

Technology Assessment



**Technology
Assessment Program**

HORIZON SCAN: TO WHAT EXTENT DO CHANGES IN THIRD-PARTY PAYMENT AFFECT CLINICAL TRIALS AND THE EVIDENCE BASE?

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Horizon Scan: To What Extent Do Changes in Third-Party Payment Affect Clinical Trials and the Evidence Base?

Technology Assessment Report

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Dr. Amy Abernethy does not have any industry relationships relevant to the topic at hand, but does have industry relationships relevant to her work in supportive oncology and palliative care.

Dr. Nancy Allen Lapointe has declared financial interests with Pfizer and Sanofi Aventis, as well as business/professional interests with Duke Clinical Research Institute, Duke University Health Systems IRB, United States Pharmacopeia, American College of Clinical Pharmacy, University of North Carolina (Chapel Hill), and Campbell University.

Contents

Synopsis	1
Background	1
Purpose	1
Design	1
Results	1
Conclusion	2
Glossary of Abbreviations	3
Background	5
Current Patterns of Enrollment in Clinical Trials	5
Factors Influencing Patient Recruitment and Retention	6
Third-party Payment Policies	7
Current Legislative Climate	7
Clinical Trials Policy National Coverage Decision (NCD)	7
Coverage with Evidence Development (CED)	8
Access to Cancer Clinical Trials Act of 2007	8
The Medicare Improvements for Patients and Providers Act (MIPPA) of 2008	8
Reimbursement under an Investigational Device Exemption (IDE), 1995	9
Design and Methods	10
Study Purpose and Objectives	10
Overview of Design	10
Structure of Report	11
Strategy 1: Advisory Panel	12
Purpose	12
Methods	12
Strategy 2: Literature Review	14
Purpose	14
Methods	14
Data Collection and Management	15
Results	15
Discussion	18
Strategy 3: Public Forum	19
Purpose	19
Methods	19
Data Collection and Management	22
Results	22
Discussion	35
Strategy 4: Key Informant Teleconferences	37
Purpose	37
Methods	37

Data Collection and Management	39
Results	39
Discussion	49
Personnel.....	54
References.....	56

Appendices

Appendix A: Introduction of Study to the Public and Questions for Public Comment.....	A-1
Appendix B: Peer-reviewed Articles Abstracted from Literature Reviews	A-3
Appendix C: Articles from the Non-Medical Press Included in Literature Review	A-6
Appendix D: Preliminary List of Clinical Trials	A-8
Appendix E: Clinical Trials in Which Payment Policy has Impeded Participation.....	A-12
Appendix F: Teleconference Script for Obtaining Oral Consent.....	A-16
Appendix G: Key Informants	A-19

Tables

Table 1: Advisory Panel	13
Table 2: Public Forum Speakers	21
Table 3: Written Comments Received Prior to the Public Forum	24
Table 4: Key Informants – Categories 1-3	44
Table 5: Key Informants – Categories 4-5	47

Figure

Figure 1: Four Interrelated Project Components and Their Relationship to the Report to AHRQ and CMS	11
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Synopsis

Background

The principles of evidence-based medicine increasingly govern healthcare policy and practice in the United States. The hallmark of the evidence-based approach is research data generated through clinical trials, and particularly through “gold standard” randomized controlled trials (RCTs). Healthcare policy increasingly relies on evidence furnished by RCTs. It is therefore of paramount importance that investigators are able to execute RCTs, and that those trials include a fair representation of the general population, as well as of the specific populations of relevance to topics being studied. Currently, valid concerns surround low rates of participation in clinical trials and disparities in clinical trial participation. Various factors might influence patients’ interest and willingness to participate in clinical trials. Financial repercussions, which depend upon the payment policies of third-party insurers, may be an important element in patients’ decisions regarding whether or not to participate in a clinical trial, as well as whether patients stay in the trial once initiated. Payment policies may exert an influence on clinical trials in other ways, impacting not only recruitment and retention, but also conduct of the trial and the subsequent quality of the evidence base.

Purpose

The Duke Center for Clinical Health Policy Research and Duke Cancer Care Research Program conducted this study, supported by a contract with the Agency for Healthcare Research and Quality (AHRQ), to ascertain whether, and to what extent, payment policies may be influencing participant recruitment to clinical trials, rates of participation, and retention in clinical trials. A further objective was to gather input on the issue of whether or not payment policies, through influencing clinical trial participation, may have a deleterious effect on the resulting evidence base. This report will help to inform the Centers for Medicare and Medicaid Services (CMS) if there is causal relationship between the timing of initiating coverage for new therapeutic technologies and beneficiary participation in clinical trials to provide evidence of effectiveness of these new technologies in the elderly and disabled Medicare population.

Design

We employed a variety of strategies to gather data and experiences relevant to the topic. These strategies were: (1) a nationally selected Advisory Panel to provide expert input; (2) a systematic literature review of MEDLINE and ClinicalTrials.gov; (3) a Public Forum held on the CMS campus in Baltimore, MD, to gather public input; and, (4) a series of teleconferences with “key informants” representing diverse stakeholders including government, industry sponsors, third-party insurers, clinical trials investigators and staff, and patient advocates. Flexibility in the study design permitted iterative expansion of the inquiry based on information and insights gathered during the exploratory process.

Results

Published data are virtually non-existent to quantify the difficulties encountered by trials with recruitment and retention, as it pertains to third party payment policies. However, in practice several large-scale clinical trials have encountered substantial difficulties due to the deterrent effect of payment policy on participation. Medical device trials have been more

affected by these issues than have drug trials. Lack of a common understanding of which costs should be assumed by which party (sponsor, site, third-party payer), and lack of common definitions of “standard of care” versus “research-related” costs complicate payment policy and likely impact enrollment. To ensure that trials get completed, investigators are developing creative solutions to assure participants’ coverage on-trial. To ensure that payment policy does not result in a financial loss, sites are analyzing financial impact and may decide not to initiate trials if the financial prospects are negative. Poor coordination among government agencies, industry, third party payers, patients, and researchers is contributing to the difficulties.

Conclusion

Payment policy does bear an impact on clinical trial participation, though this impact is difficult to quantify and unevenly felt across different types of studies, stage of trials, and study populations. The issue of payment policy is closely related to issues of access to care and disparities in care. Payment policies do affect evidence development, in that their impact on clinical trial enrollment results in slower accrual, longer time to completion of studies, and sometimes early termination of studies due to lack of sufficient sample size. Better coordination among government agencies, and between government, third-party payers, sponsors, and sites is necessary. Presuming that participation in clinical trials is a good thing for individual patients and the public at large, a coherent strategy that stipulates when coverage should be initiated, specifies which costs should be covered, and assigns responsibility for those costs to specific payers, coordinated to maximize clinical trials enrollment and retention, could help to (1) rationalize the process of reimbursement when patients are enrolled in clinical trials, (2) ensure equal access to clinical trials for patients interested in participating, and (3) facilitate the generation of high-quality evidence to support future policy-making and clinical practice.

