National Leadership Summit on CER Priorities, Methods and Policy

Exploring the Challenges & Opportunities for Improving Evidence Generation and Care for Cardiovascular Disease

Final Report

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Table of Contents

Executive Summary

Cardiovascular disease remains the number one cause of death for Americans, despite years of research, remarkable increases in the likelihood of survival following a heart attack, and a veritable explosion in the number and type of diagnostic and therapeutic options available to patients. Public health initiatives to eliminate smoking in public places, improve treatment of hypertension, lower cholesterol, and treat high-risk individuals with aspirin receive much of the credit for these gains, but uptake of evidence-based recommendations has been regrettably slow, health disparities persist, and health care expenditures have reached what many believe is an unsustainable level that threatens American competitiveness in a global economy.

In October 2011, the Center for Medical Technology Policy hosted its second annual Comparative Effectiveness Research (CER) Summit, bringing together patients, clinicians, advocacy groups, researchers, professional medical society representatives, regulators, and insurers to identify the gaps in cardiovascular comparative effectiveness evidence and to discuss potential strategies to close those gaps. Key topics included examination of barriers to participation and best practices to promote inclusion of members of underrepresented populations in research, development of an outcomes-based paradigm for the evaluation of diagnostic imaging modalities, assessment of new therapeutic modalities including the need to collect more meaningful and patient-reported outcomes, and the use of CER to generate the evidence needed by regulators and payers when they review new treatments and make coverage decisions.

From these discussions came the following key recommendations:

1. Many examples exist of successful engagement of under-represented populations, including racial and ethnic minorities, women, and individuals with limited health literacy. CER investigators should adopt proven strategies and also establish partnerships with trusted organizations and individuals with deep knowledge of and connections to underrepresented communities in order to overcome the legacy effects of racial discrimination. Knowledge of the differences in how men and women perceive the risk of participation in a clinical trial should inform efforts to recruit more women into CER studies. There is a need to address at-risk groups that are not defined by race, ethnicity or gender, such as individuals with limited health literacy.

2. At the present time, research may fulfill the evidentiary needs of only a subset of stakeholders, particularly researchers, funders, regulators and payers. This approach can result in persistence of gaps in the information needed by patients and clinicians in the real world and can result in suboptimal use of health care dollars. Investigators should enlist patients,

clinicians, regulators, and payers to participate early in priority setting, study design, selection of outcomes, and when planning for the dissemination and translation of results.

3. CER investigators will be expected to produce evidence about more than just the diagnostic accuracy of an imaging study in the "ideal" patient. Given the explosion in imaging options, researchers will be increasingly required to compare diagnostic imaging modalities, including the effect on important outcomes and the incremental value of sequential testing. Analysis of the long term health effects of medical radiation exposure must be considered when comparing imaging modalities, especially in children.

4. Clinical research, including CER, must develop methods to account for the effect of time and learning curves on outcomes. Patients, clinicians, regulators and payers should explicitly demand rational dispersion of new technology in order to promote safety without unduly limiting patients' access to life-saving therapies.

5. Large observational data sets, including registries, will continue to provide real-world information about the comparative effectiveness of new therapies such as transcatheter aortic valve replacement (TAVR). However, registry data are unlikely to match the completeness and validity of data obtained in a randomized clinical trial. CER investigators will need to apply methods such as propensity score matching when making comparisons and arriving at conclusions. While such methods allow sub-group analyses and identification of heterogeneous treatment effects, the lack of information about non-participants in a procedural registry limits our understanding of therapies in the whole population. Disease-specific registries may be necessary if we are to truly understand the real world effect of complex treatment options. Observational registries will generate hypotheses that will still need to be rigorously tested in randomized clinical trials. However, not all worthy hypotheses developed using registry data can be tested in an RCT as funds for research are not unlimited.

6. The existing extensive infrastructure for cardiovascular research that includes clinical research institutes and consortia, data dictionaries, registries, and ongoing longitudinal studies, should be shared broadly to promote comparisons among studies, minimize redundancy, and promote efficiency. Natural barriers to resource sharing exist, because research institutions compete with each other for limited grant and contract funds. Funders are in the best position to promote resource sharing by making this one of the metrics during proposals review.

7. Greater investments in behavioral economic research are needed to identify the most effective incentives for patients, clinicians and other stakeholders and thereby ensure that the Triple Aim promise, of better health, better healthcare, at lower cost, is fulfilled.

In October 2011, the Center for Medical Technology Policy (CMTP) hosted a Comparative Effectiveness Research (CER) Summit on Cardiovascular Disease to explore the challenges and opportunities in using CER to improve evidence generation and care for cardiovascular disease. The Summit brought together experts and stakeholders who were asked to:

- Identify the gaps in evidence and methods in cardiovascular CER;
- Share examples of successful approaches to removing obstacles to recruitment to research of hard to reach populations;
- Discuss CER study design considerations in cardiovascular disease;
- Address key questions in comparing diagnostic testing modalities;
- Identify opportunities and challenges in comparing therapeutic modalities such as trans-catheter and surgical aortic valve replacement for aortic stenosis;
- Identify improvements needed to enhance the research infrastructure;
- Identify gaps and propose solutions to improve translation of evidence into practice;
- Address key CER issues related to the value and cost of cardiovascular care.

Evidence and Methods Gaps in Cardiovascular Disease

Cardiovascular patients and their families continue to benefit from decades of investments by federal and private sponsors of basic science, clinical, pharmaceutical, device, and epidemiologic research. As a result, the major risk factors for cardiovascular disease have been identified and can now be effectively modified to improve outcomes. The death rate from acute myocardial infarction (AMI) has plummeted. Anticoagulation therapy, once contraindicated in AMI because of an increased risk of hemorrhagic pericarditis, has become an essential part of evidence-based care. Congestive heart failure is now treated with a combination of lifestyle, pharmacologic, device and surgical interventions. The absence of long term benefit from drugs used for symptom control, such as digitalis and diuretics, is now well understood.

Despite considerable progress, cardiovascular disease remains the leading cause of death for Americans.[1] Evidence gaps remain and disparities in health outcomes defined by age, gender, race and ethnicity, health literacy, and socioeconomic status persist. Members of these population groups are often underrepresented in research, and successful strategies for patient recruitment and enrollment need to be identified, shared and adopted more broadly. While there have been advances in secondary and tertiary prevention of cardiovascular diseases, reversal of the alarming upward trend in obesity, associated with Type II diabetes mellitus and a major contributor to cardiovascular disease risk, remains a challenge. Additional studies to

identify what does and does not work in primary prevention are needed. As cardiovascular biomarkers and imaging modalities increase in number and sensitivity, a nuanced understanding of the value of the information they provide needs to be coupled to prudent dissemination and translation into practice.

Of particular relevance to CER, evidence is needed about "real patients," who may be quite different from the relatively homogeneous subjects enrolled in randomized trials. In addition to real-world pragmatic clinical trials (PCTs), there is a need to develop, test and apply new CER methods to overcome the limitations of randomized controlled trials (RCTs) and PCTs. New therapeutic options such as trans-catheter aortic valve replacement draw headlines but real world clinical practice data will be needed to compare its benefits and risks, as compared to existing options.

