CERT had the fewest. The mean number of projects per research center was 37. The individual CERTs varied in terms of what constituted a project. One of Arizona's projects, the QT registry, already had 12 publications from it – in contrast to other CERTs which typically had only 1 publication per project. Some CERTs had multiple projects that were subsumed under a project number in the CC database of projects. Additionally, labeling a project "complete" was at the discretion of the individual CERT. The database did not include dates so all completed and ongoing projects were included. Therefore, the differences in definitions across the individual CERTs make interpreting the apparent variability in projects difficult to assess. In addition, the project database does not attribute a date to each project.

Coordinating Center staff indicated: "Generally projects are considered complete when the analysis is done and the results are presented and manuscripts written/published." The CERTs indicated that "the project status categorization recognizes the variability of projects, e.g. education projects, multi-component research projects, evolving research projects."

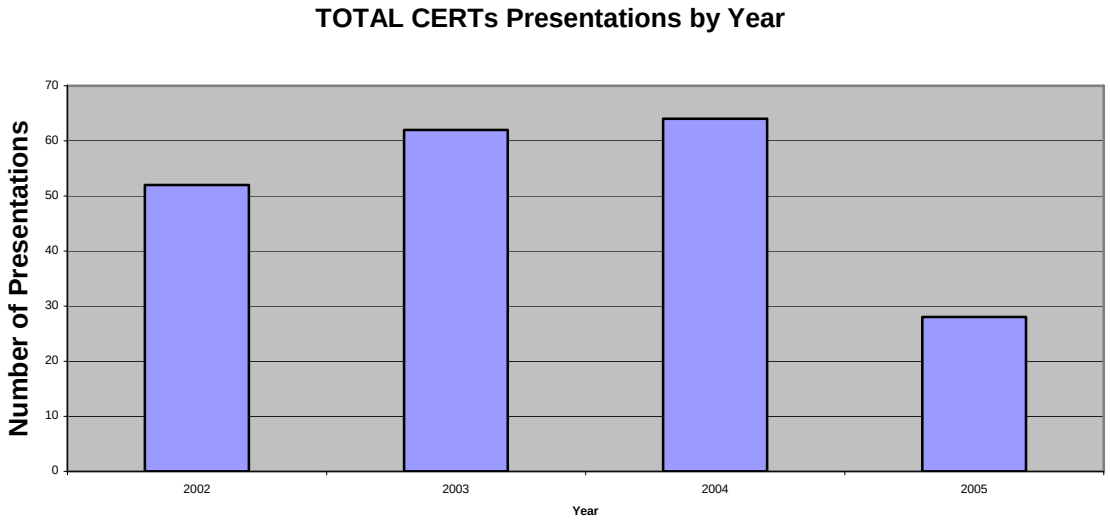
The CERTs Coordinating Center publication database included the project number with which the publication is associated. Of the 235 publications, 230 had CERT project numbers attributed to them (5 did not). The range of publications per CERT project was from 0 to 12. Of the ones that had publications associated, some had more than one publication attributed to the project. The 230 publications are attributed to 134 projects, with an average of 1.71 publications per project.[27]

CERTs Presentations

CERTs investigators made presentations for various purposes, including dissemination of findings, educational purposes, and policy or regulatory purposes. From 2002 through 2005 the CERTs program as a whole made 206 presentations at professional meetings, clinical conferences, research conferences, hospital grand rounds, government advisory board meetings, invited professorships, academic medical centers, among other venues. Within this list of presentations was the John M. Eisenberg Memorial Lectureship on Therapeutics Research, presented at academic medical centers across the United States. The average number of presentations per year was 51.5. The trend in the number of presentations over the evaluation period (2002 – 2005) was upward the first three years, then more than halved from 2004 (64) to 2005 (28). Exhibit 9 displays this trend.

[27] Note this is not the average for all CERT projects; rather it is the average publication for the projects that do have an associated publication.

Exhibit 9: CERTs Presentations by Year



The HMO Research Network and the Vanderbilt CERT conduct research that leverages their clinical databases. These centers can focus on numerous topics and therapeutic areas as a result. In contrast, the UAB and Duke CERT focus on clinical areas, musculoskeletal disorder therapies and cardiovascular therapies respectively, so the scope of their research is more varied and includes intervention studies and education outside their centers. UNC focuses on research on therapeutics in the pediatric population and Arizona focuses on therapeutics drug events relating to women.

Grant Outputs

The Portfolio grants for the period 1999 – 2005 examined antibiotic prescribing, use, and resistance (4); adherence (1), drug cost sharing (1), quality indicators (1), prescribing (1); formularies (1); and medication errors (1). Of the 12 non-CERT grants (center awards and key projects – risk series and prescribing safety were excluded from this analysis because they are counted in the CERTs publications), only four were completed by the time period covered by this evaluation. One of the four grants was for a conference with two products ---one on the conference proceedings and the other a psychotropic drug fact sheet. Another grantee had not fully completed the analysis and findings of the grant so had not published, although he self-reported two or more presentations at professional meetings. A third grantee reported an intervention study that the investigator reported presenting at one professional meeting. He also had submitted for publication and was rejected, and was revising for resubmission to another journal. He noted: “This is the kind of material that doesn’t lead to journal articles. These are dissemination strategies that occur in a non-academic setting.” The grantee is referring to how interventions like a media campaign or educational intervention employed in a specific metropolitan area are not seen as generalizable and are therefore less likely to be accepted for publication in traditional journals. These studies may better reach the appropriate audience through dissemination efforts like a newsletter. The fourth grantee had published in six peer-reviewed journals, presented five abstracts and reported preparing two additional manuscripts for publication. The differences in the publications were related to the type of grant funded and the type of research. Conference grants, for example, would not be expected to result in as many publications as a research award. Additionally, a randomized trial might generate more publications than a non-randomized study due to greater interest.

3.2.2. Dissemination

The CERTs have employ numerous dissemination activities including the use of traditional academic vehicles of presenting at professional meetings and publishing in scholarly journals. CERTs maintain websites that are one means of potentially increasing awareness of CERTs findings. All but Vanderbilt maintain a website that is linked to the CERTs website. The CERTs, particularly in their progress reports to AHRQ, provided measures that illustrate the extent to which they are distributing materials:

- "Abbreviated versions of the table are published in Harriet Lane's Pediatric Manual and the Washington Manual, two of the most popular pocket manuals for interns and residents... 50,000 laminated copies have been requested." (AZ PR01-02).
- Draft toolkit for diagnosing and treating ADHD. Made available to 1000 pediatricians. After evaluating components, put toolkit into final form and available to all 55,000 American Academy of Pediatrics members in fall 2002. Disseminated at the National Initiative for Children's Healthcare Quality national summit. (UNC PR 01-02).
- "Over the last 12 months, we have received over 94,000 contacts to our web site and approximately 3 to 5 requests weekly from pharmacists, physicians, nurses, students, and the public for information about the cardiac safety of particular drugs" (AZ PR 04-05).

CERTs have employed other dissemination channels to tailor their efforts toward their audience. For example, the Penn CERT is associated with an institute that creates issue briefs on important research topics and provides them to different stakeholders, including policymakers. One progress report describes how and the extent to which these issue briefs are distributed.

- In conjunction with the Leonard Davis Institute of Health Economics, issue briefs have been sent to a mailing list of more than 4,000 people. (Penn PR 02-03).
- Literature review completed of interventions to improve medication use in HMOs. "Access database has been created to house abstracts and full bibliographic references" (HMO PR 01-02).

Some CERTs research has attracted media attention and additional Internet sources. For example, a Penn investigator explained that, after a report was published, it was, "disseminated in a dozen or so articles worldwide via the newspaper, radio (NPR), evening news, and by many web-based news organizations" There were other examples within the CERTs where the research was picked up by the media. One outside expert/policymaker stated that this was positive because "the message goes out farther and more widely."

The Coordinating Center has developed a system that "will combine improvements of existing systems and that will provide additional tools to replace what is now being done manually. The system will track projects, publications and other products, contacts, and partners, and it will provide a vehicle to automate what has been a manual process. A Coordinating Center member further described this CERTs Information Tracking (CIT) system.

> *Duke is developing a computer-based dissemination support system. There are formal processes, and in between those formal processes they get updates. What they are hoping to do with this) project is to have connected with this database all information about*

partnerships and products that anyone can add to and take information out of. For instance, AHRQ could pull out a search on Diabetes. A part of moving towards this system is refining how data are collected because current variability.. They hope the system will be applicable beyond the CERTs to external parties on a case-by-case basis.

Dissemination efforts to consumers are particularly difficult. One CERT described a first step to achieve this, "translate the research into tools that can really make a difference out in the world where patients live and providers practice." As the director of education at a CERT stated, "the work I do is revolves around finding the best way to disseminate information on prescription drug safety." Additionally, a staff member at the Coordinating Center focuses on the dissemination of CERTs work and efforts. A special effort that expands the dissemination of CERTs research "government day," which a Steering Committee member described:

It is quite unusual for a federally funded independent program of research centers to undertake an environmental scan to try to move the field forward, but that's what we do..., one of our government agency members said, "well, that's nice but if you're coming to Washington you ought to brief our government, our power agency." This was our FDA representative... and that then created a second major conclave where all of the PIs and the Steering Committee got together with leadership from NIH, VA, AHRQ, FDA, and others to create "government day."

CERTs respondents identified dissemination as a key mission of the CERTs; they therefore identified dissemination as a key aspect of some of their projects or the component of the project that was financially supported by their CERT. A recent publication on the use of ACE inhibitors in pregnant women was anticipated to have a big impact and the investigator described the support he received from AHRQ and the CERTs regarding dissemination:

I presented that at a steering committee meeting last year and got good feedback on dissemination efforts.... AHRQ staff through CERTs really helped to facilitate a lot of our dissemination efforts... helping to... shape our message to allow consumers to understand a little bit about what the potential implications might be for them... We ended up with a theme message. Whenever the reporter would ask "what do you want people to understand?" the answer would be "A woman who is on blood pressure medicine should talk to her doctor about the medicine she's on and come up with another medicine that she might use." It was really helpful to have the AHRQ staffers and press office give us input.

The grantee respondents also described their dissemination efforts. It was evident that dissemination was a key focus of their efforts:

We're up to six papers published and two others submitted and some of those were papers we planned, and some of those were papers that these findings encouraged us to write….we wrote a piece for the member newsletter that went to approximately 800,000 enrollees. ... there was already a lot of lay press about antibiotic resistance, and there were fewer requests for our materials than we had expected…. AHRQ was very good about publicizing these important results.... AHRQ put out press releases and got attention for the findings.

This grant recipient, a member of one of the CERTs, stated, "we took seriously AHRQ's mandate not only to do research and publish it in academic journals but to try to get the products of the research

out there as much as we could." The investigator attributed to his involvement with the CERT his additional effort to seek a vehicle to disseminate the materials to an even broader audience than his State. Another grant recipient described in her final report the extent of the dissemination efforts:

> *The proceedings were published by the Center for Health and Health Care in schools and by Spring 2005, 2,500 copies had been distributed (mail or conference)...to key leaders and the report was posted on the Center web site where a large number of visitors viewed it Although not anticipated in the original grant application, concerns registered by conference participants about the specific issue of psychotropic drugs at school led the Center to prepare a fact sheet. This publication has been well received by state policymakers and building-based school nurses. The Center has mailed out 4,400 copies of the fact sheet and 23,134 visitors have viewed the publication on the Center web site.*

Another grant recipient described submitting publications; however he also stated "journal articles are not an effective way to disseminate your message to the people who are really going to make something happen with it. That's my feeling at least."

Among the outside individuals who were contacted to provide external feedback, one individual who praised the CERTs products (i.e. QT registry) indicated that it was not always apparent that these products were CERTs-related. This comment, although from just one individual, could indicate the lack of association of products and publications with the CERTs and/or AHRQ.

The distinction between awareness, diffusion, and dissemination are important to consider. If effective dissemination implies targeting the appropriate audience, than Portfolio intervention studies and educational efforts may best be disseminated not only though traditional channels like journals, but also through channels that are targeted toward highly specific audiences.

3.2.3. Educational Outputs

Of the five Pharmaceutical Outcomes Portfolio program goals, three directly reflect an emphasis on education: to better understand risks and benefits of therapeutics; to help consumers derive maximum benefit; and support to providers, researchers, and students. Portfolio grants and CERTs research affirmed a commitment to these educational goals, although there was considerable perceived variability across centers. Two of the individual grants were R13 or conference grants that inherently focus on education.

One researcher summed up the need:

"We need centers with a critical mass of seasoned investigators to train younger people."

Part of the CERT mission is to provide education to advance the optimal use of drugs, medical devices, and biological products. Therefore, the CERTs have provided education on clinical topics and research methods in therapeutics to researchers, practitioners, patients, and policymakers; developed educational resources (e.g. toolkits, continuing education), fostered the development of future researchers and practitioners; and initiated educational initiatives. The focus on both research and on education was designed "to develop a field that would perpetuate itself," stated an AHRQ representative. The educational outputs and outcomes of the CERTs are in two primary categories, within the CERTs and beyond the CERTs (i.e. public, patients, providers).

CERTs Educational Outputs

Education beyond the CERTs, including consumers, patients, practitioners, and policymakers is a focus of the CERTs program generally, but not all of the Centers appear to share those priorities. Most CERTs have contributed to educational outputs of the Portfolio, but some have contributed far more educational resources than others. For example, the Arizona CERT is a Center that demonstrates a steadfast commitment to educating the public, particularly providers, patients, and consumers by having an Educational Core as one of three cores within their organization. The Arizona CERT also has aimed to develop educational tools aimed at consumers with low health literacy. The Arizona CERT has a multidisciplinary team that assists with their ability to provide educational tools by having a social scientist in their CERT. Similarly, the development of the QT interval educational module at Duke was a collaboration between a psychologist and other social scientists. The production of educational tools and a commitment to educational materials focused on the consumer requires a skill set different from that of the typical clinician in practice or research. This has implications for the CERTs program on Education Projects, because some needed skills may be lacking at the CERTs.

Exhibit 10 includes a sample list of educational outputs produced to date from the CERTs and the primary audience for each.

Exhibit 10 Sample Educational Outputs Produced by Each CERT

CERTs Educational Outputs	CERT	Audience
Drug Interaction Card: Reference Guide for Providers and Patients	Arizona	Providers & Patients
Drugs That Prolong the QT Interval and/or Induce Torsades de Pointes: List for Providers and Patients	Arizona	Providers & Patients
Medications That Interact with Methadone: Wallet Card for Patients and Providers	Arizona	Providers & Patients
Over-the-Counter Medicine “Interaction” Cabinet: Web Tool for Patients	Arizona	Patients
Preventable Adverse Drug Reactions—A Focus on Drug Interactions: Education Course for Providers	Arizona	Providers
Webliography	Arizona	Patients
My Medication Record	Arizona	Patients
Practical Approach to Long QT Syndrome and Torsades de Pointes	Arizona	Providers
Drug Interaction Advisory	Arizona	Patients
Beta-Blocker Fact Sheet for Providers	Duke	Providers
Duke Heart Center Dosing Guide 2005 for Providers	Duke	Providers
Saving Lives with Beta-Blockers: Cyber Session for Providers	Duke	Providers
Treating Congestive Heart Failure with Beta-Blockers: Brochure and Videotape for Patients	Duke	Patients
Understanding the QT Interval: Web-Based Education Module for Providers	Duke	Providers

Exhibit 10 Sample Educational Outputs Produced by Each CERT

CERTs Educational Outputs	CERT	Audience
REACH: Reducing Antibiotics for Children: Education for Providers, Patients, and Families[28]	HMO	Providers & Patients
Tools and Techniques of Improved Medication Use: Web Site for Providers	HMO	Providers
Head and Chest Colds: Brochure for Patients	Penn	Patients
Arthritis Outcomes Initiative Resource for Patients and Families	UAB	Patients
Arthritis Self-Help Web Site for Patients	UAB	Patients
Challenging Cases in Musculoskeletal Medicine: Online Education Course for Providers	UAB	Providers
Osteoporosis Management: Online Case-Based Disease Education Program for Providers	UAB	Providers
Safer Use of Nonsteroidal Anti-Inflammatory Drugs: Online Education Course for Providers	UAB	Providers
Taking care of yourself with Arthritis	UAB	Patients
Attention Deficit Hyperactivity Disorder Online Toolkit for Providers, Patients, and Families	UNC	Providers & Patients
www.harryguess.unc.edu (a resource for pharmacoepidemiology and pediatric therapeutics)	UNC	Providers

All of the CERTs centers are located at colleges and universities, and many of the investigators are also professors, lecturers, and involved in the formal or informal training of students. The CERTs are likely contributing to formal education beyond what is considered CERTs work, although potentially on CERTs related research and topics. For example, six of the seven research centers have a website for their CERT and each of the six has educational information on the website both for consumers and practitioners. A brief description of some of the educational products includes: curricula, educational modules, web-based resources, printed resources, toolkits, workshops, and other educational interventions.

Curricula and Educational Modules

In their AHRQ progress reports, the Arizona, Penn, UAB, and UNC CERTs described having developed curricula. The Arizona CERT developed course materials on therapeutics for the clinical pharmacology curriculum which led to the development of an educational module for health care practitioners and students that is now available on the Arizona CERT website. The Arizona CERT "collaborated with the FDA to develop the first of several planned educational modules that will be shared with medical student and residency training directors in the US. The product of this partnership was a three ring notebook containing a CD with a PowerPoint presentation entitled "Preventable Adverse Drug Interactions: A Focus on Drug Interactions," and a printout of the PowerPoint slides with lecture notes to guide an instructor" (AZ PR01-02).

The Alabama CERT reported providing lectures at various health professional schools, as well developing continuing medical education (CME) materials on osteoporosis management for pharmacists and nurses. Alabama also collaborated with the Alabama Department of Public Health

[28] This educational resource was created for a Portfolio grant that is described in the grant section,

and the National Arthritis Action Plan to create a tailored website focused on patient education in arthritis (www-cme.erep.uab.edu/ArthritisPatient/welcome.html)"(AB PR02-03).

The Penn CERT has developed and implemented courses to improve knowledge and skills in the use of therapeutics by future physicians for use in medical school as well as in a course on Pharmacoepidemiology Research Methods taught for the first time in summer 2003 (Penn PR02-03).

The UNC CERT described local presentations, including an invited "Meet the Expert" session on aminoglycoside monitoring at a national infectious disease meeting. (UNC PR03-04).

Educational Web Resources, Toolkits

The CERTs have developed web-based educational resources on the web, some of which are described below.

The Arizona CERT has developed many web-based tools for both clinicians and patients including:

- www.drug-interactions.com predicts clinically relevant drug interactions based upon their metabolism by specific cytochrome P450 enzymes. Abbreviated versions of the table are published in Harriet Lane's Pediatric Manual and the Washington Manual described under "Dissemination" above. (AZ PR01-02).
- A pilot interactive web-based module to educate consumers about potential interactions between over-the-counter (OTC) drugs and prescribed medications." www.arizonaCERT.org/index.html (AZ PR03-04).
- The Education Core has developed a consumer-targeted medication "Webliography" --- an annotated list of websites that have met specific evaluation criteria --- to serve as a trustworthy and reliable source of medication information for consumers.
  The Education Core is addressing practice-based factors associated with prescribing outcomes by developing a web-based interactive causal diagram showing causal pathways of factors that contribute to adverse drug events in community settings (AZ PR04-05).

An external respondent associated with a medical center praised the Arizona CERT's clinical resource of the list of drugs that can cause arrhythmias. He stated that the tool is a key trusted, and used resource.

Duke and the HMO CERT have produced and posted resources on the web, including:

- An Internet-based educational module on the QT interval was developed as part of the Duke CERTs patient safety supplement. The American Heart Association expressed interest in posting this module on their web site (Duke PR03-04).
- With the American College of Cardiology (ACC) Duke developed methods to disseminate medication, device alerts, and recalls to practitioners, and implemented 2 programs. The first was the addition of selected FDA alerts related to cardiovascular issues to the Cardiosource.com website. The second is a MedWatch PDA application available through Skyscape.com or the ACC website (Duke PR 04-05)
- The HMO CERT's - Chronic Disease Score – SAS programs and drug tables were posted to AHRQ Patient Safety website for public use of a chronic disease score program.

- The Duke CERT developed print materials, an online web session, and an educational video to inform caregivers about beta-blocker use for heart failure patients. (Duke PR 01-02).
- Duke reported working with professional societies (AAFP, AHA, ACC) to create English and Spanish language brochures on beta-blockers and heart attacks.

The UNC CERT has also developed educational products related to pediatrics, including:

- A pilot toolkit for diagnosing and treating ADHD was made available to approximately 1000 pediatricians. After evaluation of the pilot, the kit was revised and made available to all American Academy of Pediatrics members in Fall 2002. Disseminated at the National Initiative for Children's Healthcare Quality national summit. (UNC PR 01-02).
- UNC collaborated with the North Carolina Statewide Asthma Improvement Project (jointly funded by another foundation). Held educational programs that provided clinicians with practical tools and effective strategies for improving the care of children with asthma. Approximately 600 physicians participated. Due to the positive response to the asthma sessions, the NC Division of Medical Assistance expressed support for more intensive improvement efforts involving a specific number of practices in the Access I Medicaid network. AAP will use several key concepts and tools as a template for its online CME/QI program targeted at improving the care of children with asthma (UNC PR 01-02).

In addition to the educational products, a UNC investigator described how their CERT was trying to leverage educational efforts:

> *We've decided that we should work with existing national organizations (AAP, American Board of Pediatric Medicine) and help them do better getting educational material into practice...Our goal with the Board is to try to get our findings inserted into guidelines and the practitioner re-certification process...*

Educational Interventions

Beside the traditional educational outputs the CERTs have also developed educational interventions with the aim of changing behavior of health care professionals and patients. For example, Arizona reported completing three educational interventions including: a program for provider education, a program for ancillary staff education, and a program for patient education (Over the Counter/Supplement Use and Therapeutic Interactions). The Alabama CERT is working on a multi-modal intervention applicable to administrators, physicians, nurses, and patient care technicians in the nursing home setting. They have completed the educational module, toolbox, and educational teleconferences" (AB PR 03-04). Alabama implemented a three-module physician intervention aimed at improving the prevention and treatment of glucocorticoid-induced osteoporosis and the safe use of glucocorticoids. In addition to the educational interventions, the Penn CERT also developed and validated an instrument for evaluating educational processes targeted at children with regard to appropriate antibiotic use" (Penn PR 04-05).

Workshops and Think Tanks

The individual CERTs and the CERTs program as a whole have held workshops and convened key stakeholders. The CERT research centers described in progress reports hosting workshops with different stakeholders on a variety of topics. Some examples include:

The Duke CERTs with several partners sponsored a workshop attended by more than 50 clinicians, government, and industry representatives. Conference participants reached consensus on six principles related to post marketing surveillance of cardiovascular devices (Duke PR01-02).

UNC held a Summer Institute on "Using the Evidence on Therapeutics to Enhance Quality" for private practitioners across North Carolina (UNC PR 01-02).

Besides the efforts of individual CERT, the CERTs program as a whole has supported educational events. The CERT network sponsored the John M. Eisenberg Memorial Lectureship on Therapeutics Research that was established by AHRQ and the CERTs leverage the CERTs network through a variety of educational and translation of research into modalities. [29] As part of this initiative, representative of the CERTs presented seven lectures at different institutions during 2003-2004.

The CERTs program collaborated for the AHRQ conference grant "Risk Series"--- five think tanks held between 2001 and 2003 on: risk communication, risk assessment, benefit assessment, risk communication and the media, and risk management. The risk series was an initiative developed by the CERTs and included a partnership with AHRQ, the Center for Drug Evaluation and Research (CDER) of the Food and Drug Administration (FDA), and the Pharmaceutical Research and Manufacturers of America (PhRMA). It convened health care providers, researchers,[30] experts from government and industry, and representatives of the media and consumer groups. A few CERTs PIs identified the Risk Series as among their most important advances as a group. Two of these PIs described the Series:

> *The Series helped to shape national views about risk, and importantly, we were able to work as a group. Demonstrating how one can work with professional societies is an important component of the evolving fabric of therapeutics.*
>
> *We had meetings with diverse people and achieved consensus about what research was needed. There has not yet been a sufficient response to what has been agreed upon for research needs, such as statistical approaches and measuring adverse reactions. What should be the role of the press in risk communication?*

Another PI continued:

> *The Risk series was a great example... it turned out to have a major impact…. It lead to the idea that we don't know how much is being spent on post-approval drug safety, benefit assessment, and risk management...it [included] voting on unifying principles at a time when the FDA was developing risk assessment guidelines for industry. The FDA staff drafting these guidelines were at the CERT think tank, which was a completely CERT PI- initiated effort.*

[29] http://www.CERTs.hhs.gov/programs/eisenberg/rfa/index.html

[30] Risk Series: Program Overview http://www.certs.hhs.gov/programs/risk_series/index.html

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In summary, the CERTs program has developed various initiatives focused on education in therapeutics for providers and patients. Most centers demonstrated an effort to educate providers, but only a few centers demonstrated a commitment beyond the traditional development of continuing education. The CERTs focused less on patient education than on provider education, although five of seven CERTs maintain websites that have information for consumers/patients. Similarly, some CERTs focused more on developing educational tools and products for consumers than did others.