Glossary of Abbreviations

Term Definition

ACCC	Association of Community Cancer Centers
AMD	Age-related macular degeneration
AREDS2.....	Age-Related Eye Disease Study 2
ASCO	American Society of Clinical Oncology
CAD.....	Coverage with Appropriateness Determination
CAS.....	Carotid artery stenting
CATT.....	Comparison of AMD Treatment Trials
CEA.....	Carotid endarterectomy
CED.....	Coverage with Evidence Development
CMS	Center for Medicare and Medicaid Services
CORAL.....	Cardiovascular Outcomes in Renal Atherosclerosis Disease
CREST	Carotid Revascularization Endarterectomy vs. Stenting Trial
CRP.....	Clinical Research Policy
CSP.....	Coverage with Study Participation
CTP	Clinical Trials Policy
EDICT	Eliminating Disparities in Clinical Trials
FDA	Food and Drug Administration
HCFA	Health Care Financing Administration
HDE.....	Humanitarian device exemption
HHS.....	Health and Human Services
HMO.....	Health maintenance organization
IDE	Investigational device exemption
IRB	Institutional review board
MDMA	Medical Device Manufacturers Association
NCCN.....	National Comprehensive Cancer Network
NCD	National Coverage Determination
NCI.....	National Cancer Institute
NIH.....	National Institutes of Health

NPRM..... Notice of Proposed Rule Making
PFO..... Patent foramen ovale
PI..... Principal Investigator
PMA Pre-market approval
QOL..... Quality of life
RCT..... Randomized controlled trial
SCOT Scleroderma: Cyclophosphamide or Transplantation
TROPICS2 .. Tenecteplase for Restoration in Dysfunctional Central Venous Access
Catheters

Background

Evidence-based medicine, classically defined as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients,”¹ depends fundamentally upon the existence of a rigorous scientific base of research evidence. Since the 1990s, evidence-based medicine has gained widespread acceptance as the best current approach to ensuring optimal patient care and outcomes.² The cornerstone of an evidence-based approach to patient care is the incorporation of findings from well-designed, well-executed, clinical trials into clinical practice. Research methodology has steadily improved in its sophistication, and clinical trial designs now involve double-blind methods, placebo control, randomization, validated assessment instruments, and large sample sizes to ensure the quality of resulting evidence. Patients benefit directly from the conduct of clinical trials; by participating, they gain access to potential improved outcomes and receive the best available care in the form of individual guidance and expert medical attention from the clinical research team.³ Ultimately, society benefits through the advancement of medical science and corresponding improvement in medical care. Clinicians and institutions benefit from clinical trials; the evidence generated enables them to elevate the quality of care, improve multiple health outcomes, extend survival, and advance educational and research objectives.⁴ Third-party payers, including federal, state, and private insurers, benefit from clinical trials in that rigorous trials provide solid evidence upon which they can base policy decisions, thereby ensuring that coverage is extended to those interventions proven to enhance outcomes. Clinical research of all types contribute meaningful evidence for decision-making, including observational studies such as registries, non-randomized controlled trials, and more formal randomized controlled studies. This report will focus on more formally controlled trials, since these studies are often difficult to conduct for many reasons, and this may be exaggerated by issues concerning third-party payment policies.

Current Patterns of Enrollment in Clinical Trials

High-quality clinical trials require sufficient sample size to afford statistical power to detect differences between intervention and control arms. Furthermore, clinical utility of evidence hinges on its generalizability, that is, the validity with which it can be applied to a larger population outside of the study cohort. Thus, a sufficient number of patients willing to participate in clinical trials is necessary not only to enable the conduct of those trials, but also to ensure that results from trials can be generalized to clinical populations of interest. Ideally, the composition of the clinical trial participant population should be representative of the population to which the study results pertain.

At present, clinical trial participation rates are dismal. A recent analysis found that only 2.3 million individuals – less than 1% of the US population – enroll in the approximately 80,000 clinical trials conducted each year.⁵ Less than 5% of the 1.3 million patients diagnosed with cancer each year take part in clinical trials^{6,7}; rates of participation are disproportionately low among elderly patients.^{8,9} While 61% of all cancer cases occur among the elderly (age >65 years), this age group accounts for only 32% of participants in phase II and III clinical trials. Although the average age of all cancer patients is 63 and of new cancer patients is 61, the average age of cancer clinical trials participants is 32.^{8,9} A recent meta-analysis examined the characteristics of the >40,000 patients who participated in 141 trials included in cardiovascular

disease technology assessments that CMS uses to inform coverage decisions; the meta-analysis found that study populations differed significantly from the Medicare beneficiary population, with participants more likely to be male, younger, and non-US residents.¹⁰

Low and sociodemographically uneven participation rates in clinical trials reduce the capacity of investigators to build a robust evidence base. The advancement of evidence-based medicine is impeded when lack of participants leads to the closure or failure of important studies, prolongs research schedules, and slows the translation of new therapies into clinical practice.¹¹⁻¹³ When study populations are not representative of the relevant clinical population, the validity and utility of the resulting evidence is suspect. Millions of public dollars are lost when scientifically-important National Institutes of Health (NIH)-funded clinical trials cannot be completed due to inadequate recruitment. It is therefore critical to identify, clarify, and address issues that lead to patients' nonparticipation, limited participation, or termination of participation in clinical trials.

Factors Influencing Patient Recruitment and Retention

Many factors are likely to be at play during the recruitment process. From the clinical side, limiting factors may include physician bias or awareness, trial availability, and selection processes. In one American Society of Clinical Oncology (ASCO)-sponsored survey, for example, 3,550 oncologist-respondents stated that they considered 20% of their patients appropriate for trial participation. However, due to limited time, staff, and resources, the physicians approached only 10% of their patients, and only 5% were actually enrolled.¹⁴ Among patients who are approached to enroll in a trial, some may be excluded simply because the protocol is not available in their area, some may fail to meet eligibility requirements, while others may mistrust the medical system or simply be unwilling to participate.^{15,16}

Although 70% of U.S. adults indicate that they would be somewhat or highly willing to participate in a study⁷, the reality of participation behavior is quite different. According to a landmark study of nearly 6,000 cancer patients, of the 15-20% of patients who were aware of trial availability, approximately 75% chose *not* to participate. Patient respondents indicated various reasons for declining to enroll: 37% felt the standard treatment to be better; 31% feared receiving placebo; 22% feared being treated as a “guinea pig”; 21% cited travel requirements; and 20% *declined due to uncertainty about insurance coverage*.¹⁷ Other studies have cited as barriers the following patient perceptions: treatment might be too severe or too toxic; the trial might involve additional testing and discomfort; the primary-care physician might know less about the study treatment than about standard care; and trial requirements might be too inconvenient.⁷ Although such fears are generally inconsistent with the experiences of patients who actually participate in trials, these misperceptions nevertheless significantly affect rates of enrollment.¹⁷

In addition to factors that influence participation among patients of all ages, there are special considerations that may affect recruitment of the older adult into clinical trials: eligibility requirements including protocol age limits, comorbidities, or previous disease history; concomitant medications; lack of awareness of advancements in reduction of treatment toxicity; perceptions of reduced potential benefit and reduced tolerability; possibility of functional impairments; and lack of financial, logistical, and social support.^{17,18}

Third-party Payment Policies

Third-party payment policies may be significant among factors that influence patients' willingness to participate in clinical trials. Guidance from the Office for Human Research Protections requires researchers to inform subjects of the alternatives available to participating in the trial, and this would include making subjects aware of the availability of third-party reimbursement for treatment outside the research setting. Various plausible scenarios are supported by anecdotal evidence, though data do not exist to describe and quantify the actual impact of payment policy on clinical trial participation. First, when third-party payers reimburse for a diagnostic or therapeutic treatment outside of a trial setting, patients may be less likely to participate in trials studying that intervention. They do not need to be enrolled in a trial in order to gain access to the intervention, and by not participating in a trial, they avoid the risk of being randomized to a control condition rather than to the intervention. Second, when third-party payers initiate coverage for an intervention under study while clinical trials investigating that intervention are still open, enrollment may slow down or even halt. Patients lose the financial incentive to participate, and may make a rational decision to avoid the extra demands entailed in the clinical trial (e.g., completing study questionnaires) by simply accessing the intervention off-trial. Third, when third-party payers decide, after a study has begun, to cover treatment for patients who are *not* involved in the clinical trial, but not to reimburse patients who are enrolled, patients may become less willing to enroll, or continue, in the trial. Fourth, when two arms of a trial involving two interventions have distinct payment structures for each intervention, patients may take financial factors into account in their decisions regarding participation. And fifth, third-party payment structures may contribute or may be perceived to contribute additional financial and time burdens to people who participate in trials (e.g., additional paperwork, timing of reimbursements).