Strategies are needed so that the existing widely distributed research infrastructure is more efficiently deployed to answer CER questions, more accessible to researchers, and interoperable. Networks of experts that use a common language and health information systems that share data are important features of some integrated health systems such as Kaiser Permanente, the Geisinger Health System, and the Department of Veteran Affairs. Practice-based research networks that include different patient populations in additional settings have the potential to generate the additional evidence needed by these stakeholders.

The Million Hearts Initiative, launched by the Centers for Medicare and Medicaid Services (CMS) and the Centers for Disease Prevention and Control (CDC), aims to close the gaps in translation of clinical trial results into everyday practice.[2] The Initiative's ambitious five year goal of preventing one million deaths due to heart attack focuses attention on improving translation of evidence for the ABCS into practice: Aspirin for those who should be on it; Blood pressure control in hypertensive individuals; Cholesterol levels at goal; and further reduction in Smoking prevalence.

The societal cost of health care is not sustainable. Unless current spending trends are arrested and reversed, it is estimated that 100% of the United States gross domestic product will be spent on health care by the year 2050. Despite near universal concern about the rising cost of healthcare and its effect on the competitiveness of American businesses, public discussion of cost containment and cost-effectiveness are often interrupted by assertions of rationing, litigation and politics. Nevertheless, consensus seems to be emerging about the importance of high value high quality care that is worth what we pay for it, and the elimination of waste, care that is ineffective or not needed.[3] In 2010, the estimated economic cost for cardiovascular disease was $324 billion in direct health expenditures, $42 billion in indirect costs due to morbidity, and $137 billion in indirect costs of mortality.[4] Cost-effectiveness analyses of care remains an imperfect science, that is "only as good as the data inputs, does not work well with

long time frames, e.g. prevention, and with issues surrounding the 'rule of rescue' and whether standards should be the same for high cost/high yield interventions as for low cost/low yield services."[5]

Participation, Recruitment and Retention

Many groups are underrepresented in cardiovascular clinical trials, including those identified as priority populations by the Agency for Healthcare Research and Quality (AHRQ): low income groups, members of racial and ethnic minority groups, women, children, the elderly, and individuals with special health care needs, including individuals with disabilities and individuals who need chronic or end of life care.[6] Disparities in cardiovascular health status have been associated with low income, being a member of a non-white ethnic and racial minority group, and with female gender.[7] Women remain underrepresented in cardiovascular research despite the requirements of funding agencies such as the National Institutes of Health (NIH) that investigators provide justification when enrollment of women does not reflect the prevalence in women of the condition under study. Additional factors that can result in underrepresentation in research and merit attention include having English as one's second language, limited health literacy (distinct from literacy in general), adolescence, having congenital heart disease, having limited or no access to health insurance, and being incarcerated.[6]

Strategies to improve the recruitment and retention of underrepresented groups in clinical trials should be based on an understanding of barriers to participation. Investigators should emulate successful initiatives that overcame these challenges.

The Legacy of Racial Discrimination

Negative legacies affect participation in research when a group has a history of unethical or unfair treatment by researchers, and when that experience was associated with racial, ethnic or cultural discrimination. To overcome negative legacy effects, investigators working with populations previously harmed by research should work closely with organizations that have earned their trust.

The Tuskegee Study of Untreated Syphilis, in which African-American men did not receive antibiotic therapy for their condition so investigators could observe the natural history of syphilis, is a searing example that continues to affect the African-American community's perspective on medical research. Although community outreach efforts have been used to change attitudes and gain trust, there is evidence of an association between African-Americans' knowledge of the Tuskegee Study and their mistrust and reluctance to participate in medical

research.[8,9] The Association of Black Cardiologists (ABC) is committed to elimination of disparities in cardiovascular health through education, research and advocacy.[10] The ABC has issued recommendations for reducing health disparities, expanding research efforts, improving patient education, increasing adherence to therapy, improving patient-physician communication, and creating the infrastructure needed for research. The Eliminating Disparities in Clinical Trials (EDICT) Project identifies resources for complementary projects and collaboration with other organizations including the National Medical Association and the Society of Clinical Research Associates (SoCRA) Partnership.[6]

Leaders of the Zuni Indian Tribe in New Mexico have described members' experiences of "dishonest and unscrupulous research and researchers," including collection of blood samples for diabetes research without disclosure of the intended purpose nor the results, kidney biopsies that did not meet criteria for the procedure, and unauthorized disclosure of religious practices.[11] The Zuni Governor and Tribal Council have established principles for medical research that involves tribal members. The proposed research must address critical questions about conditions such as diabetes and alcoholism that seriously affect the health of tribal members in ways that can reasonably be expected to provide tangible results. Tribal taboos do not permit autopsies, nor the storage and permanent usage of biological specimens because of beliefs that the spirit may be damaged if parts are missing from the body for long periods of time or upon death. The Tribal Health Board acts as a tribal Institutional Review Board (IRB) during the initial consideration of a research proposal. Only following Tribal Council Review of the Health Board's recommendations is the National Indian Health Service IRB asked to conduct a courtesy review of studies to be conducted on tribal land.

Latina women were subject to sterilization campaigns in Puerto Rico in the 1930s at a time of high unemployment and poverty. The Puerto Rican government received federal funds to promote and provide sterilization services in the territory, creating a legacy of distrust of government-sponsored health programs.[12] Currently, Latinos throughout the U.S. are more likely to lack health insurance than other ethnic groups, even when they are employed. This has been attributed to economic, linguistic and cultural barriers, due in part to having less fluency in the dominant language in the United States and long-held beliefs including that health depends on a balance between hot and cold, a paradigm that is part of traditional Western medicine.[12]

Identify Patient and Community Organizations that Promote Clinical Trial Participation

Investigators should partner with trusted medical organizations such the ABC and tribal health boards, or enlist respected non-traditional healers such as medicine men, promotoras, and community health workers, to reach hard to reach groups in a culturally and linguistically competent way. Dr. Lisa Cooper and colleagues at Johns Hopkins University have pioneered

creation of community-based advisory committees to guide research and educational programs in the predominantly African-American community in East Baltimore. The Hopkins Center to Eliminate Cardiovascular Health Disparities conducts research to test the effectiveness of programs for improving outcomes and reducing disparities in hypertension care. Dr. Cooper's relationship-centered principles for stakeholder engagement emphasize early and consistent engagement, mutual learning, equitable involvement, shared decision-making, responsiveness to stakeholder concerns, effective communication, transparency, and a commitment to follow-up. Gaps that still need to be addressed include how relationships impact processes and outcomes, how to sustain and incentivize partnerships, how to identify and build on stakeholder strengths, and how to advocate skillfully for research.[13]

PatientsLikeMe is a social networking site established to meet the information needs of patients. It also fosters patient enrollment into clinical trials.[14] The National Patient Advocate Foundation connects uninsured and underinsured individuals to clinical trials.[15] These disease- and facility-agnostic organizations connect patients with rare diseases and individuals without access to healthcare services to CER studies.