Portfolio Grants

Of the four individual grantees who were respondents for the evaluation, one held a conference and two other grants involved educational interventions. The two grants on antibiotic resistance included educational interventions and media campaigns that involved the development and dissemination of educational materials. One grant was awarded to convene a conference on medication management in school systems. The grantee explained:

> *We invited 35-40 people to participate with the goal of providing documentation on what actually happens in the school setting, what the issues are, and what some of the recommendations one might make about how to strengthen the process. It was really less about prescribing than about improving quality... a follow-up was a fact sheet on psychotropic drugs.*

As the grantee described, she made publicly available the proceedings of the conference. She also in response to conference attendees' stated needs, developed a fact sheet on psychotropic medications because the need was identified in the conference, which demonstrated responsiveness. The selection of a fact sheet format was intended to accommodate the school nurses' schedules.

3.3. Outcomes and Impacts of Portfolio Research

Portfolio research and awards have contributed to the knowledgebase of diverse areas in therapeutics, clinical practice, and research methodologies. The research findings of the Portfolio funded grants and research funded through the CERTs program also have contributed to the field of therapeutics research. The research outcomes relate to the specific areas of CERTs specialization, including drugs, biologics, and devices. The contributions are aimed at various end users including: patients, consumers, health care providers, HMOs, PBMs, government agencies, professional organizations, and others. The research has focused on children, women, elderly, and racial and ethnic minorities and has included studies on various diseases and organ systems (e.g. cardiovascular, musculoskeletal systems).

In the following section, we use the "Levels of Impact Framework" developed by Tunis and Stryer to classify areas in which the Portfolio has had significant impacts. This framework "outlines an idealized process by which basic findings in outcomes and effectiveness research are linked over time to increasingly concrete impacts on the health of patients."[31] The levels of impact illustrate how research may ultimately contribute to a patients' health. Below we describe the levels, and we provide

[31] The Impact of Studies funded under the Outcomes of Outcomes Pharmaceutical Research. AHRQ. October 2001.

examples from the Portfolio.[32] The tables summarize the studies (note that the source of these summaries includes documents (DOC) and interviews (INT), so the amount and type of information available for each study varies considerably) and include the study population or population impacted by the findings. These summaries are followed by several in-depth case studies.

3.3.1. Level 1: Research Findings

Level 1 impacts are "effects of research studies that do not represent a direct change in policy or practice" and include examples such as new tools and methods for research, instruments and technique to assist in clinical decision-making. Level 1 impacts also occur when studies produce results in conflict with "current clinical paradigms, and stimulate rethinking and questioning within a clinical specialty."[33] The CERTs and Portfolio projects have contributed to research findings in the following areas: data and methods; adherence; medication safety; medication errors; trends; cost and economics of therapeutics; QT prolonging medications; health information technology; and antibiotics and antimicrobials.

Data and Methods

The CERTs researchers have not only contributed to the knowledge base in their specific content areas, but some have also contributed to the advancement of research methods in therapeutics, epidemiology, and health services research. Besides investigators' use of data, measures, and methods the Portfolio has also produced material on the utility and limitations of certain data for therapeutics research, has compiled datasets, and has developed methods and algorithms. Understanding the utility and limitations of available data and databases is important for future research on therapeutics. Themes include:

The development of large datasets as a resource for the CERTs to shape research questions, and assessment of the limitations of electronic data for surveillance and research.

- Linkage of clinical and administrative data and the utilization of other types of data sources and algorithms to leverage the use of databases and registries.

Development of methods to enhance the understanding and practice of therapeutics including registries to conduct pharmacoepidemiologic studies (and which potentially can contribute to understanding the genetic/genomic basis of therapeutic response).

- Advancement of methods in therapeutics research and pharmacoepidemiology through educational efforts at the CERTS and through seminars, published books, discussions

One study, for example, found that automated claims and pharmacy databases are not sufficient on their own for assessing appropriate renal dosing to determine prescribing errors of QT interval prolonging medications. Another project developed the web-based drug-induced arrhythmias registry

[32] The characterization of CERTs work was primarily based on interview data and further description of the findings beyond the titles of the projects – which can be difficult to determine. The level of impact research was also based on the review of CERTs annual reports, individual CERTs annual progress reports, and available Grantee final reports.

which has been attributed with providing the information that contributed to identifying the cardiotoxic effects of methadone. Table 1 provides additional examples.

Adherence

Non-adherence to medications is a pervasive problem. A number of Portfolio funded projects examined patient adherence in different populations and medical conditions, expanding the understanding of adherence for eventual use in practice. One study, for example, found that 10-20% patients discharged from hospitals with myocardial infarction or heart failure and prescribed follow-up medication do not fill the hospital prescription and therefore do not receive the benefits. Table 2 provides additional examples.

Medication Safety

The Portfolio has conducted much research on medication safety, including prescribing, therapeutic risks, and risk management and assessment. The CERTs jointly applied for an AHRQ Patient Safety grant under the auspices of the HMO CERT, whose PI described the prescribing safety program as having identified safety issues in the outpatient setting. The research generated data potentially useful for future projects. Themes of Portfolio research on medication safety include:

Age-specific risk in pediatric and elderly populations
Medication use among pregnant women
Culture-specific research
Medications not previously of concern

Table 3 provides additional examples.

Medication Errors

With the release of the Institute of Medicine (IOM) Report "Crossing the Quality Chasm"[33] the prevalence of medical errors was brought to the attention of practitioners, researchers, and policymakers. In late 2006 the IOM released the pre-publication findings of the Medication Errors[34] report. The CERTs and Portfolio grants have conducted research to further the understanding of medication errors. Themes included inappropriate prescribing practices leading to medical error, variation in error rates by mediation class, and patient-physician relationships. Examples of CERT research findings in this area included:

Errors in which the medication reaches the patient but does not cause harm account for the majority of errors reported.
Leading types of errors reported through one type of reporting system were omission errors, improper dose/quantity, and wrong time. Consistently, the leading causes of errors seen in pediatric medication errors are performance deficit, procedure/protocol not being followed, and communication.

Table 4 provides more examples.

[33] IOM Quality Chasm Report

[34] IOM Medication Errors report 2006

Trend

The CERTs have contributed to the study of trends in the use of therapeutic agents. For example, one study found that the annual prevalence of use for life saving cardiovascular therapies increased between 1995 and 2002, and another found that use of psychotropics has increased by youths in IPA-model health plans, with consistency across health plans in different geographic regions. See Table 5 for additional examples.

Racial Disparities

The CERTs have conducted limited research explicitly on racial and ethnic disparities. Two studies identified racial disparities. An HMO CERT study of Caucasian and African-American women found a lack of physicians prescribing therapy for women with osteoporosis. The trend was more prevalent in black women than in white women. The Alabama CERT in a study of Caucasian and African-American women found that Caucasian women were more than twice as likely to receive osteoporosis treatment and bone density measurement than African-American women, even among those who had suffered hip, rib, or wrist fractures.

Cost and Economics of Therapeutics

The cost and economics of therapeutics has also been a part of the research Portfolio of the CERTs and grantees. For example, increasing the co-pay to more that $10 for a thirty-day supply of oral hypoglycemics was associated with significantly reduced use. Another study found that Glucocorticoid users face non-negligible incremental health care costs compared to non-users. For an estimated one million chronic glucocorticoid users, the costs to the health care system were estimated as over $1.2 billion annually in the U.S. alone for treatment of adverse effects. Additional examples of research findings the economics of therapeutics area are presented in Table 6.

QT Prolonging Medications

Four of the seven CERTs have contributed to knowledge and understanding of QT prolongation and therapeutics. The CERTs have contributed extensively to the knowledge base on medications that affect the QT interval, including research on concomitant use of medications that affect the QT interval, creating education modules, and maintaining a registry to further understand the extent of the QT prolongation affect. For example, one CERT developed and maintains an international registry of drug-induced arrhythmias that led to the detection of unexpected drug toxicity (methadone) and a new risk of toxicity from a group of intravenously administered drugs. Contrary to recent reports in the literature, one CERT concluded from its analysis that prolonged QT and TdP (Torsade de Pointes) can occur over a wide range of methadone dosages including those recommended for addiction treatment. Additional examples are provided in Table 7.

Health Information Technology (HIT)

The use and advancement of health information technology is a growing area and is represented in the CERTs program. As stated in an annual report, “As we move into our fifth year, more and more of the CERTs projects focus on technology” (CERTs AR Y4). The CERTs have focused on the use of information technology to improve the safety and effectiveness of therapeutics in practice. This has included research on Computerized Physician Order Entry (CPOE) and other decision support technologies for practice. Findings from some of these studies are provided below:

- In a study of cardiac patients, the Vanderbilt CERT showed that a computerized physician order entry system (CPOE) at the hospital has improved the care of patients with myocardial

infarction and heart failure, suggesting that the CPOE system significantly improved discharge planning.

- An HMO CERT study exploring the laboratory monitoring alerts within a CPOE in an HMO found that passive alerts for appropriate laboratory monitoring for specific medications ordered in a CPOES do not improve adherence to monitoring recommendations.
- Another HMO CERT Study examining patient-specific order entry intervention found that clinicians prefer decision support alerts that are concise, clear, easy to navigate, and that provide minimal information in the alert text.

Antibiotics and Antimicrobials

With the ever-increasing use of antibiotics and identification of drug resistant organisms, and an entire CERT committed to antimicrobials, there has been much pertinent research in therapeutics in this area within the Portfolio. A grantee praised the Portfolio's involvement in trying to "promote judicious antibiotic use in which, to their credit, AHRQ is involved." An AHRQ representative stated that this area is "a very high priority area for the government and there are multiple agencies interested in this including the CDC and FDA because it is a really important public health problem." Also, this is a PART goal focus area. The Portfolio research has included an emphasis on anti-infectives including not only appropriate and judicious use but also further understanding of resistance and how to address it. The research on antibiotic and anti-infective therapeutics has included examining prescribing patterns.

In one example, a CERT found that the proportion of the primary bloodstream infections accounted for by gram-negative pathogens has increased significantly over the past five years. These changes have great implications for empiric antimicrobial therapy for suspected bloodstream infections, and for fostering the development of new agents with expanded gram-negative activity. Another CERT found that patients with extended-spectrum β-lactamase–producing *Escherichia coli* and *Klebsiella* (ESBL-EK) infection were 5/8 times more likely to have had exposure to an extended spectrum cephalosporin within the thirty days prior to infection and also were more likely to be female, had infection caused by a Klebsiella species, and received steroids in the thirty days prior to infection. These findings have the potential to contribute to limiting the emergence of ESBL-EK infections in children. Additional examples are presented in Table 8.

Devices

The CERTs program has also demonstrated a commitment to research on devices through its support of a new CERT focused on devices and through the Coordinating Center's sponsorship of a meeting on devices. A few studies have examined implantable cardiovascular defibrillators (Duke) and blood glucose monitors (UNC), and the UNC CERT is studying a device in the pediatric population because "most devices are inappropriately just scaled down to children as if they were miniature adults" a UNC investigator said. The Coordinating Center in 2003 sponsored a think tank workshop to develop a research agenda for the evaluation of the health impact of diagnostic and therapeutic devices.

3.3.2. Level 2: Impact on Policies and Change Agents

Tunis and Stryer state that Level 2 research impact requires "a policy or program that is created as a direct result of the research, including use of information by health plan, professional organizations, legislative bodies, regulators, accrediting organizations...etc." The level 2 impacts of the Portfolio research are described in the following areas, including: standardized quality of care performance measures, professional guidelines, drug labeling, and drug withdrawals from the market.

The concept of policy is complicated because you have to define 'policy' Is it the inclusion of a drug in a formulary, is it the inclusion of a warning in a label, is it translation of a warning in a label into an action program to make a difference? (SC)

There have been some terrific policy pieces that have come out of some of the risk workshops that have been initiated by the CERTs. (UAB)

And as mentioned earlier: We've decided that we should work with existing national organizations (AAP, American Board of Pediatric Medicine) and help them do better getting educational material into practice...Our goal with the Board is to try to get our findings inserted into guidelines and the practitioner re-certification process... (UNC)

HEDIS and Quality Indicators/Measures OR Changing Measures

HEDIS™ [35] measures illustrate an important area for potential policy impact because of the wide use of these measures by managed care plans and their potential impact on plan members. The Duke CERTs collaborated with the Council for Affordable Quality Healthcare (CAQH) in developing a national initiative to evaluate long-term use of beta-blockers in patients with previous myocardial infarction. A Duke investigator described "working with the project manager from CAQH who began talking to NCQA (National Committee for Quality Assurance) about adding long term adherence measures to HEDIS."

One of the grantees that held two Portfolio grants on antibiotic use and resistance attributes his AHRQ-funded research with affecting his subsequent work on developing a HEDIS measure. He indicated that "it was work from this project that led to my participation as their expert consultant to develop an adult measure for appropriate antibiotic use, and that just finished the testing phase last year and is being released as a new measure." (Grantee). The grantee continues:

My work has been focused on adults with acute bronchitis, because that's where the biggest quality gap is. This is a very important mechanism for disseminating the importance of appropriate antibiotic use, specifically for reducing overuse of antibiotics for adults with acute bronchitis where there's strong evidence to show that antibiotics make no difference but prescription rates remain 50-70%. Many major commercial health plans, most Medicaid managed care plans, and many Medicare plans seek NCQA accreditation and report on the HEDIS measure, so this will be a very powerful tool to get the message to physicians that this is something that's important.

The UAB CERT has contributed to the development of quality indicators for osteoporosis and arthritis. A CERT Annual Report stated that the UAB CERT "worked with RAND and the National Committee for Quality Assurance to develop quality-of-care indicators for the management of patients with osteoporosis."(UAB ARY3) Additionally, the UAB CERT developed quality-of-care indicators for gout management and updated guidelines for the Arthritis Foundation Quality Indicator Project. (UAB ARY5)

[35] Health Plan Employer Data and Information Set, National Committee for Quality Assurance.

Drug regulation

Some CERTs maintain data on drugs post market and offer examples of their work having at least informed if not directly impacted the withdrawal of medications from the market. The CERTs also have conducted research on the understanding of prescription labels, including black-box warnings and assessment of the risk management programs of specific medications. These contributions appear to have had an indirect impact on policy; as an AHRQ representative clarified, "I wouldn't say that's policy per se, it's *regulation*, which is probably better than policy." The drug withdrawals in which CERTs investigators claim a role for their research are described below.

The Vanderbilt CERT described in a progress report, "In 1998 a regulatory action was taken by FDA to limit prescribing of cisapride and drugs that affect cisapride metabolism. CERT study compared prevalence of contraindicated use of cisapride before and after 1998. Little difference was found. This study, with others, led to the voluntary withdrawal of cisapride in July 2000." (VAN PR 01-02). A Vanderbilt CERT investigator said:

> *We demonstrated that a regulatory intervention designed to make use of Cisapride safer actually failed and we think that led to the drugs being withdrawn from the market... so that was a big change. The FDA put in a black box warning and publicized it highly. The FDA thought that solved the problem, but we did a study with the HMO research network site, and we found that the black box warning did nothing and as much as 20% of the use was in people for whom the drug was very dangerous. Since it was a drug for treating heartburn (and not the best drug for treating heartburn), this called into question its continued presence in the market. Shortly after the preliminary findings of our study were released to the FDA, the manufacturer withdrew Cisapride from the market.*

In September 2004, the COX-2 inhibitor Vioxx (rofecoxib) was withdrawn from the market. Some of the CERTs research centers identified their research as having contributed to that outcome. The Vanderbilt CERT described a study on rofecoxib in the progress report for 2001-2002, stating, "We noted that 17% of rofecoxib users were using this higher dose and that this proportion did not vary among those with cardiovascular disease, who would be particularly susceptible to dose-related adverse effects (VAN PR 01-02). An investigator from Vanderbilt further stated:

One of the early studies to look at some of the Cox 2 effects came out of this CERT. That really began to open up the possibility of looking further into this so further studies were done. There was then regulatory action at the FDA on the Cox 2s, and that had a direct effect.

Another Vanderbilt investigator said, "We were among the first to identify the risk associated with Vioxx." (VAN) A CERT Steering Committee member said that the CERTs, "were able to contribute to the debate relating to Vioxx; there was major policy impact... we were able to add science to political rhetoric. (SC) However, in another interview one of the CERT investigators said that it was a challenge to the CERTs diversity to take a stance on a particular, critical topic and he identified Vioxx as one such topic.

The Arizona CERT in a progress report indicated that it has "... pioneered the concept of using an Internet based registry for the study of rare adverse drug reactions. The first project…has resulted in the removal from the market of five major drugs in the past four years" (AZ PR01-02). As a result of the web-based International Registry for Drug-Induced Arrhythmia, the Arizona CERT discovered methadone to be a cause of lethal arrhythmia (AZ ARY3). Additionally, the Arizona CERT PI stated

that their work was also instrumental in getting Orlam (levo-methadyl acetate HCl) off the market, because it appeared to cause arrhythmia.

Besides the work on the medications that were withdrawn, the CERTs contributed to the FDA and drug regulation in other capacities typically with regard to the change in drug labeling. There are a few examples that were identified in the CERTs progress reports and stated by the investigators:

Retrospective study of antipsychotics and sudden cardiac death. "Among cohort members with severe cardiovascular disease, current moderate-dose users had a 3.3 fold increased rate relative to comparable nonusers, resulting in 367 additional deaths per 10,000 person-years of follow-up. These data were reviewed by the FDA prior to the thioridazine label change (VAN PR 01-02)

ACE inhibitor medications early in pregnancy. One investigator had just published a paper in the New England Journal looking at the effects of ACE inhibitor medications early in pregnancy. The FDA held a press conference about a public warning or advisory before the paper was released. This led to a follow-up AHRQ grant to the HMO Network to look at prescribing of ACE inhibitors and ARBs during pregnancy. (VAN)

Selective serotonin reuptake inhibitors (SSRI) and the serotonin-norepinephrine reuptake inhibitors. Another CERT reported in their progress report that they were contacted by scientists in the Division of Neuropharmacologic Drug Products of the FDA and asked if they had any "comparative information on the risk of TdP (torsades de pointes) with the newer selective serotonin reuptake inhibitors (SSRI) and the serotonin-norepinephrine reuptake inhibitors" (AZ PR04-05)

Additionally, as described earlier in this report, the CERTs program held five think tanks on risk, as described by a CERTs steering committee member:

The FDA recognized that it had mandated under the Prescription Drug User Fee Act a program to govern a new and evolving concept called therapeutic risk management. There were no rules of engagement, there was no experience, and it wasn't clear what FDA needed to do. The FDA came to the CERTs and asked us to convene a national think tank to help them deliberate about appropriate implementation... Not only did we do it, but after we convened the first one, it was clear that we needed to convene many, and we ended up convening five in that first wave of think tanks, which created the context for guidance development by the FDA leadership…. the National Guidance on Risk Management was configured in the CERTs think tanks.

An AHRQ representative indicated that the "CERTs have generated regulatory activity on the part of the FDA in terms of labeling changes." In addition to the aforementioned studies identifying the deleterious effects of medications and their impending withdrawal, the CERTs also evaluated a risk management program for dofetilide. Additionally, the CERTs have spoken to the FDA on at least a few occasions; for example, the CERT Coordinating Center PI spoke to the FDA about "Risk management of prescription drugs." Also, CERTs educational modules are accessible through the FDA's CDER website.

Guidelines

Clinical practice guidelines can guide practitioners' delivery of care and are indicative of an impact on policy if research effects a change in the guidelines. Many CERTs have contributed to the development, improvement, and evaluation of clinical practice guidelines as part of their research.

The CERTs have been involved with assessing the extent to which practitioners adhere to clinical guidelines. For example, the Alabama CERT examined adherence to Carpal Tunnel Syndrome guidelines. CERTs have also assessed the appropriateness of guideline components. For example, the Penn CERT examined outcomes of alternative strategies for diagnosing and treating pediatric acute otitis media. The Duke CERT conducted an evaluation of American College of Cardiologists (ACC) guidelines and indicated that this was "the first study to document that practitioners had concerns about conflict of interest,"(Duke KW) which resulted in the ACC changing this. Also, UNC has been "working with the ACC on more rapidly updating guidelines" (Duke NAL). The Penn CERT investigators suggested that their research has changed antibiotic guidelines. One example is the finding regarding changing endocarditis guidelines for dental prophylaxis for cardiac abnormalities. As a result of this research the CDC and American Thoracic Society changed their guidelines for antibiotic prophylaxis. Penn also published in the Archives of Dermatology widely disseminated guidelines on the use of antibiotics for acne.

Medication Errors

In addition to their contribution to the knowledge base for understanding medication errors, the CERTs have also impacted policies relating to medication errors. The UNC CERT investigators worked with the United States Pharmacopeia (USP) to use the MEDMARX system where medication errors are reported. They conducted an analysis of errors in pediatrics, which led to the drafting of an addition to the USP recommendations, *Error Avoidance Recommendations for Pediatric and Neonatal Medicine Use*" (UNC ARY3). A year later in their Annual Report, the UNC CERT stated that using the MEDMARX web-based reporting system (error reports), it made five sets of recommendations that the U.S. Pharmacopeia placed on its web site in April 2003 (UNC ARY4).

3.3.3. Level 3: Impact on Clinical Practice

Level 3 impact level, which is difficult for researchers in general to achieve, involves "a change in what clinicians or patients do, or changes in a pattern of care" (Tunis & Stryer). Tunis and Stryer also included a Level 3a and Level 3b, to indicate when impacts in clinical practice are "demonstrated in a limited study population as a result of a specific intervention" and when then "impacts are trends identified outside a formal research context," respectively. Little Portfolio research has had an impact on clinical practice. The nature of the study may be a predictor of the potential level of impact a study can have on clinical practice. For example, the studies that had a level 3 impact were intervention studies and controlled trials. The following CERTs intervention studies and their effect on behavior are briefly described below:

The UAB CERT in their intervention study of steroid-associated bone disease reported a change in prescribing behavior by physicians associated with a national health plan.

- Several interventions have been designed to reduce errors at various points in the ambulatory care setting: Patient Specific order entry intervention; Drug Specific Order Entry intervention; Communicating with Patients about Error; Quality Improvement intervention. (HMO PR 02-03).
- Additionally, the HMO CERT found in a study of medication alerts that "after the alerts were implemented, a steady decline in the number of apparent errors was noted …drug-specific alerts resulted in a 22% reduction in the rate of use of the target medications." The study observed a 14.9% reduction in warfarin medication interactions, due to alerts. (HMO Final

Report).

Academic detailing and printed educational materials achieved their intended purpose of reducing the odds of patient requested antibiotics for upper respiratory infection (Penn PR 02-03).

The UAB CERT reported in a study with a large national managed care organization that physicians who participate in web-based continuing medical education coupled with wider feedback of their performance may see slight improvement in their quality of care (despite barriers to changing provider behavior)

The Penn CERT found: that while physician-based interventions reduce inappropriate prescribing of antibiotics, there is substantial opportunity for improvement. That CERT designed interventions to identify patients who gratuitously seek antibiotics and designed a brochure about why not to seek antibiotics for a cold.

Additionally, two of the Portfolio grant recipients conducted research that changed medical practices. One stated that he believes even beyond the impact of his study intervention that "others have picked up on the materials after the intervention period ended." Another grantee's work on antibiotic use in Colorado involved a coalition:

> *It's really wonderful to see... that the Health Department took over sponsorship of this program so that it's still the "get Smart" campaign. Now there is an individual in the Colorado State Health Department who is the coordinator for these activities. She keeps the plans involved, and they've been doing a lot more outreach... they're doing a lot more local activities around health fairs. In fact they are planning a new mass media Spanish language campaign.*
>
> *What I feel most excited about is that a critical mass that came together after the grant ended to keep things moving, because they saw value from the public health perspective as well as from what's important from the business perspective and the community perspective. It has found a way to become self-sustaining.*

The impact on clinical practices is difficult to identify and measure; however there is an implicit assumption that some of the level 2 impacts, such as a drug being withdrawn from the market would ultimately impact prescribing and clinical practice by changing available therapeutic options. Additionally, time for diffusion of findings is needed to recognize an impact on clinical practice and significant resources would be necessary to measure and identify impact at this level.

3.3.4. Level 4: Impact on Patient Outcomes

This Tunis and Stryer impact level demands an "actual impact on health outcomes (clinical, economic, quality of life, satisfaction). There are sublevels for impacts on outcomes in a limited study population (4a) and impacts identified outside a formal research context (4b). The extent to which CERTs were able to impact patient outcomes is difficult to attribute (as for research in general and pharmacoepidemiology in particular). However, in a few intervention studies, the Portfolio investigators were able to demonstrate some impact. Limited CERT research has been conducted at the clinical level and even fewer studies have focused on impacting patient outcomes (although there has been much research on understanding patient outcomes and outcomes research). The Portfolio research that has had an impact on patient outcomes has been at Level 4a --- impact on outcomes in a

limited study population. The examples of Portfolio work that directly impact patient outcomes were intervention studies, including:

Reducing antimicrobial resistance:

> *A 3-year intervention for physicians, parents, childcare providers, and anyone we could engage to reduce unnecessary antibiotic prescribing as a community. One of the things that was fairly unusual is that we were doing a rigorous evaluation of the kind of coalition building that's often done in public health projects. The coalition was the: the state Department of Public Health and 4 of the major health plans, including the Medicaid program, and the physicians in those communities. Those kinds of coalitions to tackle public health programs do happen but they're rarely evaluated in this kind of randomized control trial …..…Could we affect antibiotic prescribing rates for children? To test that we measured very precisely with health plan data the antibiotics received by children 0-6 year old who were insured by the four health plans 16 communities. We found a dramatic trend in all the communities toward lower prescribing rates; both in the indirect and control communities there was a substantial drop, at least in some age groups, in antibiotic prescribing.*

Improving antibiotic use:

> *The primary objectives were to examine two different types of community based educational strategies to improve antibiotic use…. The first strategy was office and household based education, and the second strategy was a mass media campaign.[36] We identified approximately 12 practices located in a specific suburb area of the Denver metro area. We developed household mailings that included a refrigerator magnet, brochures, and other material about the topic of appropriate antibiotic use for respiratory infections. In addition, we developed similar materials that were branded in the same way and which were placed in the physicians' offices, so that patients would be getting the message at home and in the physician's office. The physician would also be seeing the message on exam room wall posters and displays in their waiting rooms. Our evaluation showed that there was an absolute decrease in antibiotic prescribing for adults with acute bronchitis of approximately 10% – a relative decrease of approximately 20%. However, in children with pharyngitis, which was our other target population, we didn't see any change in prescribing, but part of that was due to the fact that prescribing rates had already been down to close to optimal level probably due to a number of factors. Our conclusion was that patient and household education (small-scale education) was effective for adults with bronchitis and but not for children with pharyngitis.*
>
> *The second major component of this project was to evaluate a mass media campaign, because that would be the most easily generalizable way to improve antibiotic use, although it would also be the most expensive. It was important to have a good cost-effectiveness component, and which we incorporated into our design. We designed ... the mass media campaign to change physician prescribing behavior. While we didn't observe a change in physician prescribing behavior, we observed a fairly large decrease in antibiotic utilization in our mass media area, which can only be attributable to reduced office visits for respiratory infections. We did see reduced visits for respiratory infections primarily among children and parents of young children. The campaign cost $180,000, and the amount of antibiotic savings for the total Denver metro was in the millions of dollars. If you look just at the two health plans that provided their data and hypothesize that only those two plans paid for the entire*

[36] *The other important element of the MARC project was that this was added on top of an existing physician quality improvement program that had been, that we had implemented with the participation of the major managed care organizations in Denver, and as well as the state health department and other folks. So in many ways we're looking at an incremental gain of patient and public education.*

Denver metro area, it was still cost saving. We estimate that those two health plans saved about $400,000 in antibiotic costs.