Overall, the lack of national consensus regarding financial responsibility for clinical trial-related healthcare costs has resulted in uneven reimbursement policies. This lack of clarity has contributed to a general environment of uncertainty about third-party coverage, which may itself hamper recruitment efforts.¹⁹ Because payment policies carry the potential for widespread and long-term repercussions, their possible impact on clinical trial participation and thereby on the evidence base warrants serious consideration. Ultimately, if they weaken the research structure and lower the quality of evidence, they will undermine informed policy decision making.

Current/Evolving Legislative Climate

Because CMS plays a major role in the public policy arena, its position with regard to negotiating the tension between support of beneficiaries' access to emergent medical interventions and maintenance of high standards for evidence-based coverage is subject to particular scrutiny.²⁰ CMS has implemented several initiatives that attempt to promote evidence-based clinical and reimbursement practices, as well as respond to the evolving landscape of evidence-based medicine.²¹

Clinical Trials Policy National Coverage Decision (NCD). A Presidential Executive Memorandum was the impetus for allowing Medicare to pay for routine health care costs incurred by Medicare beneficiaries participating in clinical trials and resulted in CMS's 2000

National Coverage Determination.²² Intended specifically to encourage the participation of senior citizens in clinical trials, the NCD implemented coverage for “routine” costs – broadly interpreted as those costs normally covered by Medicare outside the context of a clinical trial. The reconsideration of the policy finalized in October 2007 expanded the definition of such costs to include additional beneficiary items and services that had not previously been covered. While expanding coverage in 2007, the implementation of this policy has been challenging and questions concerning its legal authority persist.

Coverage with Evidence Development (CED). Required by law to provide coverage only for medical interventions deemed “reasonable and necessary,” CMS faces the challenge of promoting innovation without sacrificing scientific rigor or fiscal prudence.²³ Therefore, it recently exercised its national coverage authority to help improve access to promising but unproven medical technologies via the Coverage with Evidence Development Guidance Document.¹⁸ Intended to be used infrequently, it not only speeds delivery of state-of-the-art therapies to eligible patients, but also facilitates development of the evidence base in order to inform future policy decisions. CED provides coverage for items and services for which there is demonstrable medical benefit, but that do not yet meet Medicare’s requisite standards of evidence of effectiveness in the relevant Medicare population. CED requires, as a condition for coverage, that the intervention be performed within a research context.^{23,24}

Two policy mechanisms – each with its own goals, methods, and statutory authorities – identify specific research circumstances that may qualify for CED. First, Coverage with Appropriateness Determination (CAD) applies when CMS decides that reimbursement for an otherwise eligible medical technology must be linked to the collection of extra clinical data needed to ensure its delivery to appropriate patients according to NCD specifications. Second, Coverage with Study Participation (CSP) enables certain experimental interventions to be deemed reasonable and necessary, and thus eligible for reimbursement, only when delivered in the context of clinical research study that is expected to contribute reliable and valid evidence of benefits and risks, and that furthermore affords additional safety protocols, patient protections, monitoring, and clinical expertise.²⁵ Collection of registry data may fulfill CED clinical research requirements for CSP.

Access to Cancer Clinical Trials Act of 2007. This bill seeks to amend the Public Health Service Act, Employee Retirement Income Security Act of 1974, and Internal Revenue Code of 1986 to require group and individual health insurance coverage and group health plans to cover beneficiaries who are participating in approved cancer clinical trials. Sponsored by Deborah Pryce, it was introduced into the House of Representatives (H.R. 2676) on June 12, 2007. Subsequently, it was re-introduced into the House of Representatives (H.R. 716) by Steve Israel on January 27, 2009 and into the Senate (S. 408) by Sherrod Brown on February 26, 2009. Current status of the bill can be located at <http://thomas.loc.gov/cgi-bin/thomas>.

The Medicare Improvements for Patients and Providers Act (MIPPA) of 2008. This Act became public law No:110-275 on July 15, 2008. It amends titles XVIII and XIX of the Social Security Act (SSA) to extend expiring provisions under the Medicare Program, to improve beneficiary access to preventive and mental health services, to enhance low-income benefit

programs, and to maintain access to care in rural areas, including pharmacy access, and for other purposes. Section 184 in MIPPA amends Section 1833 of the SSA with “(w) Methods of Payment – The Secretary may develop alternative methods of payment for items and services provided under clinical trials and comparative effectiveness studies sponsored or supported by an agency of the Department of Health and Human Services, as determined by the Secretary, to those that would otherwise apply under this section, to the extent such alternative methods are necessary to preserve the scientific validity of such trials or studies, such as in the case where masking the identity of interventions from patients and investigators is necessary to comply with the particular trial or study design.”

Although CMS decisions since 2000 have been most commonly cited as the national reimbursement drivers of evidence development, other policies also influence clinical trials participation, most notably:

Reimbursement under an Investigational Device Exemption (IDE), 1995. A device is any instrument, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease in man or other animals, and does not achieve any of its primary intended purposes through chemical action.

Food and Drug Administration (FDA) marketing clearance is usually required for a drug or device to be reimbursed. Prior to 1995, Medicare did not cover any experimental or investigational devices. In 1995, after an Inter-Agency Agreement between the Health Care Financing Administration (HCFA) and FDA, Medicare issued regulations exempting certain devices being investigated in an IDE trial.²⁶⁻³⁵

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Subtitle D, Section 731 required the national coverage determination process to be more transparent for the public, adhere to timelines for considerations, and required payment for coverage of routine costs provided to beneficiaries participating in certain IDE Category A clinical trials.

Design and Methods

Study Purpose and Objectives

Supported by a contract with AHRQ, the Duke Center for Clinical Health Policy Research and Duke Cancer Care Research Program conducted this study to ascertain whether, and to what extent, payment policies may be influencing recruitment to, rates of participation in, and retention in clinical trials. The purpose of this study was to develop a report that will help CMS and other third party payers understand the impact of decisions regarding payment policies that pertain to coverage of expenses of patients who are participating in clinical trials.

Objectives of this study were:

- To assess the extent to which changes in third-party payment policies affect the conduct of clinical trials, particularly the accrual and retention of patients to participate in trials;
- To consider the impact of differing payment structures for interventions being studied on patients' participation in studies of those interventions; and,
- To describe the potential impact of payment factors on the quality of subsequently accumulated evidence.

A particular interest was whether the timing at which third-party payers initiate coverage for new technologies and therapeutics influences accrual to, and retention in, clinical trials studying those interventions.