Limited Health Literacy Affects Participation and Changes Outcomes

An individual's willingness to participate in a clinical trial may also be influenced by the materials and methods used to obtain informed consent. Readability studies of informed consent documents have shown that these "gateway" documents are often written at or above an 8th grade reading level.[16,17] One study found that 88% of patients who had just provided "informed" consent for elective diagnostic cardiac catheterization had erroneous impressions about the benefits of the procedure.[18] Another study in fully-insured heart-failure patients with access to primary care providers and prescription medications demonstrated a correlation between low health literacy, all-cause mortality and hospitalization.[19] Readability can therefore be a barrier to truly informed participation by individuals experiencing the stress of an illness and by those with limited health literacy, especially if English is not their first language.

A recent review provides a roadmap that investigators and clinicians can use to obtain truly informed consent.[20] The authors recommend a variety of methods to ensure that the information delivered is understood, including teach-back techniques, provision of ample time for patient decision-making, and technologies that use an interactive informed consent process. To better assess health literacy, investigators can screen participants using three questions evaluated and validated in a Kaiser study of heart failure patients.[21,22,23] Once individuals with limited health literacy are identified, steps can be taken to ensure that they understand the purpose, and the potential risks and benefits of a clinical trial.

Underrepresentation of Women in Clinical Trials

In 1977, the FDA issued a regulation requiring exclusion of women of childbearing potential from Phase I and early Phase II drug studies. This rule came in the aftermath of the thalidomide experience, but resulted in a deficit in the data about women from critical dose-finding pharmaceutical research. In 1988, the NIH Office of Women's Health issued a statement encouraging recruitment of women in research.[24] In 1990, the American Medical Association Council on Ethical and Judicial Affairs (CEJA) published *CEJA Report B-I-90 Gender Disparities in Clinical Decision-Making*, concluding that "…medical treatments for women are based on a male model, regardless of the fact that women may react differently to treatments than men or that some diseases manifest themselves differently."[25] In 1993, the FDA reversed its 1977 policy of exclusion and called on study sponsors to submit data analyses by gender. Despite these initiatives, a 2009 review of reports from clinical trials published between 1997 and 2006 showed that recruitment of women continued to lag behind that of men.[26] In a review of premarket approval studies for cardiovascular devices, Redberg and colleagues reported that only 51% of studies included an analysis to address gender bias, and of those that did so, less than 25% found differences in safety or effectiveness by sex.[27]

Ding and colleagues found sex differences in perceived risks, distrust, and willingness to participate in clinical trials in a group of 783 patients given a handout about a hypothetical placebo controlled RCT. They reported that women were less willing to participate, and perceived greater risk of harm. Although risks were overestimated by patients regardless of gender, men were more willing than women to accept those risks.[28]

Given these challenges, examples of successful recruitment of women into longitudinal observational and randomized controlled trials should be examined and their methods adopted and modified as necessary to overcome barriers to proportional enrollment of women, including members of minority groups, in research. The Nurse's Health Study and Women's Health Initiative (WHI) used different but very successful strategies to recruit female participants.

The Nurses' Health Study is a longitudinal observational study initiated in 1976 to determine if there was a relationship between the use of contraception and breast cancer. [29] Study investigators used mailed questionnaires to collect additional information about cardiovascular disease, dietary and physical activities. Newsletters that publicize study results have reinforced the investigators' relationship with participants over almost four decades. By targeting women nurses, obstacles to participation such as limited health literacy or mistrust were avoided. The Nurses' Health Study continues to be a rich source of gender-specific longitudinal observational data about many topics including risk factors for cardiovascular disease. It has also generated important hypotheses for further research. One such observation was a three-fold lower rate of

cardiovascular disease in women who received post-menopausal hormone replacement therapy (HRT) as compared with those who did not.

The Women's Health Initiative (WHI) was designed to address the Nurses' Study finding of an apparently favorable association between cardiovascular disease and HRT. This 15-year National Institutes of Health randomized placebo-controlled trial enrolled 70,533 post-menopausal women who had not previously received HRT. WHI investigators developed, implemented and refined strategies appealing to women, to enroll members of racial and ethnic minority groups in the same proportion as in the general population, and to retain participants in a multi-year study.[30] National and local approaches included mass mailings, transportation to screening visits, enlisting the support of local celebrities, use of airplanes to pull WHI advertisements while flying over a community, materials in multiple languages, training and support of local staff, public awareness campaigns and a recruitment telephone line, among others.

The FDA issued draft guidance in late 2011 so its scientists and industry could better detect and analyze potential gender differences in medical device trials.[31] The draft document suggests strategies to increase the enrollment of women in new, ongoing, and post-market studies. These include considering early the potential sex differences relevant to the clinical evaluation of what is under study (e.g. sex-specific prevalence, sex-specific diagnosis and treatment patterns), targeting study sites with strong track records of recruiting women, creating parallel cohorts to gather data about women who do not meet study criteria, and using tailored communication strategies, among others. It describes analytical methods to overcome underrepresentation such as subgroup analysis, and tests for interaction or heterogeneity. It encourages sponsors to collect, analyze and report data from pre-specified demographic subgroups, in addition to the data from the entire study population. The guidance document, when finalized, will provide another roadmap to use to increase the likelihood that study results can be confidently applied to women.

Patients' perceptions of the potential benefit associated with participation in research also merit further study. Although much attention has been focused overestimation of risk by patients, a better understanding of the reasons and degree to which patients overestimate benefits is also needed. Considerable empiric research has been done to examine how conflict of interest disclosures may influence patient decision-making. Even when presented with scenarios in which the investigator had significant conflicts of interest, some patients assumed that the investigational therapy must be better than established alternatives, because otherwise the researcher-doctor would never recommend it. As a result, they sometimes discounted the risks associated with participation.[32] As CER increasingly complements patient-centered outcomes research and engages non-traditional stakeholders, differences in

perspective about priorities, risk, benefit, outcomes, and conflicts of interest should be examined and addressed to promote trust.

Study Design Considerations in Cardiovascular CER

The CER research paradigm complements that of the randomized controlled trial (RCT). RCTs have been used to tremendous advantage in cardiovascular research, providing answers about who will benefit from or be harmed by treatments such as coronary artery bypass surgery, percutaneous coronary intervention (PCI), anticoagulants, hormone replacement therapy (HRT), and cholesterol-lowering drugs. Many studies have been designed to compare one active therapy to another, and not just to placebo. However, important questions remain unanswered, and it is unrealistic to expect that an RCT can be launched to answer every such question. RCTs are costly and often take years to complete. Funding for research is limited and choices often have to be made among many worthy proposals. RCT efficacy studies frequently apply strict inclusion and exclusion criteria, resulting in enrollment of a non-representative subset of the affected population, and potentially limiting the conclusions that can be made about the real world effectiveness of the therapy under study.