Intervening in emergency departments:

We used a computer kiosk to deliver culturally and language concordant pre-visit information to patients and ….we showed that we did reduce antibiotic use for adults with acute bronchitis….the main outcome there was reducing antibiotic use for adults with URIs and acute bronchitis – Round 1. Round 2 was going to evaluate a diagnostic test intervention in the ER setting (e.g. the C Reactive Protein test). Many clinicians are asking for is empirical evidence that the patient doesn't need antibiotics. We observed a huge drop in antibiotic prescribing for bronchitis regardless of the test...we believe that is a very strong Hawthorne effect – by randomizing at the patient level, one sees providers change their behavior. On one hand it says that ED physicians really can reduce their prescribing for bronchitis to very low levels...but the problem is that once you've reduced antibiotic use in the comparison group, the CRP test doesn't have any marginal benefit. It's only helpful if people are over prescribing… this is the first series of studies to improve antibiotic use in the ER setting, so we've definitely increased attention in the emergency medicine literature.

3.3.5. Impact Case Studies

Four CERTs research projects were selected and highlighted here as "impact case studies" to illustrate how the individual projects and the CERTs program in general have had an impact on policy and ultimately on improving the use of medications. The cases also provide insight into mechanisms that may have resulted in an impact. Detailed descriptions of each of the four case studies are provided below including descriptions of the research, timeline, dissemination, and levels and mechanisms of impact. For the dissemination descriptions, the impact factor (IF)[37] of each journal from the ISI Citation Report 2005 is included. The case study descriptions are derived from initial and follow-up interviews with the investigators, partner or outside expert/policymaker interviews, the publications and other dissemination materials, progress reports, and other CERT program documents.

To further delineate the impact of the case studies, the Research Impact Framework and its key descriptive categories were used to categorize the areas of impact (e.g. research, policy) and the relevant descriptive categories within each of those.[38] Although the case studies were selected based on the specific project that fell within the evaluation timeframe (2002-2005); other projects may have been critical precursors of a selected project and are therefore included in the case study descriptions.

[37] See methods on document review for a description of the impact factor

[38] Kuruvilla S, Mays N, Pleasant A, and Walt G. (2006). Describing the impact of health research: a Research Impact Framework. Health Services Research, 6:134.

The 4 studies were:

Study Title	CERT	PI
FDA Drug Prescribing Warnings: Is the Black Box Half Empty or Half Full?	HMO	A. Wagner
Evaluation of physicians' understanding of the QT interval and medications that may alter it	Duke	A. LaPointe; S. Al-Khatib
Effect of AAP Guidelines on Vitamin D Supplementation recommendations in Practice	UNC	M. Davenport and A. Calikoglu
Tensions between patient and public health values in generalists use of antibiotics	Penn	J. Metlay

Impact Case Study I: Black Box Warnings

The Black box warning project has been eye opening. (CERT PI)

Project Title: FDA Black Box Warnings[39]
PI: Anita Wagner
CERT: HMO Research Network
Project Description: Assess the overall frequency of prescribing at variance with FDA 'black box' warnings or commonly accepted clinical guidelines.

Formation of the Research Question and Study Methods

Dr. Wagner described the background of the black box warning study[40]:
We are interested in improving medication use by patients and prescribers. Appropriate medication use requires that information about risks associated with drugs is effectively communicated to prescribers and patients. Risk communication through drug labeling is one of the FDA's primary approaches to risk management. A black box warning is the strongest labeling requirement the FDA has, intended to alert prescribers to the high risks associated with certain drugs.

Dr. Wagner's project was one of the HMO Research Network grants entitled "Prescribing Safety Program." Dr. Wagner emphasized the importance of studying black box warning by pointing out that that there is much research on adverse drug events in the hospital setting but less in ambulatory settings. High-risk drugs are used in ambulatory populations and black box warning drugs are presumably the highest risk drugs.

39 This project was part of the project entitled CERTs Prescribing Safety Program: Overall Safety of Current Drug Use with Richard Platt as the Principal Investigator

40 Medscape Medical News, November 18, 2005, "Inconsistent Adherence to Black Box Warnings: A Newsmaker Interview With Anita Wagner, PharmD, DPH"

Black box warnings (BBWs) are the Food and Drug Administration's (FDA) strongest labeling requirements for high-risk medicines. It is unknown how frequently physicians prescribe BBW drugs and whether they do so in compliance with the warnings. The purpose of the present study was to assess the frequency of use of BBW medications in ambulatory care and prescribing compliance with BBW recommendations.[41]

The study was retrospective and used automated claims data of 929, 958 enrollees in 10 geographically diverse health plans in the United States. Frequency of use in ambulatory care of 216 BBW drugs/drug groups between 1/1/99 and 31/6/01 was estimated and dispensing compliance with the BBW requirements for selected drugs was assessed and reported.[34]

Research Findings

The 30-month study findings included:

Most non-compliance was associated baseline laboratory monitoring recommendations: 49.6% of all therapy initiations that should have been accompanied by baseline laboratory monitoring were not.[34]
Greater than 40% of enrollees received at least one medication with a BBW.
There were few instances of prescribing during pregnancy of BBW drugs absolutely contra-indicated in pregnancy.
There was almost no co-prescribing of contraindicated drugs with the two QT-interval-prolonging BBW drugs evaluated.

Dissemination

Publication
Wagner AK, Chan KA, Dashevsky I, Raebel MA, Andrade SE, Lafata JE, Davis RL, Gurwitz JH, Soumerai SB, Platt R. FDA Drug Prescribing Warnings: Is the Black Box Half Empty or Half Full? *Pharmacoepidemiol Drug Saf.* 2006 Jun;15(6):369-86**.**

Times Cited: Lexis Nexis results returned 13 documents.[42]
Journal IF[43]: 0.750
Associated Commentary: **"**Thinking Outside the (Black) Box: A New Research Agenda" Paul J. Seligman, Director, Office of Pharmacoepidemiology and Statistical Science, Center for Drug Evaluation and Research, FDA. The journal asked Paul Seligman of the FDA to write a commentary with the publication of the article.
Key Citation: Article cited in IOM Report Preventing Medication Errors: Quality Chasm Series (2007), Chapter 2.
AHRQ: Patient Safety E-Newsletter, December 2, 2005, Issue No. 15 "1. New AHRQ study finds mixed compliance with medication warning labels"

41 Authors: Wagner AK, Chan KA, Dashevsky I, Raebel MA, Andrade SE, Lafata JE, Davis RL, Gurwitz JH, Soumerai SB, Platt R. FDA Drug Prescribing Warnings: Is the Black Box Half Empty or Half Full? Pharmacoepidemiol Drug Saf. 2006 Jun;15(6):369-86.

42 Lexis Nexis report was provided by a HMO Research Network staff person

43 ISI Journal Citation Report 2005

CERTs: Announcement 11/18/05 "warning labels on high-risk drugs not always heeded by doctors.
Media:
11/18/05
Wall Street Journal Online "Drug-safety labels often go unheeded"
HealthDay Reporter "Doctors not heeding 'black-box' warnings on Rx drugs", posted on MedicineNet.com, MedicineOnline.com and KESQ.com (news channel website)
SeniorJournal.com "Warning labels on high-risk drugs inconsistently heeded by doctors"
Medscape Medical News "Inconsistent adherence to black box warnings: Newsmaker interview with Anita Wagner, PharmD, DPH"
U.S. News and World Report "Doctors often ignore 'black box' warnings on prescription drugs"
Drug Industry News at adrugrecall.com "doctors not heeding 'black box' warnings"
Drugwonks.com "the art of the black box"
National Center for Policy Analysis at ncpa.org "black box warnings often go unheeded"
11/22/05
The Harvard Crimson "Study: Rx Warnings Ignored"

Other publications:
Interviewed for article "Relevance of Black Box Warnings" in the APSF Also had interviews" Newsletter of Anesthesia and Patient Safety" (APSF) 2006 vol 21 #1 pg 16&18
Harvard Medical School Office of Public Affairs News Release 11/18/05 "Warning labels on high-risk drugs inconsistently heeded by doctors: Better means of communicating risks needed"

Dr. Wagner also mentioned that she spoke on a radio show . Dr. Wagner also reported many contacts upon release of the electronic version, with additional interest generated by the release of the print version. Dr. Seligman was contacted by the journal *Pharmacoepidemiology and Drug Safety* to write a commentary in the issue in which the BBW warning appeared.

A. Impact of the Findings

The potential implications of the findings were described in the article's conclusions:

Many individuals receive drugs considered to carry the potential for serious risk. For some of these drugs, use is largely consistent with their BBW, while for others it is not. Since it will not be possible to avoid certain drug- associated risks, it will be important to develop effective methods to use BBWs and other methods to minimize risks.

Level 1 Impact: Research
This case study had a level 1 impact; it contributes to future research in several ways. First, this study involved compiling a list of drugs with black box warnings, because no such list existed. Another perceived potential import of the research may be indicated by the fact that the editor asked Dr. Seligman of the FDA to write a commentary in that issue. Additionally, the findings of the extent of noncompliance with BBW and particularly regarding recommendations for baseline laboratory monitoring are important results.

Level 2 Impact: Policy
The impact of the Black Box warning study on policy or FDA regulation is difficult to assess, in part because the study results were only released in November 2005 and time can be an important factor.

However, it has contributed to literature that advances the understanding of the use of black box warnings as a risk management tool and of potential ineffectiveness due to non-adherence to the warnings. An AHRQ representative characterized the to-date limited impact to the findings being outcomes that were already known, rather the more important question was what should and can be done about the limited attention to the black-box warnings.

Also, Dr. Seligman in his commentary stated, "What we really need to know is why and under what circumstances co-prescribing occurs, what patients are told, how they actually use the medicines, and whether such use is appropriate." An FDA representative who was a study respondent commented on the black box:
It's unique only in the sense that this is the kind of work that I really do believe should be done in medical practice everywhere …in an organization monitoring the quality of care being provided.... this is really an issue about how well people are paying attention to issues of concern in drug therapy. I liked the study, more studies of this type should be done...but the real issues are – are people using the results of these studies to improve the way that care is delivered?

An FDA representative thought it was too early to tell if the black box study had an impact, as the article had just been published in June 2006. We cannot assess whether this study has yet affected clinical practice or outcomes. However, given that it has informed a national level risk management program used by the FDA, it has the potential to have an impact. When Dr. Wagner was asked why she thought her research had the large amount of media attention it did, she identified the following as potential factors: the aging population with many medical conditions that are amenable to effective treatment with medications, but because patients are sicker and treatment is more complex, there is an even greater need to be clear about risks and risk communication, especially in ambulatory care where most prescribing occurs. In addition, there may be a heightened awareness in the population of the risks of medicines.

Mechanisms of Impact

While the black box warning study is recent, it has received much media attention. Other indications of the importance of the study are its selection by the journal editor for an FDA commentary and that the study was cited recently in the Institute of Medicine Medication Errors report. The study had not been released for as long as some of the other case studies and did not have the time often needed for impact such as changing or informing policies. The media attention may be an indicator potential impact, and drug safety is an important topic for the public and the research community.

Impact Case Study II: QT Prolongation

Project Title: Evaluation of physicians' understanding of the QT interval and medications that may alter it
PIs: Nancy Allen LaPointe, Sana Al-Khatib
CERT: Duke
Brief Project Description: Evaluate physicians' knowledge of the QT interval and medications, diseases, and drug combinations that may alter the QT interval.

Formation of the Research Question

This project stemmed from previous studies at the Duke CERTs and the questions those studies raised. Some of the first studies the Duke CERTs conducted were looking at the risk management program the FDA instituted for the anti-arrhythmic drug dofetilide, a drug known to prolong the QT interval and cause torsades de pointes. As a result of these studies on dofetilide (seems like you should reference these here), the Duke CERTs investigators raised the questions of whether practitioners understand the meaning of QT interval prolongation, which drugs prolong the QT interval and how to measure the QT interval? Around the same time, studies were published about practitioners' continued use of another QT prolonging drug, cisapride, with contraindicated medications that increase the risk of QT prolongation despite warnings in the product labeling (insert reference). Therefore, the Duke CERTs investigators began to assess health care practitioners' knowledge of the QT interval and medications that may prolong it along with other studies to assess real world co-prescription of more than one QT prolonging drug (insert references – Curtis et. al and Allen LaPointe et. al).

One of the first studies to assess practitioner knowledge was a pilot survey conducted with a group consisting largely of cardiologists attending a cardiology symposium. The survey included a reproduction of a ECG complex and asked respondents to measure the QT interval. The survey also included questions about which drugs or drug combinations could prolong the QT interval and clinical factors associated with increased risk of QT prolongation.

A. Research Findings

> From a total of 334 survey respondents, 157 (47%) were physicians; 271 (81%) stated that cardiology was their area of specialization. Most of the respondents (86%) said that they would check an ECG before and after starting QT-prolonging medications, but less than half (42%) of all respondents and only 60% of physician respondents were able to accurately measure a sample QT interval on the survey. Less than two-thirds (63%) of respondents were able to accurately identify possible QT-prolonging medications, while only about half (51%) could accurately identify medication combinations that might prolong the QT interval.[44]

Given the findings, the investigators went on to conduct a more rigorous study to determine the generalizability of the results. They conducted a survey to assess health care practitioners' ability to correctly measure the QT interval, and to identify factors and medications that may increase the risk of QT-interval prolongation and torsade de pointes. Participants included practitioners attending

[44] *LaPointe NM, Al-Khatib SM, Kramer JM, Califf RM*. Knowledge deficits related to the QT interval could affect patient safety. *Ann Noninvasive Electrocardiol.* 2003 Apr;8(2):157-60.

internal medicine and psychiatry Grand Rounds at six academic institutions and practitioners at six community hospitals in the same geographical areas as the academic institutions.[45] The results were:

> Of approximately 826 attendees, 517 (63%) completed the survey. Of about 608 attendees of internal medicine conferences, 371 (61%) responded, and of about 208 attendees of psychiatry conferences, 146 (67%) responded. Of a total number of 20 questions, the median number of correct answers for the whole group was 10 (interquartile range 7-13). The median number of correct answers for internists was 12 (interquartile range 9-13), for psychiatrists 10 (interquartile range 7-13), and for other specialists 10 (interquartile range 5-13). Respondents who graduated between 1990 and 1999 and academicians performed significantly better overall than other respondents. Of the 517 respondents, 224 (43%) measured the QT interval correctly. Physicians in training and academicians were more likely to measure the QT interval correctly.[4]

Given the finding of limited knowledge of the QT interval and QT prolonging medications, the Duke CERTs investigators developed a QT educational module to address the knowledge deficit (insert reference for website). The module was designed to provide information to healthcare practitioners on how to measure the QT interval, what the QT interval means, and what drugs and other clinical factors could change the QT interval. The module was designed to be not only a case-based learning tool, but to serve as a resource practitioners could return to when questions arose in their daily practice (e.g. does this drug prolong the QT interval?). Prior to development of the module, the investigators solicited the advice and opinions of experts in cardiac repolarization to refine the module contents. Results of this expert survey and collective knowledge regarding the QT interval was submitted as a manuscript and published in 2003 in JAMA. Prior to the official public launch of the module, numerous practitioners including some of the experts in cardiac repolarization were asked to review the module and provide feedback. The module was revised and underwent pilot testing to determine if knowledge of the QT interval improved among a group of medical residents who completed the module.

The QT educational module was launched (with an announcement of its release) on the Duke CERTs' website initially. To reach a larger audience, the Duke CERTs investigators leveraged their relationship with the American Heart Association (AHA) to post the module to the AHA website.

Dissemination

Publication I: Allen LaPointe NM, Al-Khatib SM, Kramer JM, Califf RM. Knowledge deficits related to the QT interval could affect patient safety. *Annals of Noninvasive Electrocardiology*. 2003 Apr;8(2):157-60.
Journal IF: 0.790

Publication II: Al-Khatib SM, Allen LaPointe NM, Hammill BG, Chen AY, Kramer JM, Califf RM. A survey of health care practitioners' knowledge of the QT interval. *Journal of General Internal Medicine* 2005;20:392-396
Journal IF: 3.013

[45] Al-Khatib SM, Allen LaPointe NM, Hammill BG, Chen AY, Kramer JM, Califf RM. A survey of health care practitioners' knowledge of the QT interval. *Journal of General Internal Medicine* 2005;20:392-396.

Publication III [46]**:** Al-Khatib SM, Allen LaPointe NM, Kramer JM, Califf RM. What clinicians should know about the QT interval. JAMA. 2003. 289:2120-2127.
Journal IF: 23.332

Publication IV: Curtis LH, Ostbye T, Sendersky V, Hutchison S, Allen LaPointe NM, Al-Khatib SM, Yasuda SU, Dans P, Wright A, Califf RM, Woosley RL, Shulman KA. Prescription of QT-prolonging drugs in a cohort of about 5 million outpatients. *American Journal of Medicine 2003*;114:135-141.
Journal IF: 4.388

Publication V: Nancy M. Allen LaPointe Frequency of High-Risk Use of QT-Prolonging Medications. Pharmacoepidemiology & Drug Safety 2006;15:361-368
Journal IF: 0.750

Media: U.S. News & World Report
Presentations: Presented at the American College of Cardiology (ACC) meeting in 2002 and 2004. Presentations also provided in medical centers titled, "what you should know about the QT interval." A presentation on the dofetilide risk management program was also given at the Drug Information Association meeting in 2002.

Impact of the Findings

Level 1 Impact: Research
This research was an important contribution to the understanding of medication risks and safety, particularly the role of the prescribers. From the first study the researchers identified knowledge deficits of various prescribers. The second published study suggested that many healthcare practitioners cannot correctly measure the QT interval and cannot correctly identify factors and medications that prolong the QT interval. The findings suggest that greater attention to the QT interval is warranted to ensure safer use of QT prolonging medications. The potential impacts of the findings on future research are numerous, including: the potential to examine the impact of the educational module on physician knowledge and prescribing behavior.

Level 2 Impact: Policy
Although this research did not have direct impact on policies, it has important regulatory implications. For example, drugs that prolong the QT interval with limited clinical efficacy beyond other treatment options have a poor risk-benefit profile, particularly if one takes into consideration the findings of these studies – that practitioners have a knowledge deficit of QT prolongation and QT prolonging medications.

Level 3 Impact: Clinical Practice
The QT educational module has the potential to impact health care practitioners prescribing, drug monitoring, and drug utilization review (DUR) behaviors if their knowledge gaps are addressed; however, these studies cannot be directly attributed with impacting clinical practice, either in terms of practitioners or patients.

[46] Publications III-V were identified by Duke CERTs investigators as associated/applicable publications beyond the linked publications in the CC databases

Mechanisms of Impact

There were several mechanisms that supported the impact of this research:
Connections of stakeholders to a specialty organization (i.e. AHA),
Recognition of the gap and responsiveness of the researchers
Exploration of the problem via a pilot study
Conceptualization of the problem in the context of a larger population to understand its extent.
Recognition of the need for education regarding the QT interval and medications that cause QT prolongation
Context, given the withdrawal of cisapride from the market largely due to its QT prolonging effects

Impact Case Study III: Rickets, Vitamin D Supplementation and AAP Guidelines

Rickets is everybody's favorite [project/study] because clearly it was one of those "a-ha moments" for policymakers. The research was immediately taken up, programs were adopted to change things and it has changed things. So that was fabulous. (SC)

Project Title: Effect of AAP Guidelines on Vitamin D Supplementation recommendations in Practice[47]
PI: Marsha Davenport and Ali Calikoglu
CERT: UNC
Partners: NC WIC Program, America Association of Family Physicians (AAFP), American Academy of Pediatrics (AAP)

This case study is about a line of research that identified and understood vitamin D deficiency and rickets in breast fed infants, explored the impact of AAP guidelines on vitamin D supplementation, and contributed to the change in the guidelines.

Formation of the Research Question

Dr. Calikoglu and Davenport were co-investigators on these CERTs studies. They described how the study began, specifically that they started diagnosing rickets in African-American children in their practices. Additionally, Dr. Calikoglu recalled that there was one father, a professional athlete who was "up in arms" about his child having rickets, perhaps providing an extra impetus to explore what was happening. Dr. Schwartz at the Wake Forest University Baptist Medical Center was a key partner on the research with CERTs investigators, and he recalled seeing more and more rickets and vitamin D deficiency cases, such that he and another colleague wrote the cases up in the NC Pediatric Society bulletin. Together they compiled information on 30 cases of vitamin D deficiency rickets, which they submitted to the Journal of Pediatrics. Dr. Schwartz describes:

> *Initially when submitted to Pediatrics, in the review process they sent it back and asked for more data and "this is where the review process worked well in that they told them they needed more information which inspired them to get more data." So they went to get two diff data 1) Dr. Schwartz got the data from the WIC program about the breastfeeding rate (increased significantly) from 1989 to 1999, Apparently the rate of breastfeeding had quadrupled among African American children and tripled in all, something like from 5% - 30% during the period 2) Dr. Davenport looked at prescribing practices.*

The article was published in 2000.[48] After the publication of the report and manuscript, the researchers looked into resources they could mobilize in NC and Dr. Schwartz at Wake Forest had close connections to NC WIC program. Dr. Schwartz described the good relationship with the WIC program and NC health department. They come to the Pediatrics society meetings and Dr. Schwartz

[47] The predecessor research project was identifying nutritional rickets in African American breast-fed infants

[48] Kreiter SR, Schwartz RP, Kirkman HN, Charlton PA, Calikoglu AS, & Davenport ML. Nutritional rickets in African American breast-fed infants. *Journal of Pediatrics*, 2000;137:153-157.

has known the WIC representative for a long time at WIC they have a long term, trusting relationship. The WIC representative gave Dr. Schwartz the WIC breastfeeding data.

Research Findings

The 30 case dataset they collected revealed the following, as described in the published article:

Thirty patients with nutritional rickets were first seen between 1990 and June of 1999. Over half of the cases occurred in 1998 and the first half of 1999. All patients were African American children who were breast fed without receiving supplemental vitamin D. The average duration of breast-feeding was 12.5 months. The age at diagnosis was 5 to 25 months, with a median age of 15.5 months. Growth failure was common: length was <5th percentile in 65% of cases, and weight was <5th percentile in 43%.[10]

After they had their cases and the finding, they approached WIC and presented to them these data. The WIC program agreed to provide nursing mothers with free vitamin D (in NC no vitamin is covered by Medicaid). The program provided $1.50/baby/month vitamin D supplement (in a vitamin D formula with A, C, D). Around the same time, the CDC convened a vitamin D expert panel meeting:

On October 11 and 12, 2001, scientists, health practitioners, and policy makers from the Centers for Disease Control and Prevention (CDC), the American Academy of Pediatrics (AAP), academic and professional institutions, and government agencies met in Atlanta, Georgia to discuss vitamin D supplementation of infants. CDC convened the meeting to examine scientific issues and policy implications regarding vitamin D supplementation and to identify current research needs. Experts presented information on the incidence of rickets in the United States; the role of sunlight in preventing vitamin D deficiency and in the occurrence of skin cancer; and the risks and benefits of vitamin D supplementation, including its impact on breastfeeding; alternatives to supplementing infants with vitamin D; and development of a communication strategy to promote a new policy on vitamin D.[49]

Dr. Calikoglu served on the expert panel to which he presented on more cases of vitamin D deficiency rickets. It was also at this panel meeting where he started learning that the AAP was looking at revising its guidelines for breastfed infants and vitamin D supplementation. So Dr. Calikoglu and Davenport developed and fielded a survey of pediatricians in NC that found that they were not supplementing vitamin D in breastfed infants in part because the AAP guidelines did not clearly address the issue, and that more recently trained pediatricians were less likely to supplement because they were following newer guidelines, while older physicians were practicing more appropriately because of older guidelines. Dr. Calikoglu or Davenport did not participate on the guideline revision committee. Given the likely, upcoming change in guidelines they sought to determine whether physician prescribing behavior would impact the prevalence of vitamin D deficiency rickets and to assess the impact of the changed guidelines. So in 2002 they sent a survey to members of AAP and member of AAFP before guidelines were changed. The UNC CERT described the results of the initial survey in a progress report:

[49] Vitamin D Expert Panel Meeting October 11-12,2001; Atlanta, GA. Final Report.