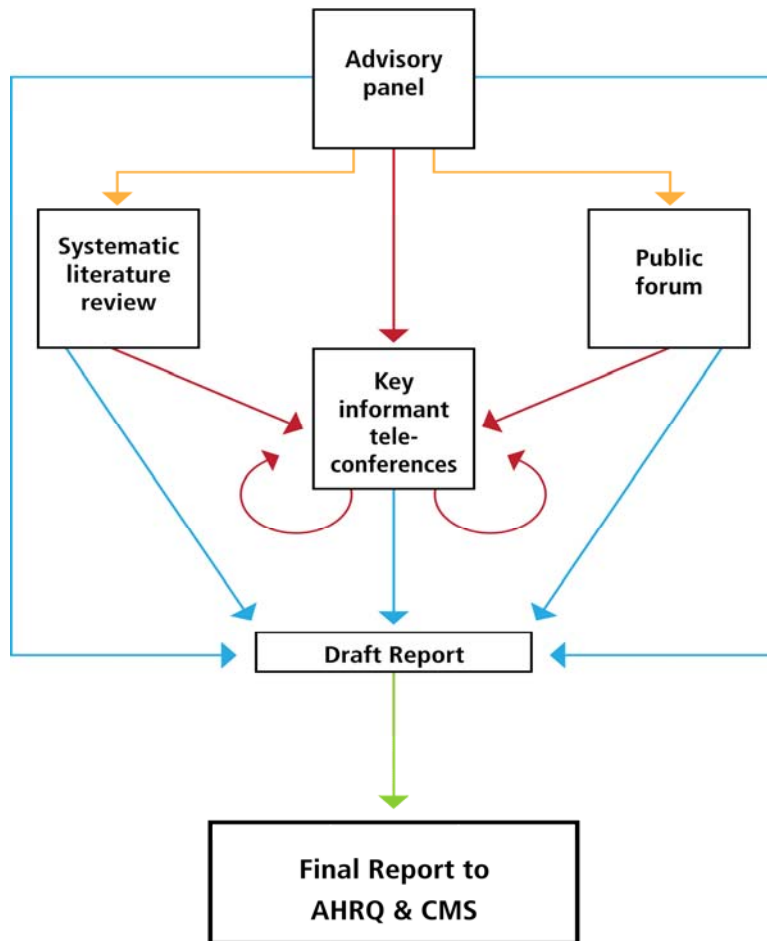
Overview of Design

The question addressed by this study – how do payment policies affect clinical trial participation and the subsequent evidence base? – was unlikely to be answerable using standard methods of literature review or survey. To accommodate various avenues of gathering evidence, a study design was constructed that used four main pathways to gather both published and unpublished/anecdotal experiences related to the impact of payment policy on the conduct of clinical trials (Figure 1). Each strategy contained within it the flexibility to pursue leads emerging during the course of the inquiry.

The project structure contained four primary components:

1. An expert Advisory Panel comprised of leading national figures in positions to advise on the design, content, and sources for this study;
2. An iterative literature search of MEDLINE, ClinicalTrials.gov, and the other media sources;
3. A Public Forum held at the CMS headquarters in Baltimore, Maryland; and,
4. Key informant teleconferences involving representatives from government, industry, third-party insurance carriers, the research community, and patient advocacy.

Figure 1: Four interrelated project components, and their relationship to the report to AHRQ & CMS



Structure of Report

Because the four strategies comprising this project differed significantly in their nature, the Methods, Data Collection and Management, and Results for each strategy are reported separately in the sections to follow. Each strategy section also includes a Discussion that summarizes the main findings and their relevance for that strategy. A full project Discussion follows the four strategy sections, and pulls together the principal results and implications from all strategies.

Strategy 1: Advisory Panel

Purpose. An Advisory Panel was convened to provide expert input into the process of inquiry, to help identify other sources of input, and to offer their perspectives on the subject of payment policy and its impact on clinical trials participation.

Methods. Advisory Panel members were selected from a national pool to represent diverse disciplines sharing the common ground of clinical health policy and/or clinical trials development. They added to the project the perspectives of bioethics, new drug discovery, clinical research methodology, healthcare policy, clinical care, and patient advocacy. Eleven eligible individuals were recruited to the study based on their ability to provide instrumental links for and direction to the project. Names of these individuals and their respective affiliations appear in Table 1: Advisory Panel.

The functions of the Advisory Panel were: to direct the investigators toward studies, either published or unpublished, which encountered difficulties due to payment policy issues that hindered participant enrollment or retention (Strategy #2); to suggest individuals who might provide critical input through either the Public Forum (Strategy #3) or the Key Informant Teleconferences (Strategy #4); and to review and provide input to a draft version of the final report. The panel served as a “think tank” resource throughout the duration of the project.

Table 1: Advisory Panel

Member Professional Affiliation(s)

Leslye K. Fitterman, PhD	Epidemiologist, Office of Clinical Standards and Quality, Center for Medicare and Medicaid Services
William Harlan, MD	Senior Consultant, NIH National Library of Medicine
H. Kim Lyerly, MD	Director, Duke Comprehensive Cancer Center; George Barth Geller Professor for Research in Cancer, Associate Professor of Pathology, and Assistant Professor in Immunology, Duke University School of Medicine
William Rich III, MD	Medical Director of Health Policy, American Academy of Ophthalmology
Kevin Schulman, MD	Professor, General Internal Medicine, Duke University Medical Center; Professor of Business Administration and Director, Health Sector Management Program, Fuqua School of Business; Director, Center for Clinical and Genetic Economics, Duke Clinical Research Institute
Lynda Szczech, MD	Associate Professor in Medicine, Medical Director of the Duke site-based Clinical Research Support Office
Robert Temple, MD	Director, Office of Medical Policy, Food and Drug Administration (nominated by CMS)
Marc Walton, MD, PhD	Director, Division of Therapeutic Biological Internal Medicine Products, Food and Drug Administration (nominated by CMS)
Deborah A. Zarin, MD	Director, ClinicalTrials.gov, National Institutes of Health
Armin Weinberg, PhD	Professor of Chronic Disease, Baylor College of Medicine; Principal Investigator on EDICT (Eliminating Disparities in Clinical Trials)
Beth Darnley	Chief Program Officer, Patient Advocate Foundation

Advisory Panel members participated by: reviewing and providing input on our planned methodology; suggesting clinical trials that might have been affected by changes in third-party payment for potential review; providing further direction to the literature search; suggesting key informants who might contribute information relevant to the study topic; and providing input on the content of key informant teleconferences and discussion questions used in those discussions.

Communication between the investigators and Advisory Panel members took place via conference calls and email. All Advisory Panel members received a consultant stipend (unless prohibited by governmental regulations) in acknowledgment of their contribution of time and effort.

Strategy 2: Literature Review

Purpose. A search of the published medical literature was conducted to fulfill two primary functions:

(1) To generate information directly. The literature search sought publications that could facilitate summarization of the published peer-reviewed information on the topic, guide development of an agenda for the key informant teleconferences, and identify potential sources of information on this topic.

(2) To identify clinical trials that illustrated issues with clinical trial participation caused by payment policies. The literature search was expected to assist in the identification of trials that encountered problems with recruitment, or that were terminated or had been redesigned due to recruitment and retention issues. Of particular interest were trials that studied the same (or similar) technologies/agents before and after coverage became available for the new technology/agent, to differentiate the effect of coverage from the impact of other factors that might have slowed or impeded enrollment.

Methods.