Increasingly it is also recognized that the questions that most concern patients may not be captured or addressed unless patient representatives participate at multiple stages of research: priority setting, selection of trial design and outcomes, translation and dissemination. Unlike efficacy studies, CER is probably best done when study drugs, devices, procedures, organizations or payment models are sufficiently mature that the comparisons made are "fair."[33]

CER also offers a methodological toolkit to address evidence gaps that cannot practically be filled by an RCT. CER study designs may use RCT designs, and also be pragmatic, with fewer inclusion and exclusion criteria and conducted in real world settings outside of academic medical centers. Bayesian adaptive designs, 'n of 1' trials, and propensity score matching can be applied to CER questions. Existing observational data sets such as patient registries, administrative claims data, electronic health and pharmaceutical records, and the Social Security Death Index can be used to answer questions that require data from large numbers of subjects, especially when looking for infrequent events. Systematic reviews and meta-analyses attempt to overcome the limited number of conclusions that can be drawn from single studies.[33]

Early Engagement of Patients and Other Stakeholders in CER

The early stage of trial design is the best time to identify questions that matter to stakeholders, including patients, who are not researchers. Multi-stakeholder advisory groups can work with researchers to balance the internal and external validity (generalizability) of CER efforts,

identify outcomes of interest, and to plan for translation and dissemination of results. For example, researchers often construct composite endpoints and measure intermediate outcomes to ensure that the necessary sample size is not prohibitively large, that recruitment goals are met, follow up time is reasonable, and costs are contained. Composite endpoints are particularly important if estimated event rates are low, hypothesized differences in outcomes small, or if outcomes such as a reduction in mortality may not be seen for years. However, formulation of composite outcomes would benefit from input from patients about the relative importance they associate with the individual elements. This can only be done if patients participate in a meaningful way early in CER study design.

Regulators and payers also have a stake in the design of CER studies. The FDA requires sponsors of new therapies to prove the safety and effectiveness of the drugs and devices. CMS requires evidence that a service is reasonable and necessary for it to be covered. Non-governmental payers, who often follow the lead of CMS, have health technology assessment groups that also require specific data for their coverage decisions.

The Center for Medicare and Medicaid Services' Coverage with Evidence Development (CED) mechanism was established in "an effort to reconcile the tension between having rapid access to new, promising health interventions, while also having reliable information on the real world benefits and risks of those services."[34] CED requires consensus among the stakeholders about key questions, study design, required variables, outcomes, and expected duration of the study. The study design and funding of CER in the context of a CED should already be in place when a CED requirement is part of a CMS National Coverage Decision.

In October 2011, the FDA-CMS Parallel Review Pilot process was established to provide a pathway for sponsors of innovative new device technologies to participate in a voluntary pilot program for concurrent review of certain FDA premarket review submissions and CMS national coverage determinations. This effort of early engagement is expected to streamline the regulatory review process, although even sponsors that have been critics of the existing process may be reluctant to adopt something new.[35]

Patient Reported Outcomes (PRO)

The FDA's patient-reported outcomes (PRO) guidance focuses on methods to obtain risk and benefit assessments directly from patients. There is evidence that PROs can differ substantially from reports by researchers and clinicians of an individual patient's response.[36] Creation, collection, validation, and standardization of PROs all present challenges for study sponsors, investigators, regulators and payers. The Center for Medical Technology Policy's (CMTP) stakeholder-driven effectiveness guidance document, "*Recommendations for Incorporating Patient-Reported Outcomes into the Design of Clinical Trials in Adult Oncology*" is a resource for

investigators in fields other than oncology to incorporate PROs during the research design process.[37]

Several patient-reported outcomes tools have been developed and validated in cardiovascular clinical trials and observational studies. The Kansas City Cardiomyopathy Questionnaire (KCCQ), which measures quality of life, was used in pre-market approval clinical trials of trans-catheter aortic valve replacement (TAVR) for aortic stenosis. The KCCQ is one of three recommended options to fulfill the CED requirement within the draft CMS National Coverage Decision (NCD) for TAVR.[38] In addition to allowing direct comparison of observational real-world outcomes with the results from pre-market approval randomized controlled trials, the KCCQ short form has additional advantages. It can be completed at home and mailed, lessening the challenge of data collection from elderly recipients who may live far from TAVR centers and are unable to travel. The SF-12 and the EuroQoL (EQ)-5D Utilities are also endorsed for TAVR. The EQ-5D™ is a standardized instrument also used to measure health outcomes. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value to report on health status. The EQ-5D was designed for self-completion by respondents, is suitable for use in mail surveys, and can also be used in clinics and during face-to-face interviews. Its developers describe it as cognitively simple, and it takes only a few minutes to complete.[39]

Validated PRO tools are available for other cardiovascular conditions. The Canadian Cardiovascular Society Severity in Atrial Fibrillation Scale captures patient symptoms associated with that condition.[40] Whenever possible, investigators should use existing PRO tools, and avoid the time and expense of developing and validating a new tool for each new trial. In addition to saving money and time, use of existing PRO tools should make it easier to compare studies, conduct systematic reviews and perform meta-analyses.

Streamline Enrollment and Informed Consent

The Veterans Affairs' Point of Care trial initiative incorporates research protocols and procedures, such as determination of patient eligibility, informed consent, study enrollment and initiation, into the electronic health record at participating centers. Early results show that up to 85% of patients invited to enroll in CER studies embedded in the electronic health record within physician order entry agree to participate in an offered study.[41] Complementary to the Point of Care trial initiative is the Veteran's Affairs Network of Dedicated Enrollment Sites (VA-NODES) initiative which provides funding for research infrastructure to study sites that are already participating in at least two funded trials. Each "node" is ready and able to participate quickly in new studies. Participants use a central Institutional Review Board, implement a single protocol adopt common procedures, and use the same documents to obtain informed

consent.[42] In another context, the University of Alabama at Birmingham is testing methods for streamlined informed consent in its Practice Based Research Network.[43]

The United States Department of Health and Human Services issued an advanced notice of proposed rule-making in July 2011, suggesting that changes in the Common Rule governing protection of human subjects in research may be considered for the first time since 1991.[44] In response to this notice, Kass and colleagues have highlighted the need to address the review requirements of low risk prospective randomized comparisons of established therapies that are used in clinical practice. The risk of such studies is seemingly low, and yet the need for such comparisons can be high, especially when the benefits, risks and cost of commonly used therapies differ significantly. The authors propose that the level of required oversight required be proportionate to the risk of the proposed research.[45]

The Office of the National Coordinator has an opportunity to use its authority to issue meaningful use rules for HIT and require that systems include modules that streamline informed consent and research. All four strategies--CER at the point of patient care, use of a common IRB, streamlined informed consent, and inclusion of CER tools in health information technology systems--have the potential to increase patient enrollment in CER studies.