"The results of initial survey indicate that inadequate Vitamin D supplementation may be an important contributing factor to the development of nutritional rickets in many infants and toddlers in the United States. It also suggests that the vagueness of established guidelines was a likely factor in inadequate vitamin D supplementation practices." (UNC PR04-05)

Then in April 2003 the AAP published their new guidelines that recommended 200 IU/day for all breast-fed infants. So the investigators, one year post AAP guidelines randomized a follow-up survey to AAP and AAFP groups and sent an intervention package with a) letter strongly recommending vitamin D supp for infants b) new guidelines from AAP c) a magnet d) a calendar 2004 with the statement "breastfed infants deserve vitamin D supplements – its not just about bones anymore" at the top. The recipients of this package were the intervention group. After a year the investigators sent a second survey to the same population to identify how family practitioners compared to pediatricians in supplementing vitamin D. They found that family practitioners only supplemented vitamin D 32% of the time in 2002 and 58% in 2004.

Dr. Schwartz said "... WIC nationally is revising their package of food. IOM report 2005 talk about the need for Vitamin D in their "breastfeeding promotion and that daily vitamin D and supplement need a recommendation on the national level that the WIC program include them.

Dissemination

Publication: Kreiter SR, Schwartz RP, Kirkman HN, Jr., Charlton PA, Calikoglu AS, Davenport ML. Nutritional rickets in African American breast-fed infants. *Journal of Pediatrics*. 2000;137:153-157.
Journal IF: 3.837
Davenport ML, Uckun A, Calikoglu AS. Pediatrician patterns of prescribing vitamin supplementation for infants: do they contribute to rickets? Pediatrics. 2003 Apr;111(4 Pt 1):908-10.
Journal IF: 4.272

Media: There was significant pickup of this work by the media and reporters calling from Canada and throughout the US. Dr. Schwartz presumed that this is because people can directly relate to this, rickets, and broken bones, and real disease and can understand "something from 1800s and diet.

CERTs and AHRQ publications:
Other publications: Stated from Australia to Japan news agencies cited the study

Impact of the Research Findings

This case study and the initial study in particular were consistently and most frequently identified by investigators from across the CERTs as an example of CERTs work having an impact.

Level 1 Impact: Research
The studies revealed the estimated incidence of rickets, which was thought to not to exist to any significant degrees. However, with the trends in promoting breastfeeding at the end of the 20th century and without the appropriate supplementation in part because of the AAP guidelines, breastfed

infants were not receiving sufficient vitamin D, and as a result, cases of vitamin D deficiency and rickets were increasing. The NC pediatricians and investigators compiled the cases to illustrate this point, along with the data showing the concomitant trend in breastfeeding from the WIC program data.

Additionally, the findings on the guidelines were important for understanding the potential impact of guidelines on practice. Also, they demonstrate the challenge that even when guidelines are changed, change in practice can be slow.

Level 2 Impact: Policy
The research had an impact in terms of contributing to a CDC-convened group of experts. The research has also impacted the NC WIC program policy that resulted in the provision of vitamin D supplementation for breastfed infants. This research also impacted the AAP guidelines on vitamin D supplementation.

Level 3 Impact: Clinical Practice
The investigators demonstrated the educational intervention and the provision of the new AAP guidelines on vitamin D supplementation in breastfed infants did have an impact on the behaviors of physicians

Mechanisms of Impact

The key factors that led to this project and portfolio of research having the impact included: connections, collaboration, and time. Drs. Davenport, Calikoglu and Schwartz indicated that a key reason for the impact of the findings with respect to changing WIC coverage policy was the connections to the NC WIC program. Dr. Schwartz described a good relationship not only with the WIC program but the NC department of health. They had already asked for the data to show the trend in breastfeeding at the time of their case studies. So when they contacted the WIC program to present on their findings they were more than willing. The CERTs investigators stated, "...key thing was joining forces with Wake Forest group to increase the numbers of collaborators with Dr. Schwartz with more than one institution in the state working on something to have a greater weight with policymakers.

Dr. Schwartz believed that the key mechanisms were communication and mutual effort (collaboration). It was 5-6 years before policy changed (AAP) he'd been working on this for a long time. He had been to the to the AAP forum/congress previously – " ...then we got the data to have them listen."

An AHRQ representative identified time as a key factor:

> *For one thing [this project] had legs and it's old and so, of course, lots of things can happen within, you know, seven years or so that's been kind of an active issue. The other thing that makes that a little bit easier for it to have legs is that I think the American Academy of Pediatrics is a real groundbreaking group... and very sensitive, I think, to these sorts of things, and the folks at the CERTs have kind of had an in there with Marcia Davenport and other people who've kind of worked with the American Academy of Pediatrics. ...it's a good example, but it certainly works because the specialty organization is a good one. It's also a good example I think of what we were hopeful of the local collaborations that the CERTs would have. You know, when we were going to fund four new CERTs one of the things we*

said is that we really think that the CERT ought to work regionally, and work with its local authorities and that's a good way to get started. And that worked out really well because they worked with the local Medicaid authority. Vanderbilt does that too, work closely with the state, the ideal situation.

Dr. Davenport and Calikoglu stated that could always use more money to further investigate the magnitude of the problem and its solutions, because they could have devoted more time, although they stated that it would not have happened without the CERTs. Dr. Schwartz felt that this project was the "most important thing he's worked on" He calls it a "new old disease."

Impact Case Study IV: Tensions in Antibiotic Prescribing

"If the only thing you focus on is antibiotic use without looking at person to person spread, then that's not sufficient" (Penn)

Project Title: Tensions between patient and public health values in generalists use of antibiotics
PI: Josh Metlay
CERT: Penn
Partners: Robert Wood Johnson Foundation
Description: Cross-sectional anonymous mail survey. PARTICIPANTS: National random sample of 400 generalist physicians (general internal medicine and family practice) and 429 infectious diseases specialists.

Formation of the Research Question

Dr. Metlay provides the context and background important for understanding the significance of the research:

Overuse of antibiotics is a key force driving the emergence of resistant bacteria.
Increasing awareness of the problem of drug resistance may be part of the solution to the problem, however the question is: How important is that for physicians when making prescribing decisions?

In some cases providing education to physicians about the risks and benefits of drugs may result in better individual decisions but in some settings providing information is less likely to change behavior.

A major risk associated with antibiotic misuse is the public health and community cost and not individual patient risk. Dr. Metlay poignantly describes:

"The fact that the benefits happen for patients and the risks happen for society could create an unequal weighting in peoples' minds as to how important" antibiotic prescribing and use are to them or their patients."

He offers another example to illustrate:

"A related example is vaccination policies, where the risks are often for the individual person who gets the immunization but the benefits are on a more societal level. it's been observed that without guiding policies, individuals will opt out from getting vaccinated because they will recognize that they can get the public health benefit without taking the individual risk. And that's why we have policies that essentially mandate vaccinations."

Similarly, individual patients and physicians may opt to keep taking and prescribing antibiotics as long as they know that most people are avoiding them because they will get the individual benefit of the antibiotics and not contribute that much to the harm. This, Dr. Metlay continues, "begs the question as to whether we can really improve the quality of antibiotic prescribing, in hospitals and outpatient settings, simply by educating patients and providers. Or do you really need to impose some kind of control on the whole system because of this imbalance in risks and benefits."

Therefore hospitals may have antimicrobial management programs that may require an individual physician obtain approval before prescribing a number of broad-spectrum antibiotics. Unfortunately, that is less common in the outpatient system because the same kind of information systems and decision support systems are not available.

The study was a survey of physicians (i.e. generalists, internists, family practitioners, and infectious disease specialists) using a nationally representative sample drawn from an American Medical Association database. The objective was to obtain "a snapshot of how physicians viewed current goals around appropriate antibiotic use in ambulatory care settings" (JM). The survey included knowledge and attitude questions and asked respondents to answer how important certain things were in their decision-making. To reveal how the prescribers think rather than having them directly provide their thoughts, so the study could identify what is *driving* their decision-making the survey included vignettes in which they had to make treatment decisions. The design of the vignettes was such that the study investigators were manipulating some of the key issues to see how those particular issues were influence their decisions.

Dissemination

Publication 1: Metlay JP, Shea JA, Asch DA. Antibiotic prescribing decisions of generalists and infectious disease specialists: thresholds for adopting new drug therapies. *Medical Decision Making.* 2002 Nov-Dec; 22(6):498-505.
Journal IF: 1.822

Publication 2: Metlay JP, Shea JA, Crossette LB, Asch DA. Tensions in antibiotic prescribing: pitting social concerns against the interests of individual patients. *Journal of General Internal Medicine.* 2002;17:87-94.
Times Cited:" At one point they published the articles that were the most cited in the journal each year.... for the Journal of General Internal Medicine that was one of the top ten or twenty"
Journal IF: 3.013

Abstracts: One abstract presented
Other publications:
Leonard Davis Institute of Health Economics Issue Brief, Vol 7, No 7, May 2002. The LDI Issue Brief[50] is disseminated to "those issue briefs are pretty widely disseminated, particularly to non academic audiences, so to hospital executives, pharmacists, executives" (JM)

Dr. Metlay described presenting his research in CERTs meetings as well as talking to the FDA about the expected and unexpected results of adding warnings to package inserts for antibiotic drugs. He

[50] Issue Briefs. These are four-page summaries of research results that highlight their social and policy relevance. They are written in easy-to-understand language with bullet points, headers, margin cut-outs and other devices to enhance delivery of the message. They are professionally written, formatted, printed and distributed to a wide, but carefully selected, audience of senators and members of congress and their staff, other politicians, key industry representatives, and other individuals who do not read scientific journals but are in a position to use the research results.

also mentioned speaking to different physician groups and going beyond the traditional dissemination of findings in peer-reviewed journals.

C. Impact of Research Findings

Level 1 Impact: Research
Findings of the first published article:

> Respondents significantly reduced their threshold for switching to a newer antibiotic as disease severity increased. Generalists were more responsive to disease severity than Infectious Diseases specialists. Thus, the adoption of recommendations to limit overuse of newer antibiotics may be variable across clinical settings and providers, reducing the impact of these recommendations on emerging resistance.

Findings of the second published article:

> Both generalists and infectious diseases specialists were more likely to prefer newer, broader drugs for the treatment of pneumonia compared to older agents still recommended by national guidelines. Physicians rated the issue of contributing to antibiotic resistance lowest among 7 determinants of their choices. CONCLUSIONS: Despite national guidelines and increasing public awareness, the public health concern of contributing to the problem of antibiotic resistance does not exert a strong impact on physician prescribing decisions for pneumonia. Future efforts to optimize antibiotic prescribing decisions will need to consider options for increasing the impact of public health issues on the patient-oriented decisions of individual physicians.

Level 2 Impact: Policy
Dr. Metlay identified two primary areas in which changes are occurring that he could not directly attribute to his research, but believes that it was part of the critical mass of research that may be influencing the changes. The changes that he is observing in the health sector are described below:

In the recent past the CDC had funded intervention studies to reduce antibiotic overuse and improve the quality of antibiotic use that primarily focused on education, however the studies had a small effect on reducing the misuse of antibiotics. More recently, investment is being made in studies and designs that are not just educationally driven. For example, Dr. Metlay stated that,
"more studies are trying to provide real time feedback to doctors about what they're doing and develop other kinds of levers, such as computerized decision support tools, that might help improve the quality of prescribing."

In the last few years the rate of antibiotic use for non-bacterial infections in children has become a quality measure for health plans and subsequently, a measure for employers choosing health plans. Whether the fact that there is now a quality measure impacts the rates of antibiotic use is unclear, but it indicates a movement toward using quality measurement and incentives to drive the change and not just education. Dr. Metlay also stated that CMS has now tied performance of antibiotic treatment for pneumonia to payment.

Dr. Metlay stated that there are starting to be stronger interventions and antibiotic management because of a general awareness that certain kinds of structure are needed to really improve quality. He concludes that not unlike other domains besides antibiotics, "maybe in some way this kind of

information helps hasten that thinking, not to close the book on education, but to point out the serious limitations to education and knowledge awareness as a quality driver."

The findings from these studies have had an impact on the research community and were recognized as a frequently viewed article on the journal's website. Additionally, they raise a critical issue about prescribing behavior and how choices are made in prescribing antibiotics. The topic of antibiotic prescribing and resistance is a critical area for AHRQ.

3.4. CERTs Program Outcomes

3.4.1. Educational Outcomes

CERTs Value - Education: Education of current and future health care providers, policy makers, and patients is critical to improving health.[51]

The CERTs are committed to education to improve the health of patients and the population. The CERTs have provided both formal and informal post-graduate opportunities. Formal training has included research centers supporting traineeships and fellowships (HMO, Penn, Alabama, Arizona). The trainees included: faculty, researchers (i.e. epidemiologists, health services researchers, clinical researchers; and social scientists), graduate students in various disciplines, medical students, pre-medical students, pharmacy students, social workers, and providers. The Alabama and Penn investigators provided many examples of their traineeships and training, and in interviews characterized it as a critical part of the CERTs and as a special opportunity given that the CERTs are centers and have money for pilot studies. "I think a critical aspect of our CERT is our ability to serve as a training vehicle for young investigators," said a UAB Investigator. The Penn CERT developed a pharmacoepidemiology fellowship-training program which had six fellows by 2002-2003 in response to the need for well-trained clinical scientists (Penn PR02-03). Less formally, some CERTs described providing access to data or access to study collaborators to further train newer investigators (e.g. HMO-affiliated students have sought access to CERTs HMO data for their dissertations).

Some CERTs stated that providing junior faculty research opportunities increased their visibility. Some CERTs centers described having internal scientific meetings, journal clubs, seminars on research methods and therapeutics, visiting professorships, and feedback opportunities. The Penn CERT has a strong commitment to education and training about anti-infective therapeutics and epidemiological research. One Penn investigator stated, "Were it not for the CERT many of these people would not be focused on anti-infectives. It has allowed us to provide support to trainees and others within the center."

Some CERTs investigators attributed their involvement with their CERT as being helping their career, for example by providing "seed money", mentorship with experienced investigators, and access to feedback (i.e. CERTs scientific calls). As one CERT investigator stated, "My involvement in the CERT certainly has helped my career" (UAB) and another attributed to the CERT his shift from basic to outcomes research. A few of the more junior CERTs investigators identified the principal investigators of their center and other senior investigators as mentors. A Duke CERT

[51] About CERTs: Values retrieved from http://www.certs.hhs.gov/about_certs/values.html

investigator stated his work on practice guidelines and involvement with the CERTs enlarged his perspective (in grad school his focus has been on medical decision making and mostly at the point of care, in physician-patient interactions) and now because of the CERT work is more focused on policy.

Additionally, the CERTs program as a whole fosters the development of junior and seasoned investigators in their monthly scientific calls in which researchers present their research or project ideas to obtain constructive criticism and feedback. Many CERTs investigators, who raised the topic of the scientific calls, characterized the calls as very helpful, collegial, and a safe environment in which to present projects. One investigator stated, "Scientific calls have been a fabulous innovation" (UNC). A CERT PI explained:

A key has been the bonding among the members of the network. We share things on those scientific calls that we never would have shared because we were rivals. Lots of organizations with therapeutics as focus come to those annual meetings....

The CERTs, partly because of the relationships they have built and their focus on education, appear to have created a less competitive environment, allowing for collaboration, networking and collegiality. A number of CERTs investigators and stakeholders identified the minimization of competition and collaboration model as unique and extremely positive.

Genuine camaraderie... Not too much competitiveness... Very frank and honest collaboration on scientific calls... has strengthened familiarity and collegiality. We need more sharing and collegiality in science....

3.4.2. Centerness

"Centerness" is a concept that is helpful for understanding program outcomes beyond research and education. Centerness as a concept has been used in federal agencies for funding and evaluating centers. The National Institute of Drug Abuse includes among the characteristics of centerness thematic focus, synergy, and involvement of different disciplines.[52] An AHRQ representative describes the original RFA for the CERTs, "We wanted them from the beginning to have a centerness about them" and to be centers that already existed. The center structure was intentional, but respondents also responded to a question about the advantages and disadvantages of the center structure. A Steering Committee member said:

Once you're designated as a center then you can let that be part of your marketing to gain a portfolio of research funders, research projects, and to build from strength to strength. Without pre-existing funding as a center, you don't have the critical mass that allows you to move this field forward, so the funding of centers, as opposed to individuals, was a critical conceptual breakthrough. And then there is the willingness to work across centers, to help all of us to move from strength to strength...

The CERTs investigators offered different interpretations of what makes their CERT a center, including:

[52] NIDA Characteristics of Centers: "Centerness", Activities, & Administrative Considerations. Retrieved from http://www.nida.nih.gov/Funding/CentersFig1.html

A number of projects that all have the same common theme…that brings people together. People have a tendency to drift on their own... it helps to have this framework. It encourages people to do things they would not normally do and keeps people focused on one area of research. (Duke)

We know each other's strengths and weaknesses. To know each other and internally critique, there's nothing like proximity...there is a huge advantage being a physical center. (Penn)

- *Fosters the sense of collaboration and reduces the sense of competition. (UAB)*
- *There is a structure... and goals that are common to the center...a center takes the next step to identify interventions...it's not just about research but about intervening" when you're a center... (Duke)*

The UAB CERT's situation is different because the University of Alabama has a center structure that is encouraged and has certain requirements. In response to our question about "center," we learned that the UNC CERT is a center in many ways, but not by the University's standards. "It's a center by designation. It's not a center in UNC's organizational status that reports directly to the provost".

The NIDA criterion that a center have a thematic focus is fulfilled for the CERTS by their focus on therapeutics research. A second criterion is multidisciplinarity. The CERTs values include multidisciplinary alliances: "the best research harnesses the collective expertise of medical practitioners, clinical pharmacologists, health services researchers, clinical epidemiologists, pharmacists, clinical researchers, and others involved in health care.[53] With this health-focused definition of multidisciplinarity the CERTs centers (with some variability) have involved individuals from these diverse backgrounds and expertise. An AHRQ representative explains the original intention of multidisciplinarity:

> *The idea was that you would have a multidisciplinary group that could look at areas in a variety of ways. It could be survey research or epidemiologic studies, or pilot clinical trials if there was enough money…the need was to have not just one discipline but many different disciplines ... to focus on a particular theme... increases the probability of success. Having a few senior investigators, a PI, and some trainees continues the development of the field; this was really important to us...*

Most investigators identified the center structure as advantageous, because a center provides opportunities for interactions with different investigators and collaboration. Additionally, a center provides researchers with an infrastructure and support that is helpful, for example, in applying for grants for which the center provides technical assistance. A center structure was identified as key for building data systems as well. Generally resources shared within a center across investigators was raised as helpful by a number of investigators in describing how the CERT center facilitated their work. A few investigators believe their research would not have been possible were it not for their CERT center and its infrastructure and support.

> *Being a designated center ... creates so many opportunities by the people we have involved with the CERTs to learn about other research opportunities... just to have a great team assembled by the PI consisting of collaborators inside and outside the university is a strength of our center. (UAB)*

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[53] CERTs Values: Multidisciplinary retrieved from http://www.certs.hhs.gov/about_certs/values.html

The CERTs bring together researchers and experts from: pediatrics, rheumatology, clinical pharmacology, cardiology, gastroenterology, internal medicine, biostatistics, psychology, communications, and pharmacy, among others. A CERT PI believed that the center structure facilitated involving multiple disciplines in the center. A few respondents stated that a center improves the credibility of the center with its supporting infrastructure. One respondent identified the center as useful for recruiting purposes. The educational components of the CERTs program have helped to "create a critical mass of seasoned investigators to train others" (CERT Investigator).

Given the wide-scoped of the CERTs program mandate, the use of a center structure and the nature of a center to bring in individuals to focus on the same topic, it was stated by some stakeholders that being a center creates synergy and a "whole that is greater than the sum of its parts" because as one respondent explained, "It is important to create centers if you want to move a field forward." An AHRQ respondent further explained that the centers would ultimately help "to have a field that would perpetuate itself."

3.4.3. Collaboration

Collaboration among the CERTs investigators and their CERT and non-CERT work was characterized by the terms synergy, inter-digitate, collaboration, networking, and leveraging. Developing collaborative relationships is a process; as one CERT investigator said "we've gone out to a number of resources within the university to create synergy... it takes time...we've made real strides." The CERTs investigators offered a few examples of projects in which they were collaborating with individuals from other CERTs (the exception more than the rule); a particular example that was often raised as illustrating CERTs collaboration was the Patient Safety grant. A Steering Committee member explains:

The CERTs agreed that, instead of competing with each other, the seven centers would collaborate, and all sign on to the HMO CERT's application, to be sure that all of the talent from all of the CERTs would be brought to bear on that program.

Therefore, the HMO CERT led the grant and involved the other CERTs centers as collaborators. Collaboration was in part driven by evolution toward the idea that "... a center could get more done collaborating and finding synergies than one could ever do alone." (SC) More specifically, "these centers have been doing research for a long time, but now the centers have a forum to discuss in advance the potential impact of their work with others in addition to the project officer of a federal agency."(SC).

The Risk Series was characterized as a key event by CERTs investigators, but others also recognized it as a venue that brought the CERTs together to collaborate if not literally with one another, to at least contribute to the topic of risk and frame their research toward that end. One CERT investigator said that one of the risk series "stimulated this project. So I had not even thought about this…. I attended those sessions ….and that prompted me to think about this project and it led to me doing this work as part of our CERTs renewal application." The investigator explained further, "This did not come up as a specific topic at that conference, but I went and heard all the discussions about risk communication, risk awareness, and risk behavior and I thought, 'well I work in musculoskeletal diseases; nonsteroidals are really an important area." Therefore I applied the methods and the line of thinking." (UAB).

When respondents identified examples of collaboration they would refer to the scientific calls, which offered a forum to obtain feedback from other CERTs and identify opportunities for collaboration. As one investigator said:

> *I think this is an important and innovative process we have in the CERTs which is forcing this collaboration across groups that have common interests and use similar methodologies... it's a remarkable example of collaboration across universities.*

The descriptions of the CERT collaborations have more to do with coming together to share ideas and offer feedback (and possibly resources) and less often to collaborate on research projects. However, the CERTs research centers were also groups of individuals or actual centers prior to becoming CERTs, "as great as they are, they were not chosen to be a network because of how well they work together." The CERTs certainly demonstrate intra-CERT collaboration, however inter-CERT collaboration has been limited. This is in part, as the UNC CERT stated, that because they are focused on pediatrics and the others CERTs are focused on primarily adult populations, there are few opportunities for collaboration other than on methodologies. However, there are opportunities that the investigators stated they were exploring with other CERTs. One investigator stated, "we are hoping to collaborate with them" while another investigator identified the crossover in one of the new CERT's work with the research they had done. Other respondents, including steering committee members, perceived that there was limited cross-CERT collaboration:

The hardest thing has been finding a theme that really allows these centers to work together around a particular concern or issue…most multicenter trials at NIH come with large amounts of money to support centers…it is hard to get people to work together when there's not a clear research question, hypothesis or priority program that everyone's working on and only a handful of support staff…it is.hard when grants are small and there is not a clear direction around what it is that you want done through a coordinated effort.

Although the CERTs have had some collaboration given the academic environments in which they are based, as many respondents acknowledged, collaboration is not the primary culture of academia. One respondent contends:

The initiative that CERT investigators have put toward collaborative effort... it is atypical of what happens in academic spheres... the competitive nature of academia normally precludes such collaboration. Scientific calls sharing results, discussing meaning, is actually very risky. Having guiding principles and really making this a true collaborative agreement the way it was from the program's initiation. ... there was so much pressure on AHRQ, especially in the political sphere to become much more directive oriented...don't answer any other questions ... don't think outside the scope (e.g. Decide Network)...

Additionally, a couple of the steering committee members identified the collaboration as a struggle for the CERTs to identify common therapeutic areas and topics to truly collaborate on. One of the federal agency representatives also stated that collaboration also requires greater funding or can be a greater financial burden than not collaborating with one another.

3.4.4. Public-Private Partnerships

> *We developed the idea of a public-private partnership activity, which we were able to do through cooperative agreements, to determine whether we could also obtain outside funding and to provide leeway to the centers to find partners so that they could fulfill the requirements of the legislation. (AHRQ)*

The CERTs program was constructed to support and facilitate partnerships, primarily to leverage funding. The CERTs program espouses a public-private partnership as a key value, stating, "For our results to apply to the 'real world,' the research must reflect a collaboration of groups with different perspectives and resources: patients, health care providers, government, academia, delivery systems, payers, purchasers, and manufacturers of medical products."[54] The CERTs have two different levels of engagements with partners. One is project partners who work with CERTs on research and education projects and the other is PATHs partners who partner with the program, attend the annual meeting, and essentially represent a sector involving no more than one person per organization.[55]

Though the CERTs program was structured to create and depend on partnerships, the program devised rules of engagement given their goal to be an unbiased, national resource of researchers conducting research that otherwise would not be conducted (e.g. by the pharmaceutical industry).

> *Through the national CERTs network we've set up principles that are very rigorous to allow us to discern whether projects that we want to consider CERTs projects satisfy a set of criteria...the private-public partnership committee reviews all the proposed CERTs projects and determines whether or not they satisfy those principles. (UAB)*

We compiled from lists of partners provided on CERT websites and upon request of staff at each CERT the partnerships between each CERT and its partners and the CERTs program as a whole. The data help to provide an indicator of the quantity, scope, and diversity of CERTs' partners. The partnership levels can serve as indicators of a CERTs involvement and collaboration in both the research and practice communities as well as indicate the potential for practical application of their research. The prominence of certain partner types also serves as an indicator of a CERT's primary research focus.