MEDLINE search. We conducted a literature search through MEDLINE, 1966 to July 2007, in order to explore the extent to which published literature had addressed the impact of third-party payment policies on accrual to, conduct of, and results of clinical trials. A corollary question was whether the literature mentions the impact of a change in payment policy during the course of a clinical trial on participant accrual, or on randomization. All English language articles and abstracts, involving or relevant to human subjects, without date restriction, were included if they met the following eligibility criterion: has relevance to the impact of third-party payment policies on participant accrual to, conduct of, and results of clinical trials.

It is not common practice for investigators to publish failures in clinical trials, or difficulties encountered in their conduct. We therefore did not expect that the volume of this literature would be large. Moreover, standard MeSH terms and other search terms do not include subject headings that pertain to enrollment processes or insurance parameters, therefore we did not expect that the literature would be systematically coded or otherwise amenable to a comprehensive systematic search. We addressed this challenge through two strategies: (1) a “bottom-up” review process that drew heavily on guidance provided by our Advisory Panel to direct the literature search; and (2) an iterative literature search in which results of the search directed key informant discussions and, conversely, key informant input guided additional literature searches. Identified MeSH terms were searched via MEDLINE to follow leads and themes suggested by identified articles.

ClinicalTrials.gov search. ClinicalTrials.gov (<http://clinicaltrials.gov/>), a federal resource developed by the National Library of Medicine, provides regularly updated information about federally and privately supported clinical research in human volunteers. It contains information about a trial's purpose, participants, locations, and contact information. We searched this source to locate clinical trials which may have experienced early termination or difficulty in enrolling participants. The Advisory Panel and key informants also directed searches for relevant studies in clinicaltrials.gov.

Advisory Panel suggestion. The Advisory Panel was contacted for suggestions of additional articles, search terms and strategies, abstracts, or other published sources of information relevant to the topic. This was achieved through standardized email requests, and in the context of planned teleconferences.

Key informant suggestion. As a part of Strategy #4, Key Informant Teleconferences, we asked teleconference participants if they could suggest studies which they believed had encountered difficulty with participant recruitment or retention due to payment policy issues, or other sources of information on the topic. Any suggestions forthcoming in this way were pursued to determine whether or not the suggested information could contribute to the report.

Data collection and management. Data from the initial literature search were compiled and tabulated using Microsoft Excel, with updates, based on input from key informants, Advisory Panel members, and other interested parties, later added to the existing framework.

Results. The MEDLINE search yielded 96 citations, of which 60 abstracts met the inclusion criteria. The full-text articles of these 60 abstracts were reviewed; through review of the full article, 22 of the 60 citations were eliminated from the pool due to lack of relevance. Of the remaining 38 full-text articles, most were tangential, in that they did not specifically address or describe issues of recruitment or retention. (see Appendix B: Peer-reviewed articles abstracted for literature review)

Main points abstracted from fully reviewed articles were the following:

- Medicare reimbursement for drugs, procedures, and devices being studied in clinical trials should be the same on-trial as off-trial.³⁶
- Patients should not bear any additional financial burden associated with participating in a clinical trial, as that would discourage participation.³⁶
- Predetermination impacts patients' enrollment in clinical trials. A study in bone marrow transplantation for breast cancer reported that predetermination was examined in 533 patients; 23% were denied coverage, with the primary reason for denial being the investigational or experimental nature of the therapy. Frequency of approvals varied both between and within insurance carriers.³⁷
- Off-trial coverage for as-yet incompletely studied drugs, procedures, and devices causes too-rapid diffusion of unproven technologies.³⁸
- By appropriate coverage policies, Medicare can help to ensure collection of adequate data to evaluate effectiveness. (example: National Emphysema Treatment Trial)³⁸
- Coverage for procedures off-trial impedes recruitment to clinical trials studying those procedures; patients will seek the procedure off-trial to avoid the possibility of being randomized to a control arm. (example: bone marrow transplantation for metastatic breast cancer patients)³⁹
- Physicians in community practice function as gatekeepers to clinical trials, and may be unlikely to refer patients if clinical trials incur additional financial expense to the physician, practice, or patient.⁴⁰
- Coverage policies for clinical trial participants in four states (1999) resulted in a 22% annual increase in Phase II clinical trial enrollment, compared to a 16% annual decrease in states without coverage policies. This translated into a 1.59 greater likelihood that a

patient from a state with coverage policy would enroll relative to a patient from a state without coverage policy.⁴¹

- The 2000 Medicare trial reimbursement policy, authorizing payment for study-related routine costs, was not associated with a significant increase in enrollment in NCI-sponsored clinical trials of patients aged ≥ 65 years.⁴²
- The 2000 Medicare trial reimbursement policy resulted in a 7% increase in accrual of older patients to Southwest Oncology Group clinical trials (31%, 1997-2000; 38%, 2001-2003).⁴³
- Less than 5% of 373 websites of cancer research institutions and advocacy organizations contained information explaining coverage for clinical trial participation to patients.⁴⁴
- In California, legislation that requires third-party coverage of clinical trial costs increased accrual rates slightly (from 51% to 69%), but not significantly.⁴⁵
- A large-scale, NIH-funded trial of renal artery stenting has encountered major difficulties in enrollment due to coverage of the procedure off-trial. (case: Cardiovascular Outcomes in Renal Atherosclerotic Lesions, CORAL)⁴⁶
- Approval thresholds for coverage of new drugs and new devices may differ, thus causing an imbalance in the evidence basis required before diffusion.⁴⁷
- If Medicare and other third-party payers reimburse more generously for established therapies than for those under study, payment policy may inhibit testing and promotion of new, more effective therapies.⁴⁷
- A proposed strategy for circumventing the issue of payment policy for new devices is that new technologies be reimbursed based on the service performed rather than on the device used.⁴¹
- Clinical trial enrollment can be negatively impacted by difficulties in obtaining prior approval from insurance carriers. (case: Phase I trial of interleukin-2)⁴⁸
- Industry sponsors are outsourcing clinical trials to non-U.S. sites at an increasing rate, in large part due to cost advantages.
- For drugs under development, payment policy that links access to a new drug to participation in a clinical trial can be used to the sponsor's advantage in so-called "seeding trials." In these scenarios, the pharmaceutical manufacturer exploits the clinical trial as a marketing strategy for advancing a drug into clinical care and for influencing clinical practice, particularly the prescribing practices of physicians involved in the trial. Patients unwittingly participate in advancement of the sponsor's marketing objectives because the trial affords them potential access to the new therapy.⁴⁹

An additional 27 articles, primarily non-peer-reviewed, were identified by the study investigators, staff at CMS and AHRQ, Advisory Panel members, and key informants who participated in Strategy #4 teleconferences; several websites were also suggested. (see Appendix C: Articles from non-medical press included in literature review).

Key points gleaned from these articles and websites were the following:

- Physicians sometimes have an economic incentive not to enroll their patients in clinical trials. In the example of carotid stenting for low-risk patients, two payment policy forces are at work to impede clinical trial enrollment: Physicians are frequently implanting these

devices in low-risk patients, off-label with reimbursement, and therefore study accrual is slow. Surgeons are reluctant to refer patients to the study because of the potential loss of income if a patient is randomized to not receive a stent.