Examine Patient Subgroups and Heterogeneity of Effect

Many clinical trials limit the number of pre-specified patient subgroups to maintain statistical power. However, this approach means that heterogeneity of treatment effect among subgroups, particularly related to benefit and risk may be missed, especially if only aggregate results are reported. Large observational data sets make additional subgroup analyses possible. However, investigators analyzing patient data from settings in which treatment assignment is not controlled often have to use tools such as propensity score matching in an effort to make the comparison groups as similar as possible except for the variable of interest. Use of propensity score matching can be associated with the downside risk of missing unspecified variables that exert a significant effect on outcomes, either because those variables are not collected or not included in the analytic model. A recent review suggests that propensity-score matching methods, although used frequently, have been poorly applied in cardiology. The authors provide recommendations for improvement.[46]

Pragmatic Clinical Trials (PCTs)

PCTs conducted in real world settings, such as practice-based research networks, are often designed with broader inclusion criteria than efficacy trials, and can lead to easier translation of results into clinical practice. Landmark PCTs in cardiovascular disease include the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[47], The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial[15], The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO*)* trial[48],

and the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE)trial[49]. The Dual Anti-Platelet Therapy (DAPT) Study is a more recent example of a large, pragmatic public health CER trial bringing together FDA scientists, an academic research center (the Harvard Clinical Research Institute), four manufacturers of drug-eluting stents and the manufacturers of anti-platelet drugs to answer questions about the benefit of extending thienopyridine treatment beyond one year in patients receiving a drug-eluting coronary artery stent.[50] In DAPT, investigators, sponsors and the FDA agreed to a common set of definitions, variables, outcomes, and study design. Inefficiencies which would have been expected if each stent manufacturer had done its own clinical trial were avoided. However, even if a clinical trial is pragmatic in design, this does not mean it is inexpensive. The cost of the DAPT has been estimated at approximately $100 million.[51]

The Pragmatic-Explanatory Continuum Indicator Summary (PRECIS)

PRECIS is a tool developed to "assist trialists in making design decisions that are consistent with their trial's purpose." It has also been used by investigators and others to estimate the "pragmatism" *vs.* efficacy of a planned or completed trial across 10 domains.[52] Some researchers have applied PRECIS early during study design and used it to modify a clinical trial during development.[53]

Investigators comparing PRECIS to the IOM's six defining characteristics of CER found that both tools were useful but that reduction of inter-rater variance required discussions to reach consensus.[54] Glasgow and others applied PRECIS to three moderately pragmatic NHLBI-funded effectiveness weight-loss trials.[55] They examined the inter-rater reliability of the estimates made by investigators at the three study sites. Ratings varied across the three sites, and among the ten domains. Investigators often rated their own study as more pragmatic than the other two trials. Further research is needed to know if inter-rater and inter-facility variation can be reduced, and whether reports should include scores for all ten domains or a composite score.

Although attempts to maximize pragmatism across all domains is usually not feasible, necessary or appropriate, researchers could consider routinely assessing a study design in each PRECIS domain, so their teams, sponsors, other researchers, and end-users are better able to compare studies and results. CER entities such as the Patient-Centered Outcomes Research Institute (PCORI) could provide the option of including a PRECIS analysis with applications for funding. The International Committee of Medical Journal Editors could similarly create this as an option when CER results are submitted for publication. Additional validation studies and experience with PRECIS will be needed if PRECIS reporting is ever required for funding or publication. . If PRECIS or other tools such as the six IOM CER-defining characteristics are proven to be valid, reliable, and broadly applicable, more widespread use could improve CER

trial design in the same way that submission of statistical analysis plans and disclosure of conflicts of interest have enhanced biomedical research.

Registries, Observational Cohorts, and Other Large Data Sets in CER

Patient registries have been used to identify optimal treatment strategies such as the use of the left internal mammary artery as the preferred conduit for revascularization when compared to a vein graft. Registry data from large numbers of patients have been used to perform subgroup analyses, detect rare events, and build risk-adjustment models, difficult to accomplish using the smaller data sets of most RCTs. Multiple comparisons can be made. Follow up data, when available, can lead to detection of differences in long term outcomes. Weaknesses of registries include the absence of patients who did not receive the study intervention, such as an implanted defibrillator, ventricular assist device or coronary artery bypass graft surgery. Subsequent events including repeat procedures may not be captured if patients move into a health system that does not participate in a registry. Immortal time bias and confounding by indication pose additional challenges. Data quality varies, and is dependent on the resources available for collection and audit functions. The Society for Thoracic Surgery (STS) database and the National Cardiovascular Data Registry (NCDR) currently hold information on millions of patients and serve as resources for CER investigators.

Registries and administrative claims data can be used for post-market surveillance and to compare the effectiveness of products that were not evaluated head to head in pre-approval studies. This capability has been demonstrated using the NCDR-Cath PCI data to show that one arteriotomy closure device (Vasoseal) underperformed when compared to other approved devices.[56] That device was subsequently removed from the market.

The Transcatheter Valve Therapy (TVT) Registry has been established with the American College of Cardiology NCDR and the Society of Thoracic Surgery Database in a partnership to compare alternative therapeutic strategies for management of aortic valvular heart disease in the real world. This initiative builds upon the experience of surgeons and cardiologists with a collaborative team approach developed to conduct the RCTs that led to regulatory approval of catheter-delivered aortic valves.[57] The STS/ACC TVT registry is envisioned as one part of a comprehensive platform that will be used to evaluate the safety and effectiveness of newer valves with a premarket Investigational Device Exemption, to collect data if a National Coverage Decision includes a Coverage with Evidence requirement, to perform post-market surveillance, ensure compliance with labeling, and promote the rational dispersion of new technology. It will be linked to the Social Security Master Death File and CMS claims data. Society leaders have developed the TVT registry as a platform for a suite of activities including the evaluation of future technologies.

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) is a North American registry established in 2005 for patients receiving mechanical circulatory support device therapy to treat advanced heart failure. INTERMACS™, is a joint effort of the National Heart, Lung and Blood Institute (NHLBI), the Centers for Medicare and Medicaid Services (CMS), the Food and Drug Administration (FDA), clinicians, scientists and industry representatives in conjunction with the University of Alabama at Birmingham. The registry now contains data from over seven thousand patients, and shares that information with the United Network for Organ Sharing (UNOS). Because many patients who receive a left ventricular assist device are also candidates for heart transplantation, consent to be enrolled in INTERMACS includes consent to data sharing with UNOS. This registry fosters evidence collection about an infrequently-used very complex therapy.[58]

The FDA Mini-Sentinel Initiative supports a distributed network of databases than can provide information captured by insurers, pharmacy benefit managers and others derived from over one hundred million patients. . In the pilot project, the FDA has used Sentinel to distribute queries in order to investigate potential post-market safety signals. FDA queries are forwarded to the coordinating center for distribution to the participating databases. Because existing post-market surveillance of devices and drugs suffers from underreporting to manufacturers, infrequent return on devices for analysis, duplication of effort, the absence of real-time reporting, and a lack of feedback to clinicians who report possible safety signals, expansion of the Sentinel Initiative, or something similar to medical devices is recommended.