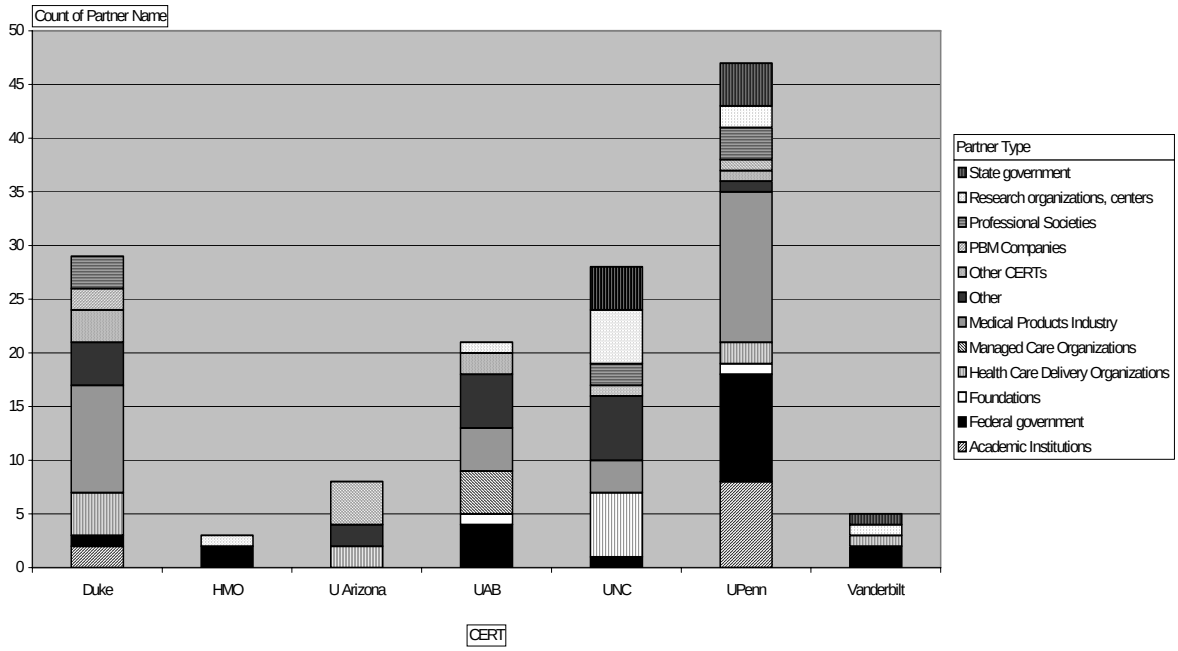
The Penn CERT had the highest number of partners (47) between 2002 and 2005 (Exhibit 11). Across the CERTs, the medical products industry (includeing pharmaceutical companies) was the most common partner, followed closely by federal organizations. The Duke and UNC CERTs displayed similar partnership levels. A UNC CERT investigator touted, "we developed a most interesting range of public-private partnerships….we understood what AHRQ wanted to see in terms of crafting genuine public private partnerships." The Duke CERT held twenty-nine different partnerships across the evaluation period, also most frequently partnering with members of the medical product industry. The UNC CERT entered into twenty-eight partnerships, most frequently either with health care

[54] CERTs Values: Public-Private Partnerships retrieved from http://www.certs.hhs.gov/about_certs/values.html

[55] CERTs Program NCP Committee Recommendations: Partnerships internal document provided to Abt by the Coordinating Center

delivery organizations or "other" organizations.[56] The UAB CERT entered into twenty-one partnerships between 2002 and 2005, and an Alabama CERT investigator said that, "partnering is the thing that we believe we've done the best" (UAB). Alabama's partners were most commonly from federal or other organizations.[39] The Arizona, Vanderbilt, and HMO Research Network CERTs each has fewer than ten different partnerships between 2002 and 2005. Both Vanderbilt and the HMO Research Network partnered most frequently with federal organizations. The UAB CERTs most frequent partners were from federal organizations or others. Additionally, the CERTs collaborated with partners representing local, regional, and national organizations and government agencies, non-profit organizations, and private companies.

Exhibit 11 CERT Partners Types



Some CERTs investigators characterized the nature of their relationships with partners. The CERTs worked with partners to obtain data, have access to patients, to disseminate findings, to impact the partner's policies, and as collaborators on the research. For example, CERTs collaborated with professional societies to disseminate findings. In another example, a CERT worked with a professional society to administer a survey about clinical guidelines to ultimately improve the society's guidelines. One CERT investigator characterized her experience as positive and gratifying to work with a professional society to increase dissemination. Other CERTs listed partners as the sites of data collection. Another investigator included access to a professional society partner as one of the impressive resources that the CERT makes available to a researcher. The HMO CERT, in contrast to the other CERTs, is structured as a network or built-in set of partnerships, and the Vanderbilt CERT has a longstanding history of partnering with the state's medical assistance program (TennCare).

[56] Category includes non-profit groups, national and state councils, organizational/professional boards, and software companies.

I'm impressed with the collaboration around not only what we were funded for but with how it has expanded to involve all kinds of other organizations, industry, and government in ways that I have not seen in most other projects which are funded by the federal government… I don't know of any other government-funded project that has gotten this kind of cross collaboration. (UAB)

The CERTs have had partnerships for many reasons including:

- Data (e.g. pharmacy data, outcomes data, VA data, MA data),
- Databases (i.e. membership database – cardiologists; MA, VA),
- Dissemination,
- Evaluation (e.g. risk management program for a CV medication),
- Data Collection sites (e.g. hospital, academic health centers),
- Leverage funding to use a partner to evaluate or conduct research locally or regionally to move to the national level (leveraging funding of CERTs work);
- Educational intervention (with partner);
- Co-investigators or true collaborators, scientific collaboration,
- Administration of a grants program for a disease organization (MD Arthritis Foundation),
- Access to patients,
- Provided venue for conducting research, community clinics, methadone clinics, pain center; other centers (academic),
- Other medical school or health care professional school,
- Blood glucose monitors provided by the partner for research,
- Private research organization, collegial partnerships and collaboration on projects (Partner – provided part of salary (leverage funding), provided access to data, and capacity to study some of these questions in the veteran setting,
- Publications.

"CERTs has facilitated and leveraged our ability to partner in a dramatic way." (UAB)

The CERTs has program partners or PATHs partners. "The Partnerships to Advance Therapeutics program aims to facilitate opportunities for public and private organizations to collaborate on research and educational projects to optimize the use of therapeutics."[57] We characterize the different CERTs PATHs (Partnerships to Advance Therapeutics) partners that were involved with the CERTs from 2002 through 2005 in Exhibit 12.

Exhibit 12: PATHs Partners

The number of PATHs partners remained fairly steady between 2002 and 2005, rising from thirty-one partnerships in 2002 to forty-one partnerships in 2003 before dropping to thirty-five partnerships in 2005. In each year there was a diverse array of PATH partner types. Professional societies were the most common PATH partners across all four years followed by the Medical Products Industry and partners categorized as "other."[40] The "public-private partnership model encourages a responsiveness to what questions need to be answered." (CC). While the CERTs program was designed to encourage public-private partnerships primarily to leverage funding, the partnerships

[57] http://www.CERTs.hhs.gov/partners/paths/index.html

have also helped to further dissemination, identify research collaborators, provide unusual data sources, and further impact policies.

3.5. CERTs Program Strengths & Successes: Results of the Appreciative Inquiry Exercise

As described above, while the purpose of this evaluation is to analyze the impact of AHRQ's Pharmaceutical Outcomes Portfolio and to determine if the program is moving toward its goals, the "Appreciative Inquiry" focuses only on those aspects of the program that have promise for the future. In addition, this technique can help encourage favorable organizational change among Portfolio stakeholders. The methodology was designed to answer these research questions: (1) What do various stakeholders view as the most successful processes and outcomes of the CERTs? and (2) How can this information be used to maximize, leverage, or build upon success in the future?

Strengths

Current Strengths of the Program

The current strengths of AHRQ's Pharmaceutical Outcomes Portfolio as perceived by the various participants can be categorized into the following five areas:

- Collaboration
- Cross-Disciplinary Composition of CERTs Researchers
- Flexibility of Program and Researchers
- Role of Steering Committee
- Role of Coordinating Center

Collaboration

In terms of collaboration, Participants cited the following examples of collaboration as being among the greatest strengths of the CERTs:

- Collaboration among different CERTs
- Collaboration between CERTs and the Steering Committee and/or Coordinating Center
- Collaboration between CERTs researchers and outside partners, both public and private

"Through collaboration on the CMS proposal, we were able to achieve spontaneous collaboration with political forces." Group Readout[58]

Key stakeholders and AI participants highlighted the following outcomes of such collaboration:

- Overall greater productivity within the CERTs and within the Portfolio at large
- Additional funds, e.g., funds obtained for the Risk Series
- Equitable distribution of AHRQ's supplemental funds
- Greater leverage of external partnerships

[58] "Readouts" are output from the AI exercise described in the Methods.

- Number and "prestige" of articles published

Cross-Disciplinary Composition of Portfolio

In addition to collaboration, participants felt that one of the greatest strengths of the Portfolio was the fact that it brought together people from a diverse set of backgrounds, each with their own unique yet complementary perspective. In particular, AI participants pointed to the cross-disciplinary nature of the Steering Committee and the value that diversity brings to the overall program in terms of new ideas, partnerships, resources, and possibilities for future research.

Flexibility of Program and Its Members

Participants felt the flexibility of the Portfolio with respect to its overall design and among its researchers was also one of the program's greatest strengths. For example, participants highlighted the flexibility and freedom to be creative:

- Developing new initiatives
- Identifying and developing new partnerships
- Responding quickly to new proposals (e.g., CMS proposal)
- Addressing new and emerging issues

Role of Coordinating Center

Participants felt that the successes of the program could also be attributed to the highly effective role of the Coordinating Center as thought leaders and as honest brokers between all of the different stakeholders and between the different stakeholders and outside partners

Role of Steering Committee

Finally, the role of the Steering Committee was singled out as one of the strengths of the program for the following reasons:

- The extensive leadership and involvement of committee members
- Access to other scientists or researchers, potential partners, etc. via the Steering Committee members
- Scheduled networking events and opportunities to share with one another
- Opportunity via the Steering Committee and its contacts to publicize and disseminate the success of the program and specific research outcomes

"The Steering Committee provides an informal and formal network that helps amplify what the work does." – Group Readout

Life Sustaining Forces

In addition to asking AI participants and stakeholder respondents to describe the Portfolio's greatest strengths, they were also asked to articulate the underlying forces or elements that help drive and sustain the CERTs program. Asking such a question helps to uncover some of the less tangible yet equally important program forces that may be enabling and/or fueling the program, such as shared values, commitments, or vision.

John Eisenberg's vision and the text of initial CERTs' RFA

Several respondents noted that it was the initial vision of John M. Eisenberg, M.D, the former director of AHRQ, as articulated and expanded upon in the CERTs' RFA that not only originally engaged them, but continues to inspire them in their work.

Excerpts from the Original CERTs' RFA, January 27, 1999

PURPOSE

The Agency for Health Care Policy and Research (AHCPR) invites applications from non-profit organizations to establish Centers for Education and Research on Therapeutics (CERTs). CERTs is a three-year program that will support demonstration Centers. These Centers will evaluate, develop options and methods, and conduct and perform pilot studies. These studies will consist of state-of-the-art clinical, health services, or laboratory research to increase awareness of the benefits, risks and effectiveness of new uses, existing uses, or combined uses of therapeutics. This demonstration program seeks new and more effective ways to develop, translate and disseminate objective information on therapeutics to health care providers and other decision makers to improve practice. In addition, CERTs may selectively develop protocols and possibly undertake pilot studies on the comparative cost effectiveness and safety of medical products. This will be accomplished with data on appropriate therapeutic usage and outcomes; and the identification and prevention of medical errors and adverse effects. The long-term goal of the program will be to improve the quality of care while reducing costs.

RESEARCH CENTERS

Work carried out by each Center is to be multidisciplinary and must address various health care providers, settings, and geographic areas. Multidisciplinary research may involve scientists in medicine, pharmacology, epidemiology, engineering, pharmacy, nursing, human behavior, statistics, economics, organizational behavior and related fields. The long-term goal of the program will be to improve the quality of care while reducing costs.

In addition:

- The Center will have demonstrated expertise in dissemination and translation of research on therapeutics into practice.
- The Center has demonstrable evidence of a sophisticated understanding of health care systems and current quality improvement strategies.
- The Center should have experience in working with health system leaders to translate research into practice, with potential for developing partnerships between the research centers and health care systems to enhance opportunities for broad scale implementation.
- The Center should have experience in leading multi-center research teams.

"This is exactly what needs to be done and this is exactly the mission that I have in my career." – CERTs PI

"It was the compellingness of the vision that attracted everyone to the issue in the first place." – CERTs PI

AI participants explained it was not only the fact that they were inspired by this vision, but that this vision was a strong one from the beginning (i.e., clearly articulated and practical), which has enabled the program to evolve and grow.

Commitment to Practical Science

Many Participants also cited their shared commitment to practical science as being one of the driving forces for the success of the CERTs program. Similarly, others described their commitment to applied science as a "shared altruistic goal" that unites them in their work and desire to see the program succeed.

"This is a practical science, only a few steps away from applying it to practice and changing behavior." – AHRQ member

Proof of Concept

Finally, others commented on the fact that the program has grown, produced tangible outputs, and is successfully addressing all of its objectives as being one of the self-sustaining forces that has not only validated the concept of a network of research centers collaborating and leveraging public-private partnerships, but also provided inspiration to continue to improve upon it.

"CERTs provide an excellent opportunity for longitudinal and coordinated thinking. It is a real proof of concept." – Group Readout

"We produce research that matters." – Group Readout

Furthermore, participants noted that the government has affirmed the program and its efforts.

"HHS sees the CERTs as a strategic asset." – CERT PI

Successes

Participants had very little trouble citing the successes of the CERTs so far. They included the following:

Partnership Successes

- CERT to CERT partnerships
- CERT partnerships with federal agencies
- CERT partnerships with the Department of Health and Human Services (HHS)
- Other more specific examples
  - Patient Safety

– Risk Series
– CBER /UAB/Duke – TNF Project, Arthritis Foundation
– TMR – FDA/Duke/STS
– Direct to point interventions – "BB"
– UNC/AAP – Rickets + ADHD
– CERTs/CDC/FDA – Adverse Reactions
– CAQH/NCQA/Duke
– AHIP – HMO

Successes in the Dissemination of Information

- North Carolina Rickets – The strong dissemination effort helped to resolve the rickets issue in North Carolina. Local innovation informed larger entities of the problem and the Steering Committee collaborated with these forces to represent the interests of the North Carolina communities. Results include new policies and guidelines, vitamin D coverage and most importantly reduction in rickets prevalence in North Carolina.

Successes in Setting or Influencing the National Agenda

- The Risk Management effort which changed the way the FDA and other large programs think about risk management

Opportunities

In order to uncover new opportunities for the CERTs, AI participants were asked to do the following:

1. Identify those areas that they believed were most important to the success of the CERTs program and where they would like to dedicate the majority of their future efforts.
2. Develop a vision for the future of the CERTs program at its best in five years.
3. State their commitments, requests or offers in order to ensure this future vision is realized.

Future Investments

Participants of the AI workshop were asked to identify those elements of the CERTs program that they hoped would continue into the future because of their overall contribution to the success of the program. Participants generated the following unedited list:

- Agenda Setting, e.g. setting the national agenda
- Partnerships
- The Dissemination of Information
- Practical Research
- Strength of Cross-Disciplinary Membership
- Structure of the Coordinating Center
- Strong Vision
- Innovation and Creativity
- Resourcefulness
- Flexibility

Participants were then asked to identify the three areas in which they would like most to concentrate their efforts. They were:

- The Dissemination of Information
- Agenda Setting
- Partnerships

Finally, participants formed groups around each of the above themes and were asked to identify future possibilities or opportunities in each of these areas. Their ideas ranged from the specific to the more general as evidenced by the lists below. In some cases, for example, their ideas reflected guiding principles for the future more than concrete possibilities.

Group One: Dissemination of Information

- Given its broad public appeal and high ROI, leverage the North Carolina Rickets work by introducing similar initiatives to other states across the U.S.
- Develop more "patient-focused" initiatives
- Ensure information that is disseminated meets the following three criteria: strategic, integrative and evidence-based
- Ensure the dissemination process is dynamic and sustainable
- Conduct an evaluation of the effectiveness of each education initiative
- Proactively disseminate information
- Disseminate information to a wide audience including patients, physicians, public health system, media and Internet

Group Two: Agenda Setting

Participants felt there were many opportunities both in the short term and long term to influence local, regional and national agendas as well as ultimately affect policies, but only mentioned two strategies or approaches to do so during the AI workshop.

- Identify specific gaps in the evidence base and knowledge base to guide future therapeutic research, and
- Better leverage the extensive amount of science based research that currently exists in order to inform policy decision-making.

Group Three: Partnerships

While partnerships were seen as one of the CERTs greatest strengths, participants also thought that they could be further strengthened and expanded if the following initiatives were pursued:

- Build or strengthen the "CERTs" brand image in order to strengthen its identity and reputation with partners
- Invest in building CERTs as a "national resource" or "brain trust"
- Encourage AHRQ to proactively facilitate CERTs as a resource to other government agencies
- Seek more and greater partnership opportunities between:

- CERTs – AHRQ,
- CERTs – CERTs,
- CERTs – Government partners and
- CERTs – Private Sector Partners.

Visions of the Future

Appreciating that individuals express themselves differently and that while some individuals are most creative and imaginative when they write their ideas down, while others are most creative and imaginative when they draw, during the AI workshop, participants were given the choice to either:

1. Draw an image of the CERTs program at its best, or
2. Develop a bold provocative statement of the CERTs program at its best

In addition, participants were encouraged to think about the CERTs program 5 years into the future in order to encourage them to think about new possibilities and opportunities rather than focus on any current limitations or constraints.

The following provocative statements serve as a representative sample of the "Visions of the Future" that participants developed:

Visions of the Future
PROVOCATIVE STATEMENTS

Provocative Statement #1

"CERTs is the virtual place (with 51 state centers) where government, academia, business providers and patients come together to advance the safe and appropriate use of therapeutics."

Provocative Statement #2

"As a result of CERTs education and research, Americans will receive the best possible outcomes of healthcare through the optimization of therapeutic interventions and the minimization of therapeutic risk."

Provocative Statement #3

"CERTs will be seen as the premier program to conduct health services research on therapeutics in partnership with both the private sector and various government constituencies (FDA, CMS, Etc.) As a group, CERTs will contribute to setting the research agenda on therapeutics. CERTs will be willing to debate emerging controversial issues in therapeutics (e.g., COX-2 Inhibitors) and disseminate informed summaries."

Provocative Statement #4

"Industry supported post marketing surveillance will decrease as a result of increasing capacity and requests of the CERTs to answer critical questions in Phase IV drug development/safety assessment."

Provocative Statement #5

"Headline News! Today, CERTs, the nation's oldest and most trusted resource for improved therapeutics, issued its long awaited annual report on the State of the Nation's Therapeutics: 'Healing the Nation.' This year's CALIFF award goes to the state of ….for its fully automated EMR-based real time Therapeutics Assurance and Knowledge Enhancement (TAKE) system to take therapeutics to a whole new level says the Coordinating Center's 20 year director."

Provocative Statement #6

"The CERTs are a strategic interagency asset of HHS in the domain of therapeutics. They serve as a brain trust, research enterprise and developers of dissemination strategies. In these roles, they partner with both federal agencies and private organizations."

Provocative Statement #7

"AHRQ was asked by the HHS Secretary to take the lead on an HHS-wide working group to plan a National Pharmaceutical Outcomes database that would support multiple studies and analysis to better inform therapeutic decision making. CERTS served as a key resource for the working group, as representatives of CMS, FDA, NIH, CDC and other agencies worked together to define options for linking and utilizing data from multiple administrative claims, clinical and survey course to build this infrastructure."

Provocative Statement #8

"AHRQ was asked by the HHS Secretary to take the lead on an HHS-wide working group to plan a National Pharmaceutical Outcomes database that would support multiple studies and analysis to better inform therapeutic decision making. CERTS served as a key resource for the working group, as representatives of CMS, FDA, NIH, CDC and other agencies worked together to define options for linking and utilizing data from multiple administrative claims, clinical and survey course to build this infrastructure."

Provocative Statement #9

"FDA and others were concerned about spontaneous adverse event reports related to the use of drugs in novamab class for treatment of fascinoma, amid indications of widening off-label use in patient subgroups where risk might exceed benefit. Several CERTs centers collaborated to conduct drug utilization and outcomes studies, working with their large observational datasets and their healthcare system partners. They also helped develop specs for an evidence-based review of prior studies.

Results of the evidence review and new studies showed clearly that risk exceeded benefit among patients with comorbid cryptosis. As a result, the American Academy of Fascinoma Physicians and the Fascinoma Foundation developed new treatment recommendation and national media covered the published paper. The cooperating CERTs centers worked with several large health plans, Medicaid programs and Part D PDPs on prescriber mailings, academic detailing initiatives and PRODUR edits. Use among patients with comorbid cryptosis declined 75% while it increased in subsets where the risk/benefit ratio was favourable."

Provocative Statement #10

"CERTs is sought after by policy makers of all types: research policy, health plan administrators policy, pharmaceutical regulatory policy, public payer, therapeutics.

Interpretation

The members of the CERTs and Steering Committee were asked to illustrate the visions of the CERTs program at its best. The participants drew pictures representing those visions, below are the interpretations of those pictures.

Member Illustration 1
"We are a group of individuals, centers and CERT totality made stronger because we partner with ourselves and others. We seek to improve public health by advancing knowledge, affecting policies and directly improving outcomes.

Member Illustration 2
"The CERTs program will be a trusted national resource for all with two way communication between CERT Centers and the following:

- *Health Systems*
- *Health Providers*
- *NIH*
- *CDC*
- *Policy Makers*
- *General Public*
- *Research Community."*

Member Illustration 3
CERTS as a guiding light in the form of a constellation of stars for MDs, patients and payers who are lost in a sea of therapeutic questions, uncertainty and confusion.

Commitments, Requests, and Offers

Finally, in order to realize this vision, participants offered the following commitments and/or requests:

Commitments

- "I commit to facilitate this process through my own work & through participation in the partnership."
- "I commit to doing the work."
- "I commit to getting us there" (i.e., being a trusted national resource in the eyes of the public).
- "I commit to scientific validity, collaboration and being responsive to consumer needs."
- "I commit to being proactive in bringing resources to the program."

Requests

- "I request an integrated and increased emphasis on education and dissemination"

Offer

- "I offer to help translate and disseminate findings."

3.6. Portfolio Funding

During the period 1999-2005 the Pharmaceutical Outcomes Portfolio awarded 22 grants, 8 of which were the awards to the CERTs research centers and Coordinating Center (U18: cooperative agreement). Two grants were also awarded to CERTs research centers for the Risk Series program (Duke) and the Prescribing Safety Program (HMO). There was an additional non-CERT related cooperative agreement grant (U18). There were 12 individual Portfolio grants including: eight R01 (research project) grants; two R13 (conference) grants; and one K02 grant (career development award).[59]

3.6.1. CERTs Funding

We analyzed estimates for the annual and overall percentages of CERTs research centers and the Coordinating Center (CC) funding, by source, for September 1999 – October 2005 using data obtained from the Coordinating Center and individual CERTs.[60] A description of the Coordinating Center and individual CERTs research centers' funding follows.

Financial support of the Coordinating Center outside of CERTs grants and Duke University Medical Center (DUMC) contributions were generally provided for specific program-wide projects organized and led by the Coordinating Center and approved by the CERTs Steering Committee (SC). Examples of such projects include: the Risk Series, the Device Assessment think tank meeting, and the Eisenberg Lectureship.[61] CERTs grants were the largest funding source accounting for 74% of the Coordinating Center's overall funding and as much as 94% of funding in 2000. 2002 and 2003 were by far the years with the most diversity of funding sources, with six and seven different funding sources respectively. In addition to AHRQ CERTs grants, the largest (in dollars) sources of funding were industry contributions, DUMC contributions. In 2004 and 2005 the DUMC accounted for over 35% of the Coordinating Center's funding.[62]

We also examined financial source data from the individual CERTs (Exhibit 12). AHRQ CERT grants were the largest funding source for five of the seven CERTs examined: HMO Research Network, ARIZONA, UNC, Duke, and Vanderbilt. The Penn and UAB CERTs were primarily funded through National Institute of Health (NIH) grants. Penn funds were the most diversified, reporting eight different funding sources. The remaining funding sources for all seven CERTs are reported in Exhibit 12 below.

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[59] CERTs and Portfolio grant financial data were often incomplete and inconsistent.[59] During the discussions, stakeholders offered perspectives on funding mechanisms and priorities. AHRQ expects CERTs to seek outside funding to supplement its core funding; therefore perspectives and findings on these sources of funding are described.

[60] Financial data were requested of each of the CERTs directly.

[61] Descriptions of these projects are provided in the Section 3.3 Educational Outputs

[62] In kind contributions were not included in this analysis due to the difficulty of quantifying them. Examples of in-kind contributions include personnel/experts such as the CERTs Steering Committee chair, planning committee members, and non-personnel contributions such as meeting space. As one example, the Duke Clinical Research Institute (the site of the Coordinating Center) in-kind contributions included faculty, staff, and meeting facilities.