- Use of devices and agents before RCTs have established their efficacy can prevent key efficacy questions from being answered. This is particularly a problem with devices because of differing FDA requirements for drugs vs. devices. FDA approval hinges on safety and efficacy for drugs, whereas demonstration of safety alone is required for devices.
- The impact of CMS reimbursement policies on randomized efficacy trials is an important “under the radar” issue.
- In a study of 76 cancer patients eligible for clinical trials, 49% declined participation; 8% of these patients cited insurance denial as a primary reason for the decline. Patients with private insurance were less likely to enroll in clinical trials compared to those with government-funded insurance.¹⁶
- Several prominent legislators, in 2007, began to promote the concept of comparative effectiveness trials as an efficient way to generate evidence following a call by scholars for creation of a national agency devoted to comparative effectiveness as a mechanism to support better decision making in health care.⁵⁰ More recently and supplying substantial funds for the development of comparative effectiveness evidence, the American Recovery and Reinvestment Act (ARRA) of 2009 provides \$1.1 billion for comparative effectiveness research.
- Recruitment challenges can add considerably to the cost of clinical trials.
- Registries should not be considered a comparable design to that of the RCT, and should not be allowed to replace the RCT as the primary method of generating definitive evidence. A registry, being uncontrolled, cannot answer certain fundamental research questions. They can, however, play a valuable role in observational studies of treatments, and in describing the natural history of disease; they are sometimes the only viable alternative when an RCT is infeasible or otherwise not possible.
- An appropriate place for registries may be after an RCT has determined that an intervention is beneficial. At this point, registries can provide important data without competing with RCTs for participants.
- A 2000 Harris poll inquiring about “major reasons for not participating in clinical trials” reported that reimbursement issues ranked sixth, while the amount that the patient would have to pay out of pocket ranked seventh in importance.⁵¹
- A 2004 ASCO survey found that 60% of respondents who did not participate in clinical trials did not do so because of reimbursement issues.⁵²

The two prongs of the literature review identified several clinical trials for which either the research reports provided evidence regarding negative influence of payment policies on enrollment, or retrieved literature suggested that payment policy-related difficulty with enrollment may have been encountered. These trials are summarized in Appendix E: Clinical trials that have experienced enrollment difficulty due to payment policy. (Note that Appendix E includes information yielded through all four strategies comprising this project, not exclusively those identified through the literature search.)

Discussion. The limited quantity of information available in the peer-reviewed medical literature did not allow for the drawing of definitive conclusions regarding the impact of payment policy on clinical trials participation. Rather, this literature search confirmed that certain trials have encountered recruitment and retention difficulties due to payment policy, that public concern exists surrounding this issue, and that there is substantial interest within the research community and among industry players in developing clearer and more consistent payment policies to minimize potential negative impact on patients' participation in clinical trials. Comparative studies evaluating clinical trials accrual rates before and after the legislative attempts to foster evidence development, demonstrated that the policies had minimal effect on accrual, with increases perhaps most substantial for Phase II trials.

A small number of high-profile clinical trials are known to have encountered difficulties with enrollment due to payment policy. These trials predominantly involved medical devices rather than drug therapies, tended to be very large, multi-site studies, and involved high visibility treatments. These publicized trials serve to call attention to the existence of a potentially important, broader issue. It is not possible to determine from the medical literature to what extent similar enrollment challenges have affected smaller and/or unreported clinical trials, e.g., through slowing the progress of research, limiting sample size, or causing termination of the study.

Limitations. As noted, few data are available in the medical literature to facilitate study of this issue. The literature search used a modified, flexible approach to maximize input to the report from this strategy. Given the lack of identified MeSH headings, clear key words, and other search terms, this literature review may be incomplete. Due perhaps to publication bias, the literature search did not identify a broad spectrum of clinical trials impacted by payment policy; notably, small and industry-sponsored trials are under-represented.

Strategy 3: Public Forum

Purpose. Because the topic of clinical trial participation fundamentally involves an element of public perception as it relates to decision-making and behavior, the project included a mechanism for soliciting direct public input. A Public Forum was announced to the general public, researcher scientists, industry personnel, and other interested parties as a mechanism for gathering their perspectives. The purpose of the Public Forum was to obtain information about on-the-ground experiences and perceptions related to clinical trials impacted by payment policies, and hopefully to gain anecdotal evidence on the ways in which payment policies have influenced individuals' decisions to participate, or not participate, in clinical trials. The resulting information was intended for use in framing topics for the key informant teleconferences, identifying additional key informants, and articulating areas of focus for current and future exploration.

Methods. The Public Forum was announced on the CMS website and in the August 24, 2007 issue of the *Federal Register*.⁵³ Participants had two options for attendance: by physical presence on-site at CMS, and by remote access using the telephone line set up to teleconference the session. Individuals interested in participating were also encouraged to submit comments and questions to the investigators in advance of the event; instructions for providing this input appeared on the CMS website.

Written comments. Interested parties were given the opportunity to submit comments in response to the following questions:

- How do payment policies by CMS and other third-party payers affect enrollment into clinical trials?
- How do payment policies by CMS and other third-party payers affect randomization and blinding within clinical trials?
- What is the summary impact of this effect?
- Does the timing of third-party payment in the clinical trial process impact the development of better evidence?
- Do differing payment structures within clinical trials affect the resulting evidence?

Individuals were asked to provide their responses to these questions by September 10, 2007, so that any issues thus identified could be incorporated into the discussion of the Public Forum.

Public Forum. The Public Forum was held on September 20, 2007, at the CMS headquarters in Baltimore, Maryland. The event followed a standard town-hall meeting format, in which an investigator introduced the topic and introduced speakers, and a moderator managed the question-and-answer sessions. A half-day conference, the Public Forum featured eight speakers divided into three presentation blocks: three speakers in block 1, two speakers in block 2, and three speakers in block 3 (see Table 2: Public Forum speakers). Each block was followed by a question-and-answer period to encourage public input and dialogue; both individuals in the meeting room at CMS and individuals participating via conference line were given the

opportunity to pose questions to the speakers and/or to offer additional input provided that input had direct and specific relevance to the topic.

A short list of potential speakers was compiled from national experts identified through the investigators' professional connections, Advisory Panel input, and CMS and AHRQ suggestion. Speakers were chosen from this short-list based on their knowledge and background with respect to the topic, and their ability to contribute a balanced range of perspective, background, and vision. The first block of speakers introduced the issues around clinical trials enrollment, including why people participate, what the evidence indicates thus far, patient perspectives, and ethical perspectives. The second block of speakers offered actual examples of clinical trials that have encountered difficulty with enrollment or retention due to payment policies. The third block of speakers described certain special-interest considerations, including disparities.

A list of questions was offered in order to prompt public input:

- Would you be willing to participate in a clinical trial if it were the only way to get a new, and possibly more effective, treatment?
- Would you be willing to participate in a clinical trial if you would have to pay out-of-pocket for the drug/procedure while on-trial? If you could receive reimbursement for it off-trial, how would that influence your decision? Why or why not?
- If you decided to enroll in a clinical trial comparing two treatments, and one of the two treatments would cost more than the other, would you be willing to be randomly assigned to *either* treatment?
- If you *might* be assigned to a study group where you do *not* receive the new drug/procedure (but instead receive “standard care”), would you still be willing to participate in a clinical trial? Would your decision be different if you knew that you *might* get the new treatment for free by being in the trial?
- If you have been involved in the conduct of a clinical trial (e.g., as an investigator, coordinator, manager, or administrator), have you felt that patients' decisions to enroll or continue participation in the trial were influenced by payment policy considerations?
- If you rely on the output from clinical trials to make decisions regarding healthcare (e.g., as a part of evidence-based care), have you felt that the output from clinical trials was influenced by payment policy considerations?

Table 2: Public Forum Speakers

Group 1

Speaker

Professional Affiliations

Placido Grino, MD

Associate Dean of Clinical Research and Associate Professor of Endocrinology in the Department of Internal Medicine at Baylor College of Medicine. Prior to Baylor, Dr. Grino worked for 15 years in research & development and medical affairs at four major pharmaceutical companies. He is involved in the EDICT study.