Patients Change Over Time

Patient characteristics can change over time. Aging and the development of additional co-morbidities can impact the observed benefits and risks of diagnostic or therapeutic procedures in an individual patient. Investigators use randomized clinical trial study designs in part to ensure that unmeasured or new, potentially confounding factors will be evenly distributed among study groups over time. RCTs frequently exclude patients with the conditions that they subsequently develop. PCTs with more liberal study designs and studies using observational data sets should add new information about patients over time, such as new co-morbidities. CER investigators can also use additional methods, such as propensity score matching and "n of 1" trials to analyze or obtain data from non-randomized study populations.

Key CER Questions in Cardiovascular Diagnostic Imaging

Evaluation of a new diagnostic imaging modality has typically focused on parameters such as its sensitivity, specificity, reliability and safety. However, increasingly investigators are trying to determine the value of diagnostic imaging, similar to what has been done for therapeutic interventions. Questions include when to use a modality, when to substitute one for another, whether a new test must be better than the existing ones to be approved and covered, how to determine over- and under-utilization rates and whether there are acceptable rates for both, and how closely outcomes are linked to the results to imaging studies.[59,60]

Use of medical ionizing radiation has increased dramatically over the last twenty five years. Assessments of risk are derived mostly from atomic bomb survivor studies. Subgroups analyses are critical to determining risk. Because of the potential long-term effects of ionizing radiation, cost, intermediate risk and value are not all that matter. One has to also consider organ-specific risk, deterministic effects (cell damage), stochastic effects (DNA changes) and hormesis (cancer reduction from very low doses).[61] Methods have been developed to determine the ability of a test to result in reclassification of a patient (Net Reclassification Improvement (NRI) [62]), whether reclassification results in changes in subsequent actions or outcomes, and whether there is a "warranty" benefit if a test is normal.

In cardiovascular medicine, the diagnostic coronary angiogram has long been considered the gold standard for the diagnosis of fixed obstructive coronary artery disease. However, early studies of immediate angiography during acute myocardial infarction have shown that most were due to rupture of unstable plaque, associated with thrombus formation. This evidence suggested that the presence of fixed disease might not predict patient outcomes. Review of earlier coronary angiograms in patients who subsequently had an acute infarct has shown that plaque rupture is most likely to occur at sites of mild non-obstructive disease, confirming that lesion severity does not predict outcomes, and that better predictive instruments are needed. [63,64]

The Occluded Artery Trial (OAT) compared late opening an occluded infarct-related vessel with optimal medical therapy and showed no difference between the approaches in a composite outcome measure of death, re-infarction or NYHA Class IV heart failure, demonstrating again the lack of an association between anatomy and outcomes in high-risk patients without severe post-MI ischemia.[65]

Other reports attest to the imperfect and inconsistent relationship between test results and the behavior of patients and physicians in response to those results.[66] The influence of health beliefs, the experience and belief of peers, and unrealistic optimism in the absence of symptoms is evident in studies of the behavioral response of patients to chest pain and cardiac

test results, even when disease is present.[66-68] Given the disconnect between test results, behavioral response, care delivered, and outcomes observed, decision makers may increasingly base coverage decisions for a diagnostic test on information about: 1) the impact of the test on clinical outcomes; 2) the cost effectiveness of a new test compared to existing options (including not doing the test), 3) how one imaging modality compares to another, 4) the marginal benefit, risk and cost of sequential testing, and 5) whether the information obtained using the new test changes clinical decisions and outcomes in a meaningful way. Access to necessary testing or to "the best test" for a particular subgroup, particularly at smaller or rural facilities only capable of providing one testing modality and not others, may need to be addressed if payers and others require that orders for testing are customized based on patient characteristics. The more that is known from CER of diagnostic testing, the better these tradeoffs will be understood.

CER studies conducted to examine the relationship of diagnostic imaging tests to long term clinical outcomes coupled or not to pre-specified treatment options, have the potential to increase the size, duration, and cost of trials. Low event rates may prompt investigators to utilize composite endpoints in order to have enough events to measure statistically significant differences among the study arms in a trial. The individual elements of a composite outcome measure may not be equally valued by the participants (angina as compared to stroke) and yet it is possible that only very large studies with a large number of events will generate the kind of data that real-world patients and clinicians need.

The PROspective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) Trial will randomize 10,000 patients with stable coronary artery disease to determine if an initial anatomic imaging study (coronary computerized tomographic angiography, (CTA)) will improve clinical outcomes compared to a usual care diagnostic strategy of functional (stress) testing.[69] Patients will be enrolled at 200 sites and followed for 2-5 years. The primary clinical endpoint will be a composite of death, myocardial infarction, hospitalization for unstable angina, and major procedural complications. Secondary endpoints will be each component of the composite, cumulative radiation exposure, medical costs, and quality of life. The PROMISE trial is designed to examine the relationship of a testing strategy to outcomes, and has the potential to provide the evidence clinicians need when choosing one test over another.

The International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial funded by NHLBI is a large pragmatic clinical trial in patients with at least moderate ischemia on stress testing and stable symptoms who will be randomized to an invasive strategy with revascularization if indicated and optimal medical therapy or to a conservative strategy of optimal medical therapy, with the invasive approach reserved for those with catheterization and revascularization reserved for those with an acute coronary syndrome,

ischemic heart failure, resuscitated cardiac arrest or refractory symptoms.[70] ISCHEMIA is a trial with implications not just for diagnostic imaging, but also for cardiovascular therapeutics.

Opportunities and Challenges in Comparing Therapeutic Modalities

The Office of Coverage Analysis (OCA) within CMS seeks "adequate evidence that a treatment strategy using the new therapeutic technology compared to alternatives leads to improved clinically meaningful health outcomes in Medicare beneficiaries."[71] CMS is prohibited by law from paying for services that are not "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the function of a malformed body member," not "reasonable and necessary for the prevention of illness," or not "reasonable and necessary for the palliation or management of terminal illness."[72] The statute does not define "reasonable and necessary." The Patient Protection and Affordable Care Act of 2010 states that the Secretary of the Department of Health and Human Services may only use CER results to make a coverage determination, "if such use is through an iterative and transparent process which includes public comment and considers the effect on subpopulations."[73] From an operational standpoint, the OCA is interested in new therapeutics that lead to, "longer life with improved participation and function; longer life with arrested decline; significant symptom improvement allowing better function/participation, and a reduced need for burdensome tests and treatment."[71]

These principles should be considered in the design of CER studies that evaluate new therapeutics. Often, however, new therapeutic services are evaluated for a single or limited number of indications and are then disseminated into clinical practice without evidence from studies in settings that reflect the real world environment. For example, CER studies of high volume, high cost procedures such as PCI *vs.* CABG, or stress testing *vs.* CTA, or invasive *vs.* non-invasive management of ischemia, are only now being done by the BARI, PROMISE and ISCHEMIA trials, long after the relevant services were introduced. In these instances, CER investigators may face challenges in recruitment and enrollment in the face of concerns that real-world comparison trials are unethical or unsafe.