Funding source reporting varied greatly among the seven CERTs examined. Duke's data comprised funding received for budget years 2004-2008 (2002-2007). UNC's data comprised funding received between 9/30/02 – 9/29/05. Penn's data comprised funding received between 10/02 – 9/03.

Exhibit 12 CERTs Funding Sources

	Penn	HMO	Arizona	UAB	UNC	Duke	Vanderbilt
AHRQ CERTS	12.8%	68.0%	60.0%	25.9%	83.6%	74.4%	40.0%
AHRQ (other)	22.3%	5.0%	NA	NA	NA	3.9%	NA
NIH	42.8%	NA	NA	46.7%	NA	NA	20.0%
Government (other)	12.3%	15.0%	25.0% (FDA)	12.8%	0.3%	0.5%	20.0%
Private (Foundation/ non-profit)	1.9%	NA	15.0%	NA	5.7%	NA	NA
Private (pharmaceutical industry)	6.5%	10.0%	NA	0.8%	NA	18.7%	20.0%
Private (other)	NA	NA	NA	NA	NA	0.3%	NA
Academic (host health system)	1.5%	NA	NA	NA	3.3%	1.9%	NA
Academic (host university)	NA	2.0%	NA	1.1%	5.0%	NA	NA
Academic (other)	NA	NA	NA	0.7%	1.6%	0.3%	NA
Other[63] (unspecified)	NA	NA	NA	11.9%	NA	NA	NA

3.6.2. CERTs Investigators' Perspectives on Funding

The stakeholders offered perspectives on the mechanisms and sources of funding for the CERTs specifically regarding the nature of CERTs funding, under-funding, and consequences of insufficient funding. The CERTs are funded as cooperative agreements awards (U18) with AHRQ. As an AHRQ representative said:

> *The legislation described the intent and was specific about what we needed to do. It wasn't really specific about where we were supposed to obtain the funding ……there was a large number of goals - essentially everything having to do with drugs, biologics, and devices marketed. It essentially covers the entire gamut of marketed products. So, that made it challenging to ascertain exactly how you would approach that very broad mandate with extremely limited funding.*

Stakeholders indicated that AHRQ released RFAs for cooperative agreements and expected CERTs to leverage these funds and to obtain external funding. For example, one CERT PI described the funding for the CERT from AHRQ as sufficient to support primarily the CERT's core infrastructure and some of its research, but that additional outside funding would be needed.

[63] "Others" include primarily registration fees collected from respondents of several think tank meetings and a contribution by the UNC CERT in 2001 in support of a think tank meeting.

Each CERT varied with respect to how investigators and which projects were supported by the CERTs funds. In some cases individual investigators were partially funded by CERTs, while in others an investigator's research was completely funded outside the CERT, with the investigator using the resources (e.g. databases) and infrastructure of the CERT on an as-needed base. An UAB CERT investigator provided an example:

> *We have investigators who are funded directly by the grant, and we have people who we consider affiliate members who attend our meetings and have a looser relationship but may not have direct CERTs level funding.*

Many CERTs investigators, regardless of how much funding they received from the CERT, attributed any research that was topically related to their individual CERT as "CERTs research" even if it was largely funded outside the CERT.

Of the CERT investigators who commented on funding, most characterized the amount as insufficient. Additionally, when CERTs investigators were asked about barriers or challenges to their CERTs achievement, under-funding was the most common answer (followed by HIPAA or privacy issues and its effect on research). As mentioned above, AHRQ's expectation is that investigators and CERTs centers should strive to obtain outside funding. Hence a small number of (usually junior) investigators described their CERT as having funded or supported a pilot study which they subsequently leveraged to obtain a larger study funded by another government agency (e.g. NIH, CDC). A CERT PI acknowledged the importance of the core funding they received as a center:

> *As long as we continue to get support for our infrastructure from AHRQ, we're fine. Should the CERTs program falter or should we not be competitively renewed we'd obviously be in some trouble, but we have broadened our base of support substantially from when we became a CERT so we do have substantial moneys outside of the AHRQ umbrella. We are, however, dependent on AHRQ to continue to help us to do what we've been doing.*

A few CERT investigators identified the CERTs as having been able to conduct their research because it was smaller scale, practice-based, or local and would not readily be funded by NIH or CDC. Some investigators indicated that available funding served to 'seed' important research in the form of pilot studies. One CERT investigator put this into context:

> *If it's a core-funded CERT project, the money primarily funds, a fairly small amount of research--- enough for a pilot project. It's not enough funding to give a definitive answer. If the focus is to get rigorous results out there as fast as possible, $10K pilots aren't the best mechanism. But if the goal is to get pilot projects out to then use to apply for other funding, then the mechanism works very well... it is good for developing projects appropriate for an NIH grant.*

There was considerable agreement among stakeholders that some opportunities are missed due to the CERTs resource constraints. Many CERTs investigators identified such opportunities as ancillary research activities (e.g. dissemination), the method selected (e.g. evaluation method), or the geographic focus (e.g. regional versus national).

A number of individuals identified education and/or dissemination as the elements that usually suffered because of limited funding in the research process. As a member of the Coordinating Center

stated, “We don’t really have the necessary resources for dissemination and education.” Two CERTs investigators with educational projects indicated that limited funding dictated the type of evaluation they were able to conduct. One investigator described the evaluation of an educational intervention:

> *We focus mainly on process evaluation because a major thrust of what we’re trying to do is to design the messages and get them out there. We don’t have a much money to conduct a thorough effectiveness evaluation*

The other investigator described limitations for evaluating the educational module:

> *Ideally, we would develop, disseminate, and test the module. We only had enough money to develop it and to do small scale testing. AHA posted it to their website. But we don’t have a mechanism to broadly test the module. We would like to be able to measure whether information leads to changes in practice.*

A few CERT investigators expressed their gratitude for the funding while acknowledging the missed opportunities.

> *I’m not complaining about our funding because we’re grateful to AHRQ for what we get, but what we do is basically limited by our funding. We’ve got plenty of work, it’s useful work, and we’re very grateful for the funding we get. The more funding, however, the more that can be done.*

> *More money would be better...it would support more research. We have been effective in using our funds. We’ve leveraged them into other grants and opportunities.*

A few CERT PIs indicated that the limited funding had consequences for the principles and mission of the CERTs program as a whole, including the vision of collaboration, interdisciplinary collaboration, and independence:

> *Lack of money makes it difficult to coordinate all these centers into one superstructure with major collaborations.*

> *A CERT problem is limited funding, not enough to fund even one project because an interdisciplinary team is required, and the level of funding in relation to salary makes it difficult to complete a study without some level of partnership.*

As described above, leveraging funding is an expectation and necessity for CERTs to conduct research. One CERT PI identified developing funding as an overall goal. A CERT PI also raised the concern about leveraged funding and its possible effect on the credibility of the CERTs and their ability to be seen as unbiased, independent research centers. That PI explained:

> *The Level of funding does not allow work to be totally independent, and there are several aspects to that. One can be dependent because a drug company provides support. Due to low funding levels, an alternative is to stay focused with a small number of researchers. That’s not what CERTs are supposed to do; there is supposed to be broad collaboration, which takes a lot of money. The only way we can do projects is to partner with someone who has a stake in the project. We also have to write grants and get outside funding; this is working but*

it is a very slow process --- 3 years to get an NIH grant. There is much slippage in the system because we don't have adequate funding to be totally interdisciplinary and independent.

A few CERT investigators raised a point about the change in AHRQ's priorities and its impact on where funds are available and for what area of research. A CERT investigator characterized the changing focus of AHRQ in the recent past:

Funding is always going to be a barrier and it is. There is some "trendiness" to AHRQ's priorities...patient safety was a focus... and then there was a change in focus to Medicare Part D. It is difficult to anticipate this flow in AHRQ's interests.

The large majority of respondents who commented on funding included steering committee members, policymakers, and CERTs investigators; the great majority believed that AHRQ and DHHS were receiving much from the CERTs in return for the limited funding.

AHRQ is very lucky to have the group that they have do this work, especially given the funds going into the program. CERT investigators spend a lot of time giving back to the program more than they take….It's a roaring success given the ... the limitations on funding and the difficulties of working in the context of a federally funded public-private partnership... but given who we are, the productivity has been extraordinary.

One CERT PI stated that he was proud that his CERT has been able to have "any influence at all" given the limited funding.

In summary, key CERTs stakeholders, including AHRQ, Steering Committee members, and policymakers acknowledged that the CERTs program is trying to fulfill a mandate for which there are high expectations with inadequate resources. As one AHRQ representative remarked "It really is a billion dollar mandate." Given this mandate and the resource constraints a few investigators provided recommendations on how those limited funds should be prioritized. One suggested putting CERT money toward nationally applicable and generalizable work, and the other suggested funding existing CERTs to spread funds less thinly. One stakeholder summed up the recognition of the importance of the core funding in advancing their research agendas:

It matters that Congress mandated and continues to fund the existence of independent academic centers to move this field forward. That is a statement about the importance of the field and the importance of a center supported by core grants...that no other strategy can do. It is important to create centers if you want to move a field forward.

3.7. Portfolio Progress Reporting

Comments were made on the progress reporting system by four groups involved in the AHRQ Pharmaceutical Outcomes Portfolio: AHRQ, CERTs investigators and support staff, the Coordinating Center, and Impact Case Study Researchers. The opinions of these groups can be divided into seven categories of comments:

- Administrative burden
- Timing
- Accurate capture and representation of CERT advances

- Utility
- AHRQ's performance
- Communication (between AHRQ and the CERTs)
- Recommendations for improvement

3.7.1. Administrative Burden

Based on the comments made by CERTs investigators, the CERTs perceive the progress reporting process as placing a sizeable administrative burden on the CERTs. Six investigators from four of the seven CERTs commented on the administrative burden of the progress reporting process. All six highlighted that the process is an extensive one. An investigator from one of the CERTs perceived the onerous nature of the progress reports as presenting a large challenge for the CERTs. Two separate investigators from one CERT indicated that the process is overly burdensome, overly bureaucratic, and inefficient.

Although many investigators perceived the burden of the progress reporting process to be substantial, these views were generally accompanied by the perception that some system progress reporting process is a necessity for a program such as the Pharmaceutical Outcomes Portfolio, as well as recommendations for improving the process.

The Coordinating Center staff echoed these sentiments. One staff member highlighted the annual report as being particularly time consuming and the progress reporting process as requiring much work, but as with most of the CERTs investigators, this staff member perceived this burden to be necessary. Another Coordinating Center staff member perceived the progress reporting process to be reasonable and not particularly onerous.

3.7.2. Timing

Investigators from five of the seven CERTs commented on the timing of progress reporting. Three respondents focused on the timing of reports in relation to research being conducted, highlighting that reports can be redundant when a project finished long before the report is due, as well as stating that the timing of reports can result in the omission of research that is not yet 'rolled out.' Three investigators addressed the timing in reports as it related to the administrative burden of the reports. One investigator from a CERT highlighted the difficulty of completing reports within such a short turnaround period. Another CERT investigator who highlighted the difficulty of meeting internal progress report deadlines echoed this concern. An investigator from another CERT indicated that because the administrative burden of the reports is large, it is helpful that reports do not need to be completed more often.

Another CERT investigator believed the timing of the reports is appropriate. This sentiment was echoed by an investigator from another CERT who perceived the timing of progress reports to be typical of most funding agencies.

One Coordinating Center staff member commented on the timing of the reports, stating that the process is timely.

3.7.3. Capturing CERTs Advances

Fourteen investigators from five of the seven CERTs commented on whether or not annual progress reports adequately and appropriately captured advances made by the CERTs. Thirteen of the fourteen commenting investigators believed the reports captured advances made by their CERTs as adequately and appropriately as possible. One CERT investigator emphasized that, because their CERT covers a large amount of both medicine and science, it is difficult to summarize everything into one report. No investigators suggested that the progress reports failed to adequately capture CERTs achievements, although an investigator from one CERT indicated that it is sometimes difficult to visualize the "big picture" from the progress reports. Two investigators from another CERT highlighted the difficulty of translating scientific information into lay terms. One of these investigators emphasized the great deal of effort it takes the Coordinating Center to ensure that scientific information is appropriately translated.

The perceptions of CERTs investigators on this topic are contrast with those of the Coordinating Center staff. One Coordinating staff member stated that more often than not CERTs advances are not captured by the progress reports. Two additional staff members commented on the issue, stating that the reports capture CERTs advances as accurately as possible, but that the amount of work undertaken by the CERTs is not necessarily reflected.

3.7.4. Utility

Comments on the utility of progress reports generally fell into one of two categories: utilization by the CERTs themselves, and utilization by AHRQ. Seventeen investigators from all seven CERTs commented on the utilization of progress reports, making this the most widely commented on category of the eight categories addressed.

Internal (CERTs) Utility
Thirteen investigators from all seven CERTs addressed the internal utilization of progress reports; all but one of these investigators emphasized the many positive ways the progress reports are used within the CERTs. Many investigators commented on this issue in broad terms, however, a number of investigators specified the following ways in which progress reports were internally used:

- Reflecting on current / past work (Duke, UAB, ARIZONA, UNC,)
- Analyzing possibilities for future work and advancement (Duke, UAB, UNC)
- Providing progress reports to institutional IRBs
- Preparing statements for dissemination / paring information down to the important message (Penn)
- Goal-setting (UAB)
- Organizational tool (Arizona, UNC)
- Collaboration between CERTs (UNC, Vanderbilt)
- Accountability (UNC, Vanderbilt)

Two stakeholders described the progress reports as having limited internal CERTs utility.

AHRQ Utility
Seven investigators from four of the seven CERTs commented on the use of the progress reports by AHRQ. Three investigators at three CERTs highlighted the necessity for AHRQ, as well as for other funding organizations, to have a progress reporting mechanism for holding CERTs accountable for

their research goals, but also so that AHRQ may better understand the key issues affecting the CERTs and assist in promoting collaboration among them.

However, despite the recognition of the necessity of a progress reporting process, a number of investigators from two CERTs indicated that it is unclear how AHRQ has made use of these reports. One CERT investigator added that AHRQ does not have any knowledge regarding what their CERT has accomplished while another from the same CERT expressed surprise at the fact that a recently submitted report resulted in helpful feedback from AHRQ. Another CERT investigator stated that although they have not yet received feedback from this year's report, the reports generally do generate feedback from AHRQ.

One CERT investigator stated that the annual progress reports for stakeholders, Congress, and others gives all CERTs equal advertisement and appropriately translates scientific language while still accurately delivering the message.

An AHRQ respondent perceived the progress reports as allowing AHRQ to understand what had transpired within the CERTs over the previous year and to determine if any issues existed that required AHRQ's attention. AHRQ also saw the progress reports as a method to determine if any CERTs findings/products required further dissemination.

One out of four Coordinating Center staff members interviewed stated that the annual report highlights the major findings and initiatives of each of the centers and allows non-scientists to better grasp what the CERTs have accomplished over the past year. However, uncertainty about the use of the progress reports by AHRQ was also expressed.

Coordinating Center Utility

Two out of the four Coordinating Center staff members interviewed highlight that the coordinating staff prepares an annual report of their own volition. One of these staff members additionally highlights the large number of reports the Coordinating Center has compiled for the CERTs Information Technology Transfer (CIT) project. This project is further addressed in the section below. An additional Coordinating Center staff member stated that the progress reports are "very helpful" for the Coordinating Center.

3.7.5. Recommendations for Improvement

Four investigators made unrelated recommendations for improving the progress reporting process. They recommend:

- The provision of information to AHRQ on an efficient, continual basis without burdening CERT investigators. This investigator believes that it would be helpful for AHRQ to be able to access the information included in progress reports real-time, not only through yearly reports.
- Progress reports be further used as vehicles of dissemination.
- Fewer and better coordinated progress reports.
- CERTS submit their progress reports in June or July, as opposed to May.

Coordinating Center staff members provided numerous recommendations for improvement. Two respondents emphasized the efficiency and promise of the CERTs Information Technology Transfer (CIT) project. One of these staff member highlighted that the CITs interface is better geared towards tracking results, which would be more helpful for both AHRQ and the Coordinating Center. This staff member specified that the Coordinating Center desires information on why a project was done, results, significance of those results, recommended actions, and instructions as to who should carry those actions out. This staff member also indicated that the CITs interface is compatible with many types of research and could potentially be used beyond the CERTs project. This sentiment was echoed by the second staff member. This staff member also highlighted the fluid nature of the CIT database and the hope that the CIT project will serve to make information more uniform and allow real time information to be pulled as needed.

One Coordinating Center staff member suggested that AHRQ provide feedback on how progress reports are used. An additional staff member requested that AHRQ make the progress reporting process as easy as possible for the CERTs, while another believed the progress reporting process should be made more fluid.

3.7.6. AHRQ/Coordinating Center/CERT Communication & Dissemination

Five investigators commented on the level of communication with AHRQ, both generally and as this communication relates to the dissemination of progress reports. Two CERT investigators praised the Coordinating Center for continuously updating AHRQ regarding CERT activities, so that AHRQ may appropriately respond, as well as ensuring that information provided by the CERTs is properly disseminated. This view contrasted with that of one CERT investigator who described communication with the Coordinating Center as difficult at times and praised one of that CERT's staff members for ensuring progress reports are disseminated and reviewed. An additional investigator from that CERT described their relationship with AHRQ as excellent and praised AHRQ for being supportive of changing research directions. This investigator contrasted this flexible attitude with significantly more rigid NIH grants.

One CERT investigator mentioned AHRQ's need to improve communications with the CERTs and attributed this to AHRQ's desire for non-interference from the CERTs. Some Coordinating Center staff members also highlighted the need to improve communications with AHRQ. One staff member indicated that pushing the Coordinating Center annual report through AHRQ is a very difficult. Another staff member mentioned AHRQ's concern that it is not kept adequately up-to-date on what is happening within the CERTs. This staff member perceives the once a year provision of information as appropriate but also states that this structure makes it difficult to ensure that every person needing the information provided by progress reporting receives it at the time it is needed. An additional Coordinating Center staff member stated how difficult communications with AHRQ are.

3.7.7. Portfolio Grantee Progress Reports

Administrative Burden

Only one of the four portfolio grantees interviewed commented on the administrative burden of the progress reporting process, describing it as reasonable. One grantee recommended more detailed reports that might result in a more onerous process but would be better suited for providing AHRQ needed information.

AHRQ Utility

Two out of the four Portfolio grantees interviewed questioned the utility of the progress reports to AHRQ. One highlighted the lack of clarity as to where the reports end up and who makes use of them. The second grantee states that progress reports are a low priority for them as a direct result of never receiving comments for feedback from AHRQ on the information submitted. This grantee recommends a more detailed and specifically aimed report that, despite increasing the administrative burden, would be more suited to AHRQ's needs.

3.8. Progress towards meeting Agency and DHHS objectives from 2002-2005

The Pharmaceutical Outcomes Portfolio contributes to AHRQ's mission to improve the quality, safety, efficiency, and effectiveness of health care for all Americans and the mission of the U.S. Department of Health and Human Services' (DHHS) mission to protect and improve the health and well being of the American public. The previous findings provide detail on a significant portion of the outputs, outcomes, and impacts of the portfolio on research, which provides an overview of how well the Portfolio is doing towards meeting AHRQ and DHHS objectives. In this section, the relevant Portfolio objectives and the CERTs aims are provided in tandem with AHRQ and DHHS objectives. Additionally, the OMB PART goals, as an assessment-rating tool, are key goals against which the Portfolio and ultimately the Agency are measured. The accomplishments of the Portfolio that related to the OMB PART goals are also described in this section. Lastly, a description of the CERTs program, as a key entity funded by AHRQ as part of the Pharmaceutical Outcomes Portfolio and the program's processes and responsiveness to the Agency and DHHS priorities are described.

3.8.1. How do Portfolio objectives map to AHRQ and DHHS priorities?

Below is a description of how the objectives of the Pharmaceutical Outcomes Portfolio and the CERTs mission align with AHRQ DHHS priorities. The CERTs program mission is to conduct research and provide education that will advance the optimal use of drugs, medical devices, and biological products, which explicitly works to fulfill each of the five Pharmaceutical Outcomes Portfolio goals. The CERTs program mission coincides with the Portfolio goals, subsequently fulfilling the same DHHS priorities. The Portfolio's five program goals[64] are provided as well as the relevant AHRQ and DHHS priorities to which they relate.

1. *Understanding benefits and risks*. Expand our knowledge about the benefits and risks and outcomes of pharmacological therapies so that better decisions can be made about how and when to appropriately use pharmaceuticals to improve health.

    - HHS Goal 2: Enhance the ability of the Nation's health care system to effectively respond to bioterrorism and other public health care challenges
        - Objective 2.2: Improve the safety of food, drugs, biological products, and medical devices.

    - HHS Goal 3: Increase the percentage of the Nation's children and adults who have access to health care services, and expand consumer choices

[64] Description of the Pharmaceutical Outcomes Portfolio goals in RFTO for this evaluation

- Objective 3.4: Eliminate racial and ethnic health disparities

- Healthy People 2010: #17 Medical Product Safety

2. *Advancing optimal use in clinical practice.* Identify opportunities and strategies to increase the likelihood that patients will receive the right treatment at the right time from their health care providers across all practice settings.

    - HHS Goal 5: Improve the quality of health care services

        - Objective 5.1 Reduce medical errors
        - Objective 5.2 Increase the appropriate use of effective health care services by medical providers
        - Objective 5.3 Increase consumer and patient use of health care quality information

3. *Helping consumers derive maximum benefit.* Identify and evaluate strategies for communicating the information that consumers need to make decisions about the appropriate use of therapeutics, in consultation with their health care providers.

    - HHS Goal 3: Increase the percentage of the Nation's children and adults who have access to health care services, and expand consumer choices

    - HHS Goal 5: Improve the quality of health care services
        - Objective 5.2: Increase the appropriate use of effective health care services by medical providers
        - Objective 5.3: Increase consumer and patient use of health care quality information

4. *Informing policies*. Provide government agencies, managed care organizations, employers and other decision-makers with scientific evidence to inform their decisions and evaluate the policy implications of their decisions.

This program goal is implicitly related to all of the content-related goals and objectives and the translation of those into policies, when applicable.

5. *Supporting the extension of education and research.*
   Support multi-disciplinary efforts to educate health care providers, researchers and students about how to evaluate the optimal use of therapeutics and apply scientific evidence to practice.

    - HHS Goal 4: Enhance the capacity and productivity of the Nation’s health science research enterprise
        - Objective 4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability
        - Objective 4.3: Strengthen and diversify the pool of qualified health and behavioral science researchers
        - Objective 4.4: Improve the coordination, communication, and application of health research results

The Pharmaceutical Outcomes Portfolio program goals 1 –3 all directly address AHRQ's mission to improve the quality, safety, efficiency and effectiveness of health care for all Americans. Program goal #4 helps to translate the fulfillment of 1-3 into relevant policies, and program goal 5 illustrates the capacity building component to sustain and further advance AHRQ's mission.

3.8.2. Progress toward meeting DHHS objectives

The Pharmaceutical Outcomes Portfolio appears to contribute to the United States Department of Health & Human Services (DHHS) Goals and Objectives (FY 2004 –2009)[65] in a substantial way. A brief description of the contributions of the Portfolio has made to the applicable DHHS goals and objectives is provided below:

HHS Goal 2: Enhance the ability of the Nation's health care system to effectively respond to bioterrorism and other public health care challenges

We did not identify within the Portfolio a focus on bioterrorism. We identified one CERT PI serving on a committee regarding anthrax. However, within this goal is an objective that is a primary focus of the CERTs.

Objective 2.2: Improve the safety of food, drugs, biological products, and medical devices.

The CERTs program has as its explicit purpose "to conduct research and provide education that advances the optimal use of therapeutics (i.e. drugs, medical devices, and biological products),"[66] which includes improving the safety of these products (*see 3.3 for further detail*). For example, the CERTs have explored many issues on safety of drug use in populations like pregnant women (i.e. ACE inhibitors in pregnant women) and pediatrics (i.e. pediatric devices). The CERTs have conducted research on medication issues causing QT prolongation and Torsades de Pointes and increased the knowledge of practitioners, and appears to have contributed to the knowledge that led to the withdrawal of medications from the market because of this effect. Lastly, the CERTs program held a series of think-tank conferences to discuss with policymakers and other key stakeholders risk assessment, management and communication strategies.

HHS Goal 3: Increase the percentage of the Nation's children and adults who have access to health care services, and expand consumer choices

The Portfolio has not directly affected individuals' access to health care services, however there are examples of the Portfolio research contributing to understanding health care for ethnic minorities.

Objective 3.4: Eliminate racial and ethnic health disparities

We have not found that the Portfolio has made a substantial body of awards that are focused on health care disparities per se, although we did identify a few examples. The UNC CERT worked with colleagues to identify a disease that was considered essentially eradicated, specifically vitamin D deficiency rickets in African-American breast-fed infants. This study not only uncovered rickets, but

[65] Retrieved from http://aspe.hhs.gov/hhsplan

[66] CERTs Fact Sheet retrieved from http://www.ahrq.gov/clinic/CERTsovr.pdf

impacted policy, by working with their colleagues and connections at the NC WIC program office to present on the findings and work with them to include vitamin D supplements on the WIC program. (*see 3.3.5 for further description*). Additionally, the Arizona CERT has worked with a community clinic that serves a largely Hispanic population. The UNC CERT in a research project on antibiotic resistance identified ethnic patterns specifically "*Hispanic children have higher resistance to certain species."* Additionally, CERTs investigators shared examples in which their studies included multi-lingual materials. Lastly, Portfolio grants involving interventions, both produced materials for the different languages spoken in the intervention areas. In summary, there was demonstrated responsiveness when racial or ethnic groups are part of the research population, are identified as having special needs or issues or, are at greater risk.