Cary P. Gross, MD

Associate Professor at Yale University School of Medicine and Associate Director of the Robert Wood Johnson Clinical Scholars Program. Dr. Gross did his Chief Medical Residency at Memorial Sloan Kettering and is a General Internist at Yale. His research focuses on cancer in vulnerable populations, with a particular emphasis on clinical trial participation and the impact of chronic illness on cancer care and outcomes. He has published many articles on clinical trials enrollment and the effect of payment structures.

Lori Williams, DSN, RN,
OCN, AOCN

Instructor in the Department of Symptom Research at MD Anderson Cancer Center at the University of Texas, Houston. She has worked in oncology nursing for 24 years and possesses experience in staff nursing, advanced practice nursing, and research, including functioning as a research nurse and administrator and as a nurse scientist. She is also the Chairperson of the Scientific Advisory Board of National Patient Advocate Foundation.

Group 2

Speaker

Professional Affiliations

Lance Dworkin, MD

Professor and Vice Chair of Medicine and Director of the Division of Kidney Disease and Hypertension at the Warren Alpert Medical School, Brown University, Providence, RI. He has conducted laboratory research in kidney failure, is a clinical specialist in hypertension, and is Study Chair and senior leader for the Cardiovascular Outcomes in Renal Atherosclerosis Disease (CORAL) trial.

Daniel Martin, MD

Thomas M. Aaberg Professor of Ophthalmology at Emory University School of Medicine and the Chair of the Comparisons of Age-Related Macular Degeneration Treatment Trial (CATT).

Group 3

Speaker

Professional Affiliations

Neil Bressler, MD

Chief of the Retina Division at the Wilmer Eye Institute at Johns Hopkins University, Baltimore, MD; Chair of the NIH-sponsored Diabetic Retinopathy Clinical Research Network; Chair of the Data

	& Safety Monitoring Committee for the National Eye Institute's intramural clinical trials; and involved in the AMD DOC Study (Maculopathy, Age-Related Choroidal Neovascularization).
Walter Koroshetz, MD	Deputy Director of the National Institute of Neurological Disorders and Strokes.
Armin Weinberg, PhD	Professor of Chronic Disease at Baylor College of Medicine, Houston, TX, and Principal Investigator for the Eliminating Disparities in Clinical Trials (EDICT) study, Dr. Weinberg also served on our Advisory Panel.

Data collection and management. The Public Forum was audiorecorded by Intercall.com, a firm that works with the governmental agencies and possesses the electronic resources to accommodate CMS's regulations surrounding participation in call-in forums. The Public Forum was subsequently transcribed by NetTranscripts, as recommended by AHRQ and CMS. The transcription was reviewed by the investigators in the preparation for drafting this report.

Results of the Public Forum were presented to the public through a CMS Pink Sheet which summarized participants' input. Full proceedings were also made available to the public online, at <http://www.cms.hhs.gov/ClinicalTrialPolicies>.

Results.

Written comments. Seven letters were received in response to our request for written commentary. Although the number of written responses was small, the letters represented a range of interested entities including an academic medical center, a community cancer center network, a large oncology services network, two oncology professional organizations, a medical device manufacturer association, and a public-health advisory group. In addition to those responses that directly addressed the questions suggested by the investigators, most respondents also commented on the Proposed Clinical Research Policy (CRP), which was under active consideration at the time,²⁵ and was superseded by the Clinical Trial Policy released in July 2007.⁵⁴

There was some uncertainty as to how to interpret "the timing of third-party payment" and "differing payment structures"; timing, in particular, was largely addressed as it relates to prompt reimbursement policies and simplified billing procedures, rather than as it relates to changes in policy that take place during the course of a trial.

Several common themes emerged through this method of soliciting information. Respondents concurred on the following points:

- Payment policies significantly affect the ability of clinical trials to enroll patients.
- Uniform coverage and payment policies are needed to avoid disparities, encourage enrollment, and minimize procedural and administrative burdens.
- Clarifications regarding, and practical strategies for implementing, the proposed CRP are necessary.
- The proposed CRP may have a significant impact on clinical trials enrollment, and this issue must be addressed before any policy changes are implemented.
- Timeliness of payment is important to ensure that research can proceed unimpeded.

In addition to these overall concerns, two notable related issues were introduced: the first concerned a need for clarification of Medicare's IDE policy criteria and requirements; the second concerned coverage discrepancies that create especially acute financial barriers for Medicare Advantage patients, resulting in unequal access to trials and new treatments for these beneficiaries. (see Table 3: Written comments received prior to Public Forum).

Table 3: Written comments received prior to the Public Forum

Association of Community Cancer Centers (ACCC)

Represented by Edward L. Braud, MD, Chair, ACCC Government Affairs Committee

Responding to CMS's Proposed CRP, ACCC requests that CMS:

- Instead issue a Notice of Proposed Rule Making (NPRM), which may be a more appropriate mechanism for addressing comprehensive coverage issues, given that certain CRP items – such as withdrawing coverage for items and services used in a “non-qualifying research study” when these would have been covered outside of a study – appear to have no statutory basis;
- Maintain “deeming,” using self-certification only for studies that fall outside of deemed categories;
- Provide detailed guidance for the self-certification process;
- Clarify the full scope of the CRP, including the definition of “clinical research;”
- Clarify and minimize billing requirements;
- Provide a clear transition plan, grandfathering in both ongoing trials and new sites in ongoing trials;
- Clarify that Medicare, not the trial sponsor, is the primary payer for covered medical costs.

Association of Community Cancer Centers (ACCC)

Represented by John Feldman, Medical Director, Moses Cone Regional Cancer Center

- The proposed CRP will necessitate broad-reaching changes for billing systems and enrollment practices, as well as require an administrative certification process for studies that previously were “deemed” qualified for Medicare coverage. These burdens may result in many clinical trial sites simply declining to enroll Medicare beneficiaries.
- The NCD process is not the appropriate mechanism to establish a new CRP. The scope of the Proposed CRP exceeds the authority CMS has under the Social Security Act to issue a NCD.

American Society of Clinical Oncology (ASCO)

Represented by Suanna Bruinooge, Assistant Director, Research Policy Cancer Policy and Clinical Affairs Department

- Research shows that the 2000 NCD has had a positive impact on enrollment, but the Proposed CRP may introduce new complications, leading to diminished enrollment of Medicare beneficiaries.
- Insurance coverage does not affect randomization and blinding.
- Lack of insurance coverage and uncertainty about insurance coverage are deterrents to patients' willingness to enroll in a clinical trial. Providing explicit insurance coverage for clinical trials participation makes it easier for oncologists to talk with their patients about clinical trials participation.
- While it is always beneficial for providers to receive payments in as timely a manner as possible, the timing of payment does not ultimately impact the quality of the evidence developed.
- Differing payment structures could affect the evidence base if they introduce disparities by unevenly affecting access, as might happen if the Proposed CRP were to result in decreased participation of the elderly. Differing payment structures could also affect the

evidence base if they differentially affect research models, as could occur in the context of CED.

Medical Device Manufacturers Association (MDMA)

Represented by Mark Leahey, Executive Director

Responding to CMS's Proposed CRP, MDMA requests that CMS instead issue an NRPM.