Investigators sometimes turn to existing databases to answer questions or formulate testable hypotheses. One such example is the ACCF–STS Collaboration on the Comparative Effectiveness of Revascularization Strategies (ASCERT) Study in which the STS, NCDR-CathPCI and CMS claims databases were queried to compare survival after revascularization with PCI or CABG among more than 185,000 Medicare beneficiaries with stable angina between 2004 and 2008. First-year survival favored PCI in all high-risk patient subgroups. However, after one year, a survival advantage of CABG compared to PCI became evident and increased progressively in

all subgroups of patients. Propensity score methods were used to create quintiles of patients with similar clinical characteristics. The survival advantage of CABG persisted across each quintile.[74]

CER methods will be used in the real world evaluation of transcatheter aortic valve replacement (TAVR) for management of aortic stenosis. Following FDA approval of the Edwards SAPIEN transcatheter heart valve, the ACC and the STS asked CMS to issue a National Coverage Decision (NCD) with Coverage with Evidence Development requirement (CED). The TAVR registry will be used to determine the real world effectiveness of the trans-catheter procedure compared to surgery, evaluate these approaches in patient subgroups not included in pre-approval trials, and provide the evidence needed for future coverage decisions.

Enhancing the Cardiovascular Research Infrastructure

Rich sources of data for CER include the Framingham Study, the Nurses Study, the Harvard Physicians Study, and the Women's Health Initiative. Longitudinal patient registries including the STS Database and the NCDR contain records from millions of patients who have undergone open heart surgery, percutaneous coronary intervention, cardioverter-defibrillator implantation, carotid artery stenting, and treatment of congenital heart disease. The Social Security Death Index, Medicare administrative claims data, non-government payer databases, and pharmaceutical benefit manager records have been linked together in pilot programs such as the FDA Sentinel initiative, and are expected to provide insights into long term outcomes. The Food and Drug Administration serves as a repository of data submitted for pre-market approval review of drugs, devices and biologics. Legacy data at FDA has not previously been available for CER but pilot projects are underway to see if combining individual patient level data from multiple trials can answer CER questions about drugs and devices.[75]

Current funding mechanisms and limitations have resulted in fierce competition for scarce resources. The current environment is unfortunately unable to fund many meritorious proposals. Competition among institutions and investigators results in redundant infrastructure and trial designs, and does not explicitly prevent duplication of failure. Investigators and funders should use existing resources including data repositories, data dictionaries, infrastructure, standards, and consortia, to perform CER.

Numerous clinical research organizations, including the Thrombolysis in Myocardial Infarction (TIMI) Study group, the Veterans Administration Network of Dedicated Enrollment Sites (VA-NODES), the Duke Cardiovascular Research Institute (DCRI), the Harvard Clinical Research Institute (HCRI), and others have deep and broad experience in the conduct of cardiovascular research. The NHLBI has established the Cardiovascular Research Network of fifteen

geographically dispersed health plans covering 11 million patients to examine the epidemiology, quality of care, and outcomes of cardiovascular disease and to conduct future clinical trials using a community-based model.[76]

New entrants into the field of cardiovascular CER may find it difficult to compete successfully with well-established enterprises. Newcomers can emulate successful enterprises, but still have a high likelihood of failure, and their success may undermine existing organizations. Ideally, new and established research organizations would collaborate and share resources, especially those developed using tax payer dollars. However, resource sharing is political more than practical, and is unlikely to occur unless funding agencies make it a requirement for continued support.

Funding Agreements Should Include Resource Sharing

Many institutions have invested heavily in development of infrastructure and personnel to do cardiovascular research. Public funders and large foundations have also made substantial investments. The latter can require as a condition of an award that investigators share resources, best practices and expertise, unless a voluntary sharing plan is already in place. This would be similar to the requirement that publishers provide free access to articles that report the findings of federally funded research. The Gates Foundation creates strong incentives for funding applicants to cooperate, to prevent duplicative efforts in resource-constrained settings. Professional societies such as the ACC and the STS collaborated voluntarily on dissemination of clinical trial results, FDA testimony, guidelines development and a request for a National Coverage Decision for transcatheter aortic valve replacement.[77-79] Both societies, which have existing registries (i.e. the National Cardiovascular Data Registry and the STS Database), have established a single longitudinal registry to collect data from individuals with aortic stenosis who undergo a valve procedure or are followed without intervention. Contractual or voluntary agreements that result in sharing of resources means funders would no longer have to pay for redundant infrastructure or studies.

Speak a Common Language

Medical informatics is the science of gathering, storing, managing and analyzing data, followed by conversion of that data into information, and transformation of that information into knowledge. [80,81] Efficient CER requires a strong informatics foundation with standard names, attributes, mappings, meta-data and representations to ensure semantic interoperability. Systems such as CDISC promote interoperability. There is also a need for syntactic interoperability (information concepts that people can share). The American College of Cardiology Foundation/American Heart Association Task Force on Clinical Data Standards has developed the ACCF/AHA Key Data Elements and Definitions of a Base Vocabulary for Electronic Health Records to ensure use of a consistent language in clinical and research settings.[82]

Despite the challenges of analyzing observational data, it can be used to perform analyses that cannot otherwise be done, and provide a sample size with the potential to detect rare events.

Dissemination and Translation of Cardiovascular CER Results

Rational Dispersion of New Technology (RDNT)

RDNT is an important post-approval concept that recognizes that new technology that has only been evaluated in the context of a randomized controlled trial (RCT) may perform differently in the real-world setting. A post-approval requirement for continuing data collection is a tool, but not the only one, that can be used to address this issue. Initial planned dissemination of new technology to patients, operators and centers that closely match RCT conditions, coupled to data collection, can answer outstanding questions about benefits and risk, heterogeneity of treatment response, subsets of patients, rare complications, and long term outcomes. Such information should increase the external validity of the evidence used by patients, clinicians and payers to make decisions. It can also result in a more rapid response to issues that arise when a new technology diffuses into new practice settings.

Professional societies, regulators and payers all have an important role to play at this stage. Ideally, evidence-based guidelines that specify the indications and contraindications for use, as well as the requirements for operators and institutions to provide a new service, should be issued when a new therapy is market-approved. Peer-reviewed journal articles should be published soon after clinical trial completion. Abstract presentations are no substitute for publications that have undergone rigorous peer-review. Health technology assessment groups often require access to full length publications when considering whether to cover a new therapy. Sponsors of a new technology, and others, can request a NCD with CED from CMS. A plan to resolve unanswered issues should accompany the request. The NCD with a CED issued by CMS for coverage of transaortic valve replacement (TAVR) is one such example.

Learning Curves Matter

Operator learning curves have been described for TAVR and for other cardiovascular procedures such as percutaneous pulmonary valve implantation.[83,84] The investigators in the later example made four important observations related to the learning curve. First, the incidence of high residual valve gradients (an important measure of procedural success) declined over time. Second, patient selection criteria improved. Third, the best practice for addressing device failures developed over time. Finally, most procedural complications resulted from an operator's initial 50 procedures. Similar learning curves should be considered the norm as new technology is adopted by more clinicians, facilities and patients.[83] Operator experience is therefore a key variable to consider as a new technology is introduced.