HHS Goal 4: Enhance the capacity and productivity of the Nation's health science research enterprise

Our evaluation suggests that the Portfolio has enhanced the capacity and productivity of the Nation's research enterprise. The hundreds of projects, publications, presentations, and dissemination efforts have furthered the health science research agenda. Each of the applicable objectives is described below.

Objective 4.1: Advance the understanding of basic biomedical and behavioral science and how to prevent, diagnose, and treat disease and disability

The CERTs research to some extent has contributed to the advancement of this objective, however less so than other research agendas, as the CERTs research primarily involves health services research and pharmacoepidemiology. There are examples, particularly in the CERTs with their multidisciplinary focus to have multi-method and approaches to research. There are also a few examples of investigators linking health services research with basic biomedical research (e.g. grantee's antimicrobial resistance intervention involved health services data and biological data from nasopharyngeal cultures).

Objective 4.3: Strengthen and diversify the pool of qualified health and behavioral science researchers

Our evaluation has found that the CERTs program has demonstrated a commitment to strengthening the pool of health researchers. However, the data collection did not include determining the diversity of those trained or involved with the CERTs.

The CERTs program in particular has demonstrated an intentional focus to train and prepare future researchers within the CERTs context, particularly in health services research and pharmacoepidemiology. Not only does the CERTs program have as an aim to strengthen the pool of qualified researchers in therapeutics, but the program demonstrated this and investigators attested to it. Additionally, some junior faculty attributed the CERTs with helping them advance their careers and certainly further their exposure in therapeutics research. (*see Educational Outcomes for additional information).*

Objective 4.4: Improve the coordination, communication, and application of health research results

The CERTs again have as an aim and has demonstrated a focus on how findings translate to practice with their efforts in changing guidelines and striving to disseminate their research beyond academic publications. The public-private partnership mechanism of the CERTs fosters relationships that also contribute to how the CERTs are able to communicate (e.g. professional societies) and apply health research results (e.g. change guidelines). Additionally, the Coordinating Center's continued developed of CIT, a mechanism that will centralize and facilitate collection, organization and dissemination of CERTs work will likely be a great product/output of the program and ultimately improve the coordination and communication of research findings. The Portfolio grants included intervention studies that included strong dissemination efforts and the continuation of those efforts.

GOAL 5: Improve the quality of health care services

The Portfolio has demonstrated an effort to improve the quality of health care services, specifically for the following objectives.

Objective 5.1: Reduce medical errors

The Portfolio has included research that explores medication errors. The CERTs have conducted research on medication errors in various settings and a number of topics specific to medications (*see Impact Level 1 and 2 for further detail*).

Objective 5.2: Increase the appropriate use of effective health care services by medical providers

The Portfolio research includes examples of research that explore effective health care services and the uptake by medical providers.

Objective 5.5: Accelerate the development and use of an electronic health information infrastructure

The CERTs has conducted research on the use of electronic health information, particularly for communicating risk like point of care technologies, risk communications, and computerized physician order entry (CPOE).

Healthy People 2010: #17 Medical Product Safety

The Portfolio has also demonstrated a commitment to at least one of the goals of the DHHS Healthy People 2010, #17 Medical Product Safety. The CERTs have made significant contributions in the area of medical product safety (*see Outcomes and Impacts chapter 3.3)*. This is evidenced in the research the CERTs have conducted as part of the Prescribing Safety Program. Additionally, the CERTs' Risk Series aimed:

> *1. To explore current and future methods of managing the risks of FDA-approved therapeutic products to ensure maximum benefit and safety for patients. 2. To develop a research agenda to monitor the effectiveness of these risk-management approaches and their aggregate effects on patients and the healthcare system. These aims support and facilitate objective #17 of Healthy People 2010, "To ensure the safe and effective use of medical products," particularly*

in monitoring drugs and adverse events and providing useful data about the safe use of drugs.[67]

The Portfolio as a whole and the CERTs program in particular have contributed to DHHS goals and objectives in the areas that would be expected given the focus on pharmaceutical outcomes and therapeutics. However, the Portfolio has contributed to some goals more than others. The Portfolio, specifically the CERTs program, has focused on developing the health care research workforce and understanding drug safety, whereas the Portfolio does not appear to have had as much of an emphasis on health care disparities. This is not surprising for a program that is charged with a breadth of research that encompasses all therapeutics, including drugs, biologics, and medical products.

Despite trying to fulfill the goals and objectives of DHHS and AHRQ, the CERTs have demonstrated responsiveness to the shifting priorities, as a CERT CC member describes:

> *The role per the RFA has not changed, but what we focus on at various periods of time can change. People's expectations (particularly at AHRQ) can change regarding how they perform their functions. During 2001 period, FDA was very focused on arrhythmia. So we focused on that and presented to FDA for public hearings. When CMS, with the Medicare drug benefit had a need, we applied for a contract that we thought we could add value and sent unsolicited proposals as well.*

3.8.3. OMB PART Goals

AHRQ's Pharmaceutical Outcomes Portfolio is expected to contribute to meet specific Office of Management and Budget (OMB) the performance assessments using the program assessment-rating tool (PART). Below is a description of each of those goals and examples of the extent to which the Portfolio is working towards those goals and contributing to their achievement.

1. To reduce congestive heart failure re-admission rates during the first six months after initial admission by approximately 2% per year through 2014
2. Decrease the inappropriate use of antibiotics in children by approximately 2.5% per year through 2014
3. Reduce hospitalizations for upper gastrointestinal bleeding by 2% per year through 2014
4. As an efficiency goal, improve the appropriate use of therapies to treat peptic ulcer disease by 20% by 2010.

The Duke CERT has conducted research and informed policies related to heart failure and which are important for the fulfillment of the first PART goal. The Duke CERT is conducting and conducted research on the use of evidence-based therapies and beta-blockers in heart failure, developed a registry of heart failure inpatients at Duke, studied the cost-effectiveness of treating heart failure patients with beta-blockers, and is working on an outpatient heart failure program for quality improvement. Additionally, in response to an AHRQ interest in methodological approaches to facilitate comparative effectiveness analysis the Duke CERT proposed to use inverse probability-weighted estimators to compare outcomes (survival and rehospitalization for heart failure (HF) after discharge). Besides the Duke CERT contributing to the fulfillment of the PART goals, a Duke investigator explains the impetus:

[67] Excerpt from the abstract for the Risk Series Portfolio grant, retrieved from AHRQ GOLD database

Duke has gone into doing heart failure research they had not planned to do until seeing the OMB goals and realizing they had investigators at their disposal.

This statement illustrates the responsiveness of the CERT to the OMB PART goals and ultimately AHRQ and DHHS' missions. Other CERTs conducted research that contributed to the other PART goals which is described below, however others did not explicitly state deciding to do particular research because of its fulfillment of an OMB PART goal. The Portfolio research has also contributed to the second OMB PART goal to decrease the inappropriate use of antibiotics in children to some extent, as described below. The Penn CERT has been the primary CERT that has contributed to this goal because of their thematic focus on anti-infectives.

The Penn CERT conducted research on the use of antibiotics in the treatment of acne and the impact on resistance. Another Penn study's results may be used to devise modifications in antibiotic use that may lead to the prevention of candidemia in critically ill children. A Penn investigator is developing a computerized intervention that, "using a simple computer game, a modification of 'Space Invaders,' will evaluate the usability and initial efficacy of this intervention in teaching children ages 6 to 16 when it is appropriate to request and/or use antibiotics." Another Penn study "compared predicted incremental overall antibiotic use and broad spectrum antibiotic use between strategies with looser guidelines and strategies using AAP criteria with and without tympanometry."

The HMO CERT conducted a retrospective cohort study to determine the rates of antibiotic use. An HMO CERT investigator has proposed studying changes in the incidence of serious bacterial illnesses as a result of decreasing antibiotic use in primary care settings; in the context of introducing pneumococcal conjugate vaccine. The HMO CERT is conducting a project on health plan member/physician education for judicious antibiotic use in children, on which they are collaborating with the HMO Research Network CERTs health plans, Council for Affordable Quality Healthcare (CAQH) and the Association of American Health Plans (AAHP) to reduce unnecessary prescribing of antibiotics through health plans nationally. The HMO CERT is conducting a study aimed at reducing the use of antibiotics in children.

The UNC CERT, with its focus on pediatrics, has contributed to the understanding of antibiotic use in children with projects assessing pediatric treatment guidelines that could encourage better adoption of practice guidelines (e.g. reduce overuse of antibiotics). Also, UNC is conducting a study to determine the impact of antibiotic prescribing at initial visit on the probability and frequency of acute otitis media (AOM)-related return visits among North Carolina (NC) Medicaid patients.

A Penn investigator describes the context related to the second OMB PART goal:

It's hard to know exactly what should be credited here, because certainly there's been more public awareness. Certainly the CDC in particular has invested in some public education and professional education campaigns... there have been many local activities of varying strength, and it's the kind of work that gets published. It gets us in the public domain and people thinking about it. ...I expect we're not at the targeted goal overall, but the data would suggest that in general, particularly in pediatrics, overall use of antibiotics has clearly gone down in these targeted conditions. I think that's been a little bit less true in adult and particularly in geriatric settings and less true in emergency care settings, that's one reason we focused there in our latest study, but the overall news is still generally good...but there

has been an increased use of broader spectrum antibiotics, with unintended negative consequences [where] people are perhaps prescribing less but when they do prescribe they prescribe even more broader spectrum antibiotics than they really need to. The net effect, in terms of the public health goal, which is to reduce resistant infections and make infections more treatable, is very hard to gauge. ... in terms of a number of issues things are probably better today than they were five or ten years ago. I'm not sure that we've achieved the goal, and I don't know that our improvement is going to continue... but I would say there is good news...

Besides the projects focused on the appropriate use of antibiotics in children, the Portfolio has included research on the appropriate use of antibiotics in adults and research on antimicrobial resistance, including interventions to improve antibiotic use and resistance in communities. An AHRQ representative characterizes the CERTs' contribution to the OMB PART goals in the following:

There are a number of the CERTs that have pilots that could certainly be useful if you can disseminate them to the rest of the country as a way of approaching the national goals.

The Portfolio has primarily demonstrated a commitment to meeting the first two PART goals in terms of the research content and goal two more than goal one. This may be in large part due to the nature of the CERTs research centers and their thematic focus, specifically that the Penn CERT focuses on anti-infectives, the UNC CERT focuses on pediatrics, and the Duke CERT focuses on cardiovascular therapeutics. The CERTs investigators, key leaders on the Steering Committee, senior investigators, and PIs all stated a commitment to the PART goals, regardless of how challenging they are to achieve. An AHRQ representative describes the change in goals:

I think the goals changed a few years back….I think that AHRQ is moving towards a different role and so its programs needed to also change the role that they had. AHRQ is becoming more involved in education, dissemination, and implementation, and less of a research agency. It has fewer resources to fund much in the way of research so the CERTs had to adjust to that. ...I think there's still some transition going on, but that changing role is something that was imposed on the CERTs as opposed to it being internal, so there are challenges with that, it's almost a different set of skill sets. So we'll go from just being research on therapeutics, to research and education in therapeutics.

4. Discussion

4.1. Discussion

We begin with two important caveats that apply to this and to any evaluation of this type. For example, it may take more time than has elapsed during the evaluation period for certain impacts to occur or to be apparent yet. In addition, it is always possible that further evaluation resources could allow more sensitivity in identifying impacts. We now review the objectives guiding the evaluation, which were to:

- Assess progress of the Portfolio towards meeting Agency and DHHS objectives in the past four years.
- Assess impact of Portfolio research on state and federal health care policy making.
- Assess adequacy of Portfolio progress reporting.
- Assess contribution and role of the Duke Coordinating Center (CC), Steering Committee, program office, and other partners to the CERTs.
- Identify strengths of the program and most successful or promising research, especially with respect to the PART goals.
- Assess role of Portfolio relative to other AHRQ and DHHS priorities.

In the following sections we briefly discuss the evaluation finding in the context of these objectives.

4.1.1. Progress of the Portfolio towards meeting Agency and DHHS objectives in the past four years.

The Portfolio's goals map well to AHRQ's mission to improve the quality, safety, efficiency, and effectiveness of health care for all Americans and at least some objectives within DHHS' goals 2-5. Besides the alignment of the Portfolio's goals to those of the agency and DHHS, the Portfolio has also contributed to the progress toward these goals. Specifically, the Portfolio has funded research that contributed to the knowledge about the safety and quality of therapeutics as well as expanded the capacity of the research enterprise.

The CERTs have made contributions to understanding the safety of drugs, biological products, and medical devices through the further understanding of the safety issues and risks of therapeutic agents already on the market. The CERTs have contributed to new knowledge about drugs and their risk profile. Besides the identification of unsafe medications in particular populations the CERTs have also committed extensive resources to understanding risk assessment, management, and communication in therapeutics. The Portfolio as a whole has expanded the knowledge of therapeutic efficacy and effectiveness as well as included research that aimed to further understand and improve the efficiency of health care. Additionally, the Portfolio included research that primarily contributed to the furthering of knowledge and future research (a Level 1 Impact). Furthermore, a number of projects also had a Level 2 Impact or informed policies. The level 2 impact studies were primarily on drug safety issues and risk management, change clinical practice guidelines, and quality measures. The Portfolio had only a few examples of a level 3 and 4 impact on clinical practice and health outcomes and these were usually attributed to intervention studies.

Portfolio research and awards have contributed to the knowledgebase of diverse areas in therapeutics, clinical practice, and research methodologies. The research findings of the Portfolio funded grants and research funded through the CERT program have contributed to the field of therapeutics research. The research outcomes relate to the specific areas of CERTs specialization, including drugs, biologics, and devices. The contributions are aimed at various end users including: patients, consumers, health care providers, HMOs, PBMs, government agencies, professional organizations, and other. The research has focused on diverse populations, including: children, women, minorities and ethnic groups, and the elderly. Examples of disease and organ system areas of focus include the cardiovascular and musculoskeletal system. The work of the CERTs and the Portfolio also includes the advancement of methodologies for education and research on therapeutics.

The Portfolio also demonstrated progress towards meeting the Agency and DHHS goals as evident in the outputs from the awards. The outputs included publications, presentations, as well as educational outputs. The CERTs research outputs between 2002 and 2005 included nearly 400 publications, over 200 presentations, conferences, workshops, proceedings, committee roles, and testimony to federal agencies. [68] Besides these outputs, the CERTs also developed registries and infrequently used data sources for health services and pharmacoepidemiological research.

The CERTs also aim to provide education to advance the optimal use of drugs, medical devices, and biological products. Consequently, the CERTs have provided education on clinical topics and research methods in therapeutics to researchers, practitioners, patients, and policymakers; developed educational resources (e.g. toolkits, continuing education), fostered the development of future researchers and practitioners; and initiated unusual educational initiatives. Educational outcomes of the CERTs have included the development and training of future therapeutics researchers.

The Portfolio has also contributed to the progress of the Agency and DHHS particularly via the CERTs mechanism. The CERTs are centers focused on a research theme in therapeutics funded as cooperative agreements. The CERTs yielded additional outcomes through the development of partnerships with both private and public entities. Additionally, the CERTs program was designed to create a network of collaborators, although the extent to which the investigators collaborated across the CERTs was limited. There were a few examples of cross-CERT collaboration that were viewed positively.

> *The structure is pretty consistent with original intent of the CERTs program. There are people doing a variety of work around these areas. We capitalize on that body of work and the available collaborations….from a funding standpoint, it creates the possibility of tapping into other funding streams. You can leverage multiple resources (and multiple people's networks). (CC)*

The awareness, diffusion, and dissemination of Portfolio research varied. Hundreds of manuscripts were published and hundreds of presentations were given. The Portfolio grantees and CERTs investigators employed atypical dissemination venues as well, particularly with regard to patients and consumers although the success of those was difficult to determine. The extent to which the dissemination of research important to other researchers, practitioners and policymakers was successful is unclear. It appeared from a very small number of contacts with 'external' individuals that the CERTs program itself was not always well known.

Different CERTs stakeholders (Steering Committee, AHRQ, investigators, and policymakers) identified the CERT PIs in particular as recognized experts in their respective fields. Additionally, external respondents and policymakers who were familiar with the CERTs thought they were not as successful as they could be given the capable researchers and experts in their fields, and the level of collaboration was seen as minimal. Additionally, an outside researcher believed that the CERTs did not come across as a national resource in terms of taking a stand on therapeutic issues, like Vioxx, on the market. A federal agency representative gave the example that the CERTs would have done well to demonstrate a responsiveness if for example they studied the drug needs and issues of Hurricane

[68] The research outputs may also include educational outputs if the publication or presentation is focused on an educational topic, however it was not feasible or analytically important to discern these outputs for publications and presentations

Katrina victims (e.g. how long took to get medications or where they unable to get critical medications). However, the representative also acknowledged that academic researchers and institutions are not always "nimble to respond." That said, every respondent who said something critical of the CERTs also said that the CERTs were given a large, perhaps impossible mandate, encompassing a large research area (drug, biological products, and medical devices) that with their level of funding would be difficult to fulfill.

> *"The limitation of funding, the difficulties of working in the context of a federally funded public-private partnership, and all of those represent constraints, which are a given because of who we are. But given who we are, the productivity in my view has been extraordinary." (SC)*

4.1.2. Impact of Portfolio research on state and federal health care policy making

The impact of the Portfolio research ranged from Level 1 to Level 4 impact. The majority of Portfolio research had an impact at Level 1 or future research findings whereas only a few studies had a Level 4 impact --- impact on clinical outcomes. There were additional studies that had level 2 impacts, leading to changes in clinical practice guidelines, quality measures, and drug regulation and risk management. A brief description of the research for each impact level is provided below:

The Portfolio has conducted extensive research that has had level 1 impact, specifically impact on further research studies. The areas of particular contribution have been in the following areas: advancing research methods on therapeutics, medication adherence, medication safety, medication errors, identifying prescription drug trends, cost and economics of therapeutics, QT prolonging medications, HIT, and antibiotics and antimicrobials.

The Portfolio has had level 2 impacts that inform policies or programs as a result of their research findings and interventions. The specific areas where the portfolio has contributed have been in quality measures and indicators (e.g. HEDIS), drug regulatory activities, clinical practice guidelines, and medication errors.

The Portfolio research has had some examples of impact on clinical practice, primarily with intervention studies. The CERT studies have included interventions to reduce errors, order entry alerts, educational interventions on antibiotic use and prescribing, and continuing medical education.

The level four impacts on patient outcomes were rarely attributable to the Portfolio research. The few examples include the Portfolio grantees intervention studies aimed at improving antibiotic use and reducing antimicrobial resistance.

Additionally, four case studies of CERTs projects were described to illustrate how CERTs research can have or has the potential to have: the black box warning; QT interval and prescribers' knowledge; antibiotic prescribing tensions; and rickets, vitamin D deficiency and guidelines.

4.1.3. Adequacy of Portfolio progress reporting

Progress reporting is an expected part of a grant or research funding. The available data did not allow Abt to assess the timeliness of the progress reports. Additionally, the completeness of the progress reporting was assessed from the perspective of the stakeholders. The CERTs progress reports were

different in length, content, and level of detail. Besides the variance in the progress reports across CERTs, the progress reports also varied within a CERT across years in terms of factors beyond content.

The CERTs progress report commented on reporting as an administrative burden and mentioned that the timing was sometimes poor when it coincided with other key dates. The progress reports, though sometimes burdensome, were able to accurately capture and represent the advances the CERTs had made, although not all discussants felt this way. The utility of the progress reports for internal purposes varied across CERTs. However, a number of investigators were unclear on how they were used, if at all, by AHRQ. There were some comments on how the process could be improved; however the Coordinating Center is also developing the CIT program. This may be a step in the right direction to charge an entity with coordinating the projects and outputs of seven different centers made of many more investigators and their projects and publications.

4.1.4. Contribution and role of the Duke Coordinating Center (CC), Steering Committee, program office, and other partners to the CERTs.

A Social Network Analysis was conducted to examine inter-relationships among the network constituents. In the original CERTs plan, as devised by AHRQ in conjunction with the CERT Steering Committee and its partners, the CERTs Coordinating Center was to have the role of liaison between the CERTs themselves and AHRQ, the Steering Committee, preferred partners, and other government agencies. This analysis found that the Coordinating Center is functioning very much as it was envisioned in the original CERTs plan, acting as the bridge between the CERTs and the other actors within the program. The Coordinating Center is the focal node in this network, dispersing information from AHRQ and the Steering Committee to the CERTs as well as bringing together outside partners with the CERTs based on research needs and interests. This has been both an efficient and effective way to manage the CERTs network to avoid unnecessary resource expenditures or duplication of effort to spread information and create collaborative connections.

Social network density measures indicate that the actors within the network are connected most directly with the Coordinating Center. Other measures support the liaison role the Coordinating Center plays among the CERTs, AHRQ, the CERT Steering Committee, and other partners. As noted in interviews within this study, the role of the Coordinating Center appears to be changing and evolving into the network structure as depicted in Volume 2 Attachment 9.

Additionally, the relationships of individual members of each CERT can be vital in expanding the CERTs network under the conditions of finite resources. If a principal investigator within a CERT has worked with an individual or organization prior to being involved in the CERT, that relationship can be accessed in the future without the same level of resources as would be needed to initiate and maintain a new connection. Access and trust have already been established with that potential partner that mitigates costs and geographic proximity. Thus, an actor who has a history with a CERT or member of the CERT will be more likely to work with that CERT despite potential geographical limitations. In this situation, the Coordinating Center plays a vital role in maintaining past relationships of the CERT partners to decrease the individual resource costs to each CERT and to provide for future opportunities with the CERTS and those partners. The Coordinating Center currently does a good job maintaining these linkages and bringing together CERTs with those partners who have similar interests or particular needs. If the Coordinating Centers role as the liaison between AHRQ, the CERT Steering Committee, and the CERTS is diminished or diluted through

more direct contact with each CERT, the cost to each CERT to maintain relationships and create new connections may increase. Additionally, the burden of the information processing that the Coordinating Center currently undertakes would be shifted to the individual CERTs as well, as there would be duplication in effort in providing information from both AHRQ and the Coordinating Center. It appears that AHRQ is leaning towards having more direct contact with the CERTs. The role of the Coordinating Center becomes vital to maintaining coordination and communication among and between the CERTs so that the network does not become fragmented. In most all of the CERTs network diagrams; the Coordinating Center is seen as vital actor within the networks whose removal would separate the CERT from the macro CERTs network. This confirms the vital role that the Coordinating Center plays in connecting the CERTs to each other and the broader network, providing further evidence that the Coordinating Center is functioning as originally designed within the program.

4.1.5. Strengths of the program and most successful or promising research, especially with respect to the PART goals.

The value of engaging in an Appreciative Inquiry exercise is both in the process as well as in the output. By working together to identify the strengths and past successes, as well as future opportunities for the CERTs program, Participants were able to build upon each other's ideas, better appreciate the underlying forces that have contributed to the program's success, and then use this information to envision an exciting and inspired future. The CERTs program possesses numerous assets, which participants believe have been and continue to be crucial to the success of the program, including the level of cooperation among Participants, the cross-disciplinary backgrounds of the key stakeholders, the flexibility of the program, the role of the Steering Committee, and the role of the Coordinating Center. The CERTs program's greatest successes to-date have involved the creation, development and fostering of partnerships to further advance the education and research agenda of the CERTs. In addition, the CERTs program has had significant success in disseminating its findings, and influencing local, regional and national policies and national agendas.

The "Visions of the Future" for the CERTs program entails building upon the work that the various CERTs investigators and that. AHRQ and key stakeholders have already done. It also strengthens the role and prominence of the CERTs as a national resource for practical research on the safety and effectiveness of therapeutics. All of the Participants are deeply committed to this vision and believe it is possible.

The Appreciative Inquiry exercise yielded findings that can serve as a tool for the CERTs program as it continues to strive for its goal of providing education and research on therapeutics, by capitalizing on the strengths, acknowledging the successes and furthering discussions on potential opportunities. It is hoped however that this exercise serves as the first of many such AI exercises that the participants will engage in as they continue to build upon and leverage the program's strengths.

The Portfolio appears to be making progress toward the first two PART goals. More projects are oriented toward decreasing the inappropriate use of antibiotics in children, and some toward reducing congestive heart failure re-admission rates. This may be due to the thematic focus of the CERTs. We are not aware of any projects addressing the PART goals to reduce hospitalizations for upper gastrointestinal bleeding and to improve the appropriate use of therapies to address peptic ulcer disease. The CERTs investigators, and key leaders on the Steering Committee and senior investigators and PIs all stated a commitment to the PART goals.

4.1.6. Role of Portfolio relative to other AHRQ and DHHS priorities.

The Portfolio is one of many portfolios within AHRQ. It has the unique focus of research on pharmaceutical outcomes. The FDA has regulatory oversight and management of pharmaceuticals, but AHRQ's Pharmaceutical Outcomes Portfolio provides a unique venue to focus on pharmaceuticals in the market and taken by patients, and the different types of understanding and research which that requires. AHRQ as an agency was identified by various stakeholders as the federal agency that focuses on areas that other agencies do not, specifically translation of research into practice, patient-focused research, practice-based research, applied research, and in the case of pharmaceuticals the understanding of pharmaceuticals post-market. An FDA representative spoke to the role of AHRQ explicitly and the role of the Pharmaceutical Outcomes Portfolio implicitly.