Information about learning curves, and how they can be mitigated, can inform investigators, biostatisticians, regulatory agencies, payers, credentialing organizations, facilities, new operators, and most importantly patients.

CER to Overcome Barriers to Translation of Research into Practice

Research findings lead to updated clinical practice guidelines that inform providers about what should or should not be done and under what circumstances, but guidelines do not guarantee that evidence is translated into practice. Multiple factors contribute to success, or lack of thereof. Often, Class I guidelines recommendations are based on data obtained from multiple RCTs. As a result, Class I recommendations are often based on results in homogeneous patient populations, and do not provide answers for real world clinicians and patients. Uncertainty lingers and incentives to perform more pragmatic trials may be absent once a product or a therapy is approved and has at least one Class I indication.

The Cardiovascular Research Network (CVRN) is now used to conduct CER to examine the reasons and potential solutions for suboptimal diagnosis and treatment of hypertension in the community setting. The CVRN will identify the factors associated with hypertension recognition, treatment and control; quantify the relationship between patient, provider and clinical characteristics to the care received; delineate predictors of appropriate provider responses to persistently elevated blood pressure, and characterize the factors associated with patient adherence to medication.[76]

CER to Increase Value and Address the Cost of Cardiovascular Care

Despite concern about healthcare costs, which consume 17.9% of the U.S. Gross Domestic Product in 2012, and the first place ranking of cardiovascular disease in healthcare spending, significant challenges to increasing value and lowering cost remain. American author Upton Sinclair once said," It is difficult to get a man to understand something when his salary depends upon his not understanding it." In addition, the lack of transparency to consumers of the true cost of care they receive limits their incentive to ensure value and manage cost at an individual level. When the economic incentives of participants (e.g. patient, clinician and payer) are not aligned, negative consequences arise in a healthcare system that pays providers based on volume, not value, and does not consistently provide understandable information to patients about the risks, benefits and alternatives of the care they are offered.

Overcoming these obstacles to translation of results into value-based practices requires a more nuanced approach to incentives than classical economists might predict. CER is needed to determine which incentives have the best chance of increasing value in healthcare. Lowenstein

and colleagues suggest there is a need for "different prescriptions for physicians and patients."[85] They challenge the notion that individuals are "self-interest maximizers." They cite evidence that physicians, much more so than patients, are "exquisitely sensitive" to incentives and argue for moving away from a payment model that rewards overuse of low value, high cost services, to a system that rewards high-value, lower cost services. Mitchell has shown that when a provider controls ancillary services, more testing can result,, with a lower yield, producing less value.[86]

Lowenstein also argues that patient cost sharing plans should account for differences in acute and chronic care settings. Confronted by an acute illness, patients are more likely to be a state of uncertainty and heightened emotion, and are less able to be "rational" actors. Conversely, in the context of chronic disease, patients develop a familiarity with their condition and therapeutic options, and are more likely to be informed decision-makers. Promising strategies to optimize value and minimize waste should be tested in different populations and environments, as subgroup differences ought to be expected as in any CER. Strategies that result in success during the pilot phase should also be evaluated as they are brought to scale to determine if they are effective for a broader population, and the benefits sustained.[85] The relative effectiveness of individual, population, and environmental approaches needs further study.

Not all incentives are monetary. Researchers in Michigan have shown that continuous feedback about real time performance of coronary CTA compared to ones' peers can be enough to change clinician behavior, reduce radiation exposure to patients, and incentivize facility leaders to redesign care systems.[87] CMS has recently funded a pilot project to evaluate whether community based organizations, working with hospitals, can reduce readmissions for pneumonia, heart failure, myocardial infarction.

CER that addresses the value and cost of cardiovascular care should use the results of successful early efforts and iteratively conduct studies at the patient, clinician, delivery system, and community levels to see what works, where, and for whom. Methods have been developed to perform comparative cost-effectiveness analyses. Infrastructure such as clinical research organizations, claims data, and registries can be used. An NCD with CED can be used selectively to answer important questions that could not be addressed in pre-market approval trials. Patients and all other affected stakeholders can be engaged in CER, from priority setting exercises to translation of results. Cardiovascular disease is a burden, one that presents both a challenge and an opportunity. The existing evidence base is strong, the potential diagnostic and therapeutic modalities are vast, and the opportunity to add value and decrease cost, when at a time when societal interest is great, is large.

The Department of Health and Human Services Triple Aim expresses the imperative for all of healthcare, including cardiovascular medicine: Better Care for Individuals, Better Health for Populations, and Lower Per Capita Costs.[3] The spotlight is brightly focused on the need to identify what care works (and what doesn't), what improves health (and what doesn't) and how to lower cost (because there is waste in the current system).

Appendix A: Acronym Glossary

ABC	Association of Black Cardiologists
ACC	American College of Cardiology
ACCF	American College Cardiology Foundation
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
AMI	Acute myocardial infarction
CABG	Coronary artery bypass graft
CDC	Centers for Disease Prevention and Control
CED	Coverage with Evidence Development
CEJA	Council on Ethical and Judicial Affairs
CER	Comparative Effectiveness Research
CMS	Centers for Medicare and Medicaid Services
CMTP	Center for Medical Technology Policy
CT	Computed tomography
CTA	Computerized tomography angiography
CVD	Cardiovascular disease
CVRN	Cardiovascular Research Network
DAPT	Dual Anti-Platelet Therapy
DCRI	Duke Cardiovascular Research Institute
EDICT	Eliminating Disparities in Clinical Trials
EQ	EuroQoL
FDA	Food and Drug Administration
HCRI	Harvard Clinical Research Institute
HRT	Hormone replacement therapy
IOM	Institute of Medicine
KCCQ	Kansas City Cardiomyopathy Questionnaire
NCD	National Coverage Decision
NCDR	National Cardiovascular Data Registry
NHLBI	National Heart, Lung and Blood Institute
NIH	National Institutes of Health
NODES	Network of Dedicated Enrollment Sites
NRI	Net Reclassification Improvement
OAT	Occluded Artery Trial
OCA	Office of Coverage Analysis (within CMS)
PCI	Percutaneous coronary intervention
PCORI	Patient-Centered Outcomes Research Institute
PCT	Pragmatic clinical trials
PRECIS	Pragmatic-Explanatory Continuum Indicator Summary
PRO	Patient-reported outcomes
RCT	Randomized controlled trials
RDNT	Rational Dispersion of New Technology
SoCRA	Society of Clinical Research Associates
STS	Society for Thoracic Surgeons
TAVR	Trans-catheter aortic valve replacement
TIMI	Thrombolysis in Myocardial Infarction
VA	Veterans Administration
WHI	Women's Health Initiative

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Appendix C – Speakers, Moderators, Panelists and Group Leaders

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