> *They're doing interesting and valuable work on products in the market, and how they're used, and how to basically do the research that FDA doesn't support and sponsors [pharmaceutical companies] don't do. When you have competing products out there what's the best standard of care and what's evidence based for choosing one over another or one drug class over another. There needs to be more of it done…but what they're doing is making a substantial contribution to both quality care and patient safety.*

Within the U.S. Department of Health and Human Services and its priorities, AHRQ and the Portfolio make a special contribution to the research on safety of therapeutic agents on the market, applied in practice, prescribed by providers, and taken by patients.

4.1.7. Case Study Impact

Mechanisms of Impact

To understand the process from research findings to impact on policy or a field, processing tracing informed how the researcher identified mechanisms that led or contributed to the impact the research had. To better understand the mechanisms Checkel (2005) describes: "Mechanisms connect things. They are 'recurrent processes linking specified initial condition and a specific outcome' (Mayntz 2003, 4-5)."[69] The process tracing is when "one carefully maps the process" for example from findings to impact in the case of these case studies.[39] A discussion of potential mechanisms that seemed important to the impact the CERTs research case studies were able to have are discussed below. Some of the mechanisms are clearer than others as is the impact for some of the case studies greater than others.

Most examples have not been as clear-cut as UNC. (CC)

Nature of the Findings

The findings appeared to be an important factor in the impact the results may have, both in the case studies and in the other research projects. Particularly when research findings indicated harm or safety issues and new knowledge on these topics, so for the rickets study it was a "new old disease" a disease of a previous era, that had essentially returned. With respect to the impact it was able to have,

[69] Checkel, JT. It's the Process Stupid! Process Tracing in the Study of European and International Politics. Centre for European Studies University of Ohio. Working Paper No. 26, October 2005.

it was an actionable change, (in part change in prescribers' behavior, but also just simply providing an inexpensive vitamin). The ACE Inhibitors in pregnancy study from the Vanderbilt CERT was recently published; however, it was identified by respondents as a recent example of impact (potential), in part because it determined that not only should these medications not be used in the third trimester but their study revealed that they should be avoided in the first trimester as well -a population for which safety is a large concern --- pregnant women. Actionable findings also seemed to be an important factor. For the rickets study the action was clear-cut and relatively inexpensive. However, the black box warning example refers to 200 drugs for which warnings are not heeded by prescribers. It would be a great challenge to change the behavior for prescribers of 200 different drugs for a diverse group of individuals.

End User

Study impact is determined by the type of end user of the findings. For example, if research findings were regarding the clinical guidelines published by a professional organization, then the end user (the professional organization) is clear and therefore easier to target, whereas if the findings are targeted to general practitioners as a large population, it is more difficult to have an impact. An AHRQ representative makes this point.

> *You can communicate with certain specialty organizations. They have a vested interest because they have a subset of patients that are fairly identifiable...kids, or, people with heart disease. So that I think, it makes for an easier sell if you know whom you're selling to. It's a lot harder when you're trying to deal with something like all primary care doctors...*

So both the rickets study and the QT interval involved the researchers working with the respected, specialized professional societies to impact or understand providers.

Time

Time is apparent for understanding impact. FDA stated that for the black box study it was too early to determine impact. The rickets study began around the time that the CERTs began (1999) and the clinicians' initial identification of cases of rickets was occurring even prior to that. So time has elapsed, and Dr. Schwartz pointed out that it has taken the AAP 5-6 years to change its guidelines on vitamin D supplementation.

Level of Impact

Some research findings are important to a region, however most have transferable knowledge to other regions. The rickets study is an example in NC which impacted policy, the coverage of vitamin D by the WIC program. Although the question may be an issue in other parts of the country, where they are working towards changing guidelines, this may indirectly impact national practice. Local and regional impact is easiest to address.

Dissemination/Partnerships/Networking

True dissemination is identifying who are the true end users and who can do something with the information. This was how the rickets case study clinicians and their partners came to think about the WIC. The WIC program had also given them the additional data they needed for resubmission to the Journal of Pediatrics.

It is difficult to identify mechanisms that result in a study having an impact, particularly beyond an impact on further research to impacting policies, clinical practice, and health outcomes. However, it is a worthy effort to explore the cases in which studies were able to have an impact in case there are commonalties that are mechanisms worth repeating in future research studies to further ensure an impact. Time was identified as a critical factor and when research identifies a safety concern there is a natural time lag before it can impact health outcomes, even in the best of circumstances. Context was another key variable in the ability of a research study to have impact and certainly the research findings contributed to that context. Specifically, the investigators researched topics that were timely or responsive (or at least coincided) to current issues in therapeutics, particularly safety. Connections or networking with colleagues and key decision makers was an important factor in terms of the dissemination efforts of the investigators and allowing them to impact policy and launch dissemination initiatives.

This evaluation has described the pharmaceutical portfolio from a variety of quantitative and qualitative perspectives, and in the final section above has discussed Portfolio performance against a variety of goals and objectives. Some additional summary observations follow:

- The seven CERTs evaluated appear to be making progress toward the original program goals and objectives.
- The CERTs as centers, have devoted considerable resources to what appear to be useful programs contributing to the development and training of future researchers.
- While progress reporting is one of the more mundane processes of the CERTs network, it seemed to generate a disproportionate share of potential opportunities for improvement.
- One of the advantages of the network structure is that it has led to productivity and collaboration.
- The CERTs appear to have great potential to further leverage their expertise in networking and collaborating.
- There was some indication that researchers, practitioners, or policymakers may not be as aware as they should be about the work of the portfolio as Portfolio or CERTs "products" per se.
- Participants in the AI workshop identified the dissemination of information, agenda setting, and building partnerships as three key areas in which to focus future priorities.

TABLES

Table 1: Level 1 Findings: Data and Methods

CERT	POPULATION	FINDING
HMO	Gout Patients	There are limitations of administrative data for research on gout; this study showed that there were marked differences between men and women with gout with respect to epidemiology and treatment; administrative data may lead to misclassification.
UNC	Pediatrics	Use of statewide Emergency Dept. discharge database without medical record validation would be an inadequate approach for surveillance of drug-related anaphylaxis in children
HMO	Ambulatory patients	Error-detection phase of study led to creation of 10 HMO 2,000,000 person data set to support investigations into errors in drug prescribing in ambulatory setting
UNC	Pediatric	MEDMARX dataset is sufficiently powerful to identify trends in the pediatric population that warrant systems and process changes
HMO	General population	Automated claims and pharmacy databases are not sufficient on their own for assessing appropriate renal dosing to determine prescribing errors of QT interval prolonging medications
Penn	Researchers	Guidelines for the conduct of prospective meta-analyses
UAB	Researchers/ Practitioners	Identification of tool (Achievable Benchmark of Care) for providing practitioners feedback (with benchmarks) on their performance to improve outcomes/compliance
HMO	Chrug-Strauss Syndrome patients	Development of algorithms using claims data that suggests patients with Chrug-Strauss Syndrome can be successfully identified using algorithms based on administrative data
UNC	General population	Found that many hospitals report adverse drug events differently in the emergency discharge database (ICD-9 and E codes) and the database has limitations to be used for identifying anaphylaxis related to drugs.
UNC	Pediatrics	Largest analysis of pediatric medication errors from the perioperative continuum of care. Used MEDMARX database in collaboration with USUHS to study drug-related anaphylaxis. Early findings suggest that pediatric patients are disproportionately vulnerable to an error medication.
HMO	Pediatrics	In study of prevalence of outpatient dosing errors, identified barriers to understanding the epidemiology of medication errors in children. Examples include prescribing medication that is not labeled for use in children, discrepancies in published dosing recommendations for many medications, unclear guidelines, and lack of readily available documented weights
Grantee	General population/ researchers	Large multi-community randomized trial of an intervention to reduce antimicrobial resistance which innovatively linked health services measures with bacteria resistance patterns (nasopharyngeal carriage of resistant and susceptible S. pneumoniae)
Duke	CHF inpatients	A registry of inpatients with heart failure containing data on clinical history, demographics, medications, and treatment patterns to better understand outcomes associated with heart failure management.
Arizona	General population	The web-based drug-induced arrhythmias registry (www.qtdrugs.org) has been accessed by individuals nationally and internationally. Attributed with providing the information that contributed to identifying the cardiotoxic effects of methadone.

Table 2: Level 1 Findings: Adherence

CERT	Population	Finding
Penn	HIV	Found a relationship between adherence and outcomes in HIV and subsequent need to intervene. (Follow-on work was looking at relationship between medication misperceptions and rates of adherence, and medical literacy)
Vander bilt	MI and HF patients	10-20% patients discharged from the hospital with myocardial infarction (MI) or heart failure (HF) and who should be getting follow up medication do not fill the prescription they are given in the hospital and therefore don't receive the benefits
Grantee	HIV & HTN patients	Exploration of non-adherence as a revealed preference to understand non-adherence among patients with HIV and hypertension (HTN). Goal was to further understand root causes of non-adherence through the study of preferences. Key finding: differences in ethnic group values.[70]

Table 3: Level 1 Findings: Medication Safety

CERT	Population	Topic or Finding
Vanderbilt	General population	Examined association between oral erythromycin and sudden cardiac death. Also found that risk of death is greater if erythromycin taken with CYP3A inhibitors.
HMO	Prenatal	Described the extent of prenatal exposure to prescription drugs.
Vanderbilt	Arthritis patients	Rofecoxib (Vioxx) prescribed and used at higher than recommended doses
Vanderbilt	Heart disease patients	Retrospective heart disease study found no protective benefit from NANSAIDs, suggesting that NANSAIDs should not be prescribed to protect against heart disease.
Vanderbilt	Medicaid & VA	Identified that as many as half of patients receiving NSAIDs are at high risk of ulcer disease because they are not receiving protective therapy for their stomachs.
Vanderbilt	Psychiatric patients	Among patients taking antipsychotic medications with severe cardiovascular disease, current moderate dose users had 3.3 fold increased rate relative to comparable nonusers, resulting in 367 additional deaths per 10,000 person-years of follow-up. Data reviewed by FDA prior to thioridazine label change.
Vanderbilt	Pregnant women	Much press publicity for paper in New England Journal (2006) examining effects of ACE inhibitor medications during pregnancy, early in pregnancy and the development of birth defects in babies whose mothers took those medications. FDA held press conference before paper released indicating that a public advisory would follow.
HMO	Pediatric	15% of the children were prescribed a medication that constituted a potential dosing error
HMO	Elderly (>65)	High level of inappropriate medication use in the over 65, outpatient population.
Arizona	Elderly (>65)	Using a national PBM's database to identify inappropriate prescribing. Identified many filled prescriptions for potentially

[70] Although the grant had ended, the grantee had not completed the analysis at the time of this discussion.

Table 3: Level 1 Findings: Medication Safety

CERT	Population	Topic or Finding
		inappropriate drugs; suggests need for careful monitoring of such databases.
Alabama	Arthritis patients	Assessed how patients and physicians are communicating about risk, and then completed an intervention. Baseline data show large disparities in risk awareness, risk communication, and risk behavior.
Alabama	Patients with steroid assoc. bone disease	For patients with steroid associated bone disease two studies demonstrated major deficiencies in the monitoring for side effects of glucocorticoids."
Arizona	Hispanic women with diabetes	Some herbal remedies may affect diabetes control, as well as produce adverse effects or medication interactions.
PENN	Penicillin allergic patients	Large numbers of patients were prescribed penicillin a second time, despite a prior allergic-like event.
Arizona	General population	Evaluated the accessibility and quality of information for dietary supplements promoting 'colonic health'…Manufacturers found to be unwilling/unable to provide clinicians with data on product efficacy or safety. Claimed need for independent research on the safety and efficacy of supplements.
HMO	Pregnant women	A significant number of women become pregnant while taking drugs for which the risks are unknown or demonstrated.

Table 4: Level 1 Findings: Medication Errors

CERT	POPULA-TION	FINDINGS
Alabama	Gout patients	Results of studying MEDMARX gout medication suggest that inappropriate prescribing practices are characteristic of errors occurring with the use of allopurinol and colchicines. Physician prescribing practices are a potential target for quality improvement.
Alabama	General population	Errors in which the medication reaches the patient but does not cause harm account for the majority of errors reported. Distractions were noted as the number one contributing factor to the error. MeDMARx
UNC	Pediatric	Leading types of errors reported through MEDMARX were omission errors, improper dose/quantity, and wrong time. Consistently, the leading causes of errors seen in pediatric medication errors are performance deficit, procedure/protocol not being followed, and communication.
HMO	General population	Error rates varied by medication class…for each medication, rates of laboratory monitoring errors were higher among patients with less comorbidity. Over one-fourth of patients dispensing allopurinol did not have serum creatinine monitor during one year of therapy. Lack of monitoring and lack of subsequent possible dosage adjustment puts patients at an increased risk of allopurinol toxicity. Increasing hepatic aminotransferase and thyroid function testing in outpatients prescribed amiodarone could translate into fewer amiodarone-associated adverse effects. A substantial proportion of patients receiving drugs associated with toxicity if

		concentrations are elevated did not have concentration monitoring during one year of use. Patients with spironolactone therapy and those at risk of hyperkalemia are generally monitored, but there are still many who remain unmonitored.
HMO	Physicians & General population	Findings suggest that patients are not likely to forgive a physician in circumstances where they suspect incompetence, inattention, or a lack of caring on the part of the physician involved.
HMO	Physicians & General population	Patients will respond more favorably to physicians who fully disclose medical errors than to physicians who are less forthright, but the specifics of the case and the severity of the clinical outcome also affect patients' responses.
HMO	Elderly	Recent rates of potentially inappropriate medication use by elderly HMO members were at least as great as in a 1996 national sample.

Table 5: Level 1 Findings: Trends

CERT	POPULATION	FINDINGS
Vanderbilt	Pediatric	Prescription rates of antipsychotic drugs for children with less severe afflictions are increasing, especially for ADHD and depression. It's not really known if the benefits to the children outweigh the risks. A study to determine if benefits outweigh the risks is needed.
Duke		Annual prevalence of use for [life saving cardiovascular therapies] increased between 1995 and 2002
Duke	Cardiac patients	Results of project looking at overall use of anti-arrhythmic drugs in the era of increased use of ICDs demonstrated increased use of anti-arrhythmic drugs despite, or potentially due to, the increased use of ICDs during this time.
Alabama	Patients with GIOP & Providers	Study provided evidence at a national level of poor quality of care and substantial practice pattern variation amenable to provider-targeted interventions aimed at improving GIOP prevention.
UNC	Pediatric	First round findings confirmed increasing use of psychotropics by youths in IPA-model health plans, with consistency across health plans in different geographic regions. Prescribing physician is a significant factor.
Vanderbilt	HIV	Retrospective study of prescribing rates of contraindicated combinations protease inhibitors and statins in HIV-infected people to asses impact of publications of treatment guides. Contraindicated combinations have decreased, but remain unacceptably high.

Table 6: Level 1 Findings: Cost and Economics of Therapeutics

CERT	POPULATION	FINDINGS
HMO	Diabetic patients	Increasing co-pay of more that $10 for thirty day supply for oral hypoglycemics was associated with significantly reduced use.
Duke	Cardiac patients	Examined economic effects of beta-blocker therapies. Found that there are no clear financial incentives for hospitals and physicians, even though social and Medicare costs decreased.
Duke	Cardiac patients	Study projected the economic impact of drug-eluting stents on a hospital system (Duke Medical Center) $8.1 million loss was predicted in the first year and $8.7 million loss in subsequent years
Alabama	Arthritis patients	Found that glucocorticoid users face non-negligible incremental health care costs compared to non-users. For an estimated one million chronic glucocorticoid users, the costs to the health care system would be over $1.2 billion annually in the U.S. alone for treatment of adverse effects attributed to glucocorticoids.
Duke	Cardiac patients	Study evaluated the economic effects of extending the use of clopidogrel from one month to twelve months in patients who have received a percutaneous coronary intervention. Extending therapy cost $879 and reduced the risk of myocardial infarction by 2.6%. The cost would be $15,696 per life year saved. Thus, this potential change in practice appeared economically attractive.

Table 7: Level 1 Findings QT Prolonging Medications

CERT	POPULATION	FINDINGS
Arizona	General population	Population based study found that despite information provided in the package insert, drugs with the potential for QT prolongation are prescribed and dispensed frequently in the outpatient setting.
Arizona	General population & Methadone patients	The Arizona CERT developed and continues to maintain an international registry of drug-induced arrhythmias at www.qtdrug.org. From that registry, the PI describes the most striking discovery in this project as being the detection of an unexpected drug toxicity and a new risk of toxicity from a group of intravenously administered drugs [methadone].
Arizona	Methadone patients	Contrary to recent reports in the literature, we concluded from our analysis of the cases that prolonged QT and TdP (Torsade de Pointes) can occur over a wide range of dosages including those recommended for addiction treatment.
Duke	Cardiac patients	Evaluation of the dofetilide risk management program initially found the program to be effective but also found a deficit in the knowledge of other QT-prolonging medications.
Duke	Cardiac patients	Additionally, Duke CERT studied dosage of dofetilide and sotalol, drugs to treat the same problem, but one (dofetilide) with a risk management program and one without. Found that dofetilide was used in more appropriate doses but was prescribed less often.
Vanderbilt	General population	Finalizing a list of drugs for which there is strong evidence that these agents cause both QT prolongation and TdP, and with sufficient frequency to be a factor in the clinical use of these drugs, and understand drug-drug interactions and sudden cardiac death.
Duke	General	The use of QT prolonging medications in combination with either

	population	other QT prolonging medications or medications that inhibit the clearance of QT prolonging medications…. Approximately 5% of patients who received a QT prolonging drug during the study period received one more additional QT prolonging medication and/or a medication with known potential for interaction with QT prolonging medication. Most of these potential drug interactions occurred in patients with one of more risk factors for TdP.

Table 8: Level 1 Findings Antibiotics and Antimicrobials

CERT	Population	Findings
Penn	Generalists and infectious disease specialists	Generalists and infectious disease specialists were found more likely to prefer newer drugs than older drugs when treating community-acquired pneumonia. Neither generalists nor specialists emphasized the relative societal risks of drug selection, but emphasized providing the newest and best treatments for each patient.
Penn	Nursing home residents	In the final model, prior fluoroquinolone use is a risk factor for the development of FQR-EC UTIs and absence of a urinary catheter is protective. Other studies found prior FQ use to be a risk factor for FQ resistance. None of these studies, however, focused on clinical urinary tract infection.
Penn	Patients with acne	S. pyogenes colonization and resistance in the oropharynx are associated with antibiotic therapy in patients with acne.
Penn	Patients with acne	Results from studying the General practice Research Database do support the notion that within the group of individuals who have acne and receive antibiotics […] there is an increased association with a general practitioner office visit for upper respiratory tract infections/pharyngitis. This may be one of the first studies that has actually shown an increased rate of an infectious illness associated with long term antibiotic use in a generally healthy population.
Penn	General population	Preliminary analysis reveals that the proportion of the primary bloodstream infections accounted for by gram-negative pathogens has increased significantly over the past five years. These changes have great implications for empiric antimicrobial therapy for suspected bloodstream infections, but also for fostering the development of new agents with expanded gram-negative activity.
Penn	Pediatrics - Hospitalized children	Patients with ESBL-EK infection were 5/8 times more likely to have had exposure to an extended spectrum cephalosporin within the thirty days prior to infection and also were more likely to be female, had infection caused by a Klebsiella species, and received steroids in the thirty days prior to infection. Findings might be used to limit the emergence of ESBL-ED infections in children.
HMO	Pediatrics	Study results indicate that prescribing rates have decreased by 23% in children less than three years old from 1995-2000 … The majority of the decrease in antibiotic use was because of a decreased rate of diagnosis of otitis media.
Penn	Physicians & Hospital decision-makers	Physicians are waiting until after prior-approval hours to order restricted antimicrobials. In addition, of those restricted antimicrobials ordered between 10 p.m. and 11 p.m., only 65% are actually continued.

APPENDIX

Appendix 1: Evaluation Study Questions and Objectives

Study Question	Objectives					
	A. Progress	B. Impact	C. Reporting	D. CERTs Network	E. Strengths	F. Portfolio Role
1. How do Portfolio objectives map to AHRQ/DHHS priorities?	x					x
2. What have been the inputs during the past three years?	x					
3. What have been the research outputs during the past four years?	x					
4. What have been the educational outputs during the past four years?	x					
5. What are the program outcomes?	x					
6. What are have been the program impacts?	x	x				
7. Have inputs/outputs/outcomes/impacts changed over time?	x	x				
8. Do program outcomes/impacts reflect program goals and AHRQ/DHHS priorities?	x	x				x
9. Is investigator progress reporting complete, accurate, and timely? Is it adequate to assess inputs/outputs/outcomes/impacts?			x			
10. How is the information contained in the progress reports used by AHRQ?			x			
11. Is the information and/or the process of progress reporting useful to investigators?			x			
12. What are the characteristics of the CERTs network overall? How does this vary by CERTs or CC?				x		
13. What roles do the individual CERTs constituent groups have in facilitating diffusion of information and innovation throughout the CERTs network? In particular, what role does the Coordinating Center have in the CERTs network? What is the nature and role of the CERTs scientific collaboration?				x		
14. How were the goals and priorities of the Portfolio determined?				x		x
15. What do various stakeholders view as the most successful processes and outcomes of the Portfolio? How can this information be used to maximize, leverage, or build upon success in the future?					x	

Appendix 2 Social Network Analysis Measures

Measure	Description
Network Size	The number of unique ordered pairs of actors within the network and is a basic demographic of a network. Network size matters, because it shapes the social structure of the network due to the capacity and resources needed to maintain relationships (Hanneman, 2000).[71]
Number of Ties	A basic demographic of the network and is the count of the number of relationships or ties in the network (Hanneman, 2000). It can reveal how large and connected the network is which has implications for information and resource flows.
Average Distance	The average number of relations in the shortest possible connection from one actor to another. Again, this metric has implications for information and resource flow; if distances are large it may take some time for resources to flow through the network (Hanneman, 2000).
Density	The total number of actual ties divided by the maximum number of possible ties in the network (Kilduff and Tsai, 2003). It ranges from 0-100 and is the overall measure of connectedness of actors within the network. The higher the density of a network, the more connected the actors are which increases information and resource. Although the density measure of one CERT cannot be directly compared to that of another in part because the density is in part a function of the size of the network and would be meaningful comparison if networks were the same size. The density measure is difficult weight heavily because it is a somewhat artificial measure given the data collection did not include speaking with the partners in the network to ask who their partners given resource constraints, evaluation priorities, and the ego network framework. Therefore, naturally the density measure was lowered because of this for all the CERTs.
Degree Centrality	Measure of the ego actors' position within the network by counting the total number of direct connections of that actor. Core or central actors have many more connections than do those who are on the outside or periphery of the network. Those actors that are central within the network are in a position of power within the network (Kilduff and Tsai, 2003). The lower bound of this measure is 0 and its upper bound is a function of the total number of ties. [72]
Closeness	Measure for networks that are fully connected and examines the "shortness" of the direct connections of the actor to other actors in the network. A large closeness measure positions the actor so that they can reach many other actors within the network, thus putting them in a power position within the network (Kilduff and Tsai, 2003). As with Degree Centrality, the lower bound of this measure is 0 and its upper bound is a function of the total number of ties.
Betweeness	Measure of an actor's ability to be a bridge or 'go between' for other pairs of actors by being an intermediary connecting that relationship (Kilduff and Tsai, 2003). It ranges from 0-100; a high betweeness score signifies that an actor occupies a broker role within the network, and can mitigate contacts between other actors (Hanneman, 2000).
KeyPlayer	Measure resulting from a program that identifies the optimum sets of nodes to target for either removal or observation/intervention in a given network. Thus the key members of the network are identified and confirmed by core/periphery measures in

[71] Hanneman, R. (2000). Introduction to social network measures. Retrieved June 9, 2005, from http://faculty.ucr.edu/~hanneman/networks/nettext.pdf.

[72] Kilduff, M., & Tsai, W. (2003). *Social networks and organizations*. Thousand Oaks: Sage Publications.

Appendix 2 Social Network Analysis Measures

Measure	Description
	Ucinet (Borgatti, Everett, and Freeman, 2002). A keyplayer plays a prominent bridging role in the network and its removal would result in a fragmented and less connected network. There are no upper or lower bounds to this measure, rather it locates key actors within a network based on data input. The norm is to locate 2-3 key actors, but that is a judgment based on the size of the network you are dealing with. The keyplayer algorithm is a metric designed to locate the main actors within the network diagram that if removed would fragment the network or in which their position in the network indicates an opportunity to expand the network.

Appendix 3: Documents Reviewed and Coded	
Administrative Document	Data Available
Pharmaceutical Outcomes Portfolio Award List	Grant number and type; strategic area, Principal Investigator, topic
Investigator Progress Reports[73]	Budgets; staff list; aims; leveraged projects and results; plan for the following year; assurances; publications; inventions and patents; race and minority statistics; partners
Contact Lists	Contact information for CERTs coordinators, Principal Investigators, Steering Committee
Previous Evaluations of the program (2002, 2001)	Overviews of the CERTs, organizational structure; assessment of research objectives; partnerships/networks; communication strategies; impacts of funded studies
Portfolio Strategic Plan	Planning matrix
Partnerships to Advance Therapeutics (PATHs) registry list	Partner organizations, project descriptions
Materials for Steering Committee Meeting	Governing documents
CERTs Documents	Authorizing legislation; fact sheet; vision and mission statements; assessments; current and planned projects; partners; meeting attendees; financial information;
CERTs project database	Project #, title, aim, PI, partners, etc.
CERTs publications database	Authors, titles, years, bibliographic information
Requests for Applications	Goals, requirements for applicants

[73] Only a few of the grants were completed and had final reports that included findings