Should CMS finalize the CRP, it must:

- Clarify the definition of "usual patient care";
- Justify its reasoning before applying new coverage and coding requirements;
- Maintain deeming;
- Clarify the types of trial subject to the new policy;
- Clearly differentiate the IDE policy criteria and requirements from those of the new policy;
- Clarify billing requirements;
- Clarify self-certification requirements;
- Clarify the review process for self-certification statements, as well as the liability of sponsors, PIs, and providers if a trial is determined not to be covered;
- Implement an efficient review and notification process;
- Implement a clear and efficient transition plan; and
- Clarify Medicare secondary payer issues to ensure that trials sponsors are payers of last resort for complications and adverse events and thus improve enrollment rates for Medicare beneficiaries.

US Oncology, Inc.

Represented by Atul Dhir, MBBS, D. Phil, President, Cancer Research Services

- The payer should pay for costs of drugs and services in a study if those costs would be covered outside of the trial.
- Payers should cover standard of care costs in control and placebo arms of studies, in order to avoid creating a disincentive to enrollment. Furthermore, measures must be taken to address the possibility that co-pays and coinsurances could affect blinding if they differ by arm of study and thus result in patients knowing which drug they are receiving.
- The Proposed CRP will likely limit cancer trials to non-Medicare patients.
- Procedures for processing payment must be kept simple under the CRP in order to avoid creating barriers and disincentives.
- Differing payment structures could affect the evidence base by introducing confusion, the possibility of misbilling or misallocating sponsor funds, or barriers to participation.

Robert Reinhard, Member, Community Advisory Group, San Francisco Department of Public Health Research Section

- Payment policies should have a clear separation from study objectives or designs and evidence. Thus, Medicare policies should in no way introduce disparities, that is, unfairly exclude its beneficiaries from research for which they are eligible. At the same time, recruitment techniques should not confuse elimination of disparities with undue inducement to participate.
- It is important that Medicare provide timely payments, which provide the financial security and scheduling freedom that investigators require to conduct legitimate scientific inquiry.

University of Pittsburgh Medical Center – University of Pittsburgh Cancer Institute

Represented by Samuel Jacobs, MD, Associate Director for Clinical Investigations

- Beneficiaries of Medicare Advantage, the managed care option administered under contract by private insurance providers, face a financial disincentive to participate in clinical trials. CMS allows Medicare Advantage to cover clinical research-related expenses using a fee-for-service format, rather than adopt the coverage described in the NCD.
- In areas of the country where large percentages of Medicare beneficiaries participate in Medicare Advantage plans, the current coverage barrier severely and inequitably limits the number of patient accruals to important clinical trials. The current CMS coverage determination directly contributes to lower clinical trial participation rates by Medicare Advantage patients, virtually excluding this group from clinical trial participation.

Public Forum. Participants in the Public Forum on September 20, 2007, were individuals and representatives of organizations with a pre-existing strong interest in the topic of the impact of payment policy on clinical trials. These persons engaged in the event because they wished to contribute often strongly held views, perceptions, and experiences to the conversation. The town hall meeting format provided a venue for gathering these individuals' input, and an opportunity for these persons to air their experiences and opinions. No patients participated, although the "patient voice" was indirectly contributed by representatives from patient advocacy organizations.

Presentations. Speakers in the Public Forum were selected to provide a diverse array of input to the exploration of the impact of payment policy on clinical trial enrollment and retention.^{55,56} Certain common concerns, however, did emerge. Principal themes were the following:

- Currently, rates of participation in clinical trials are dismal. It is critical to improve participation rates in order to generate research results that are robust and generalizable to clinical populations at large.
- The extent to which third-party payment policies affect clinical trial enrollment, and even whether or not that influence exists, remains unclear.
- To date, there has been no quantitative assessment of the degree to which coverage may factor into patient considerations.
- Patient *perceptions* of their insurance coverage – whether or not those perceptions are based in reality – may nevertheless drive patient behavior with regard to clinical trial enrollment.
- Extension of reimbursement to cover new treatments *prior to the completion of clinical trials investigating those treatments* can inhibit the development of the evidence base by removing incentives for patients to enroll in clinical trials, and thereby slowing or halting the progress of research. For those interventions that later prove to be of no benefit, premature coverage can also result in unwarranted expenditures, widespread exposure of patients to unnecessary risk, and deleterious friction between industry, regulatory agencies, payers, and the public.
- Current CED policies may have unintended negative repercussions for clinical trial enrollment. Registries actually compete with clinical trials for participants, in that they

satisfy CED requirements while not advancing the evidence base being developed with data from RCTs.

- Certain types of studies – notably those enrolling participants at multiple sites, engaging multiple payers, or testing multiple interventions – may be disproportionately affected by the lack of consistency among payer policies and by policy changes that occur during trial conduct.
- Payer policies have not only failed to meaningfully mitigate disparities in clinical trial participation, but may, under certain conditions, actually encourage those disparities.
- Lack of communication among various policy bodies and investigative groups seems symptomatic of an inefficient, silo-style, system that stymies rather than encourages progress in medical research.

Summaries of Public Forum speakers' presentations.

Speaker #1: Placido Grino, MD

Title: National public forum on payment policy

To facilitate enrollment and retention, institutions, sponsors, funding agencies, investigators, and research staff must better understand the often intangible factors that influence a patient's refusal to participate or decision to abandon an ongoing clinical trial. In general, when deciding whether or not to participate in a clinical trial, patients seem willing to endure some degree of risk and the possibility that there will be no benefit, but they balk if there is the possibility, whether perceived or real, for penalty or additional burden. Patients' fears or concerns often relate to study costs and treatment coverage policies. These fears include: Medicare may refuse benefits for medical care because Medicare claims that medical care is encompassed in the trial; Medicare may refuse to pay for a subsequent condition because Medicare claims that the condition arose as a complication associated with participation in the clinical trial; Medicare's coverage of treatments while the patient is on-trial may prevent Medicare from covering additional items in the future (off-trial); and, at the end of the study, the patient may be left responsible for medical bills which the sponsor refuses to pay. There is no quantitative assessment of how often these concerns play a critical role in patients' decisions to participate or to prematurely discontinue participation in a study. Better understanding of factors influencing clinical trial participation would assist in the development of payment policies that are easily applied, unambiguous, broadly communicated across the healthcare and research environments, and included in study consent forms to educate and reassure clinical trial participants.

Speaker #2: Cary P. Gross, MD

**Title: The impact of third party payment policies on trial enrollment:
What does the evidence say?**

Cancer trial enrollment is clearly inadequate, with overall low rates of participation further complicated by racial, ethnic, and age disparities.⁵⁷ To address barriers introduced by the incremental costs of trial enrollment, the June 2000 mandate required Medicare to reimburse for costs associated with clinical trial participation. A study of 23 NCI-sponsored clinical trials that recruited patients both before and after this policy change found no substantial increase in enrollment among the elderly following implementation of the policy change.⁴² A study comparing enrollment patterns in states with a coverage mandate, to those without, demonstrated no difference between phase III studies; among phase II trials there was a slight upward trend in enrollment in states with coverage.⁵⁸

Overall, in making participation decisions, patients tend to be more concerned with quality-of-life issues, the possibility of getting a placebo, and potential side effects than with coverage. In fact, coverage ranks among the least influential factors; only 15% of patients or potential participants cited payment policies as a concern.⁵⁹ Evidence does not support a major role of payer policy changes in enhancing enrollment in clinical trials. However, given that payers benefit immensely from trials-based evidence, Medicare should consider streamlining paperwork, reducing administrative burdens, and clarifying regulations in policy adjustments.

Speaker #3: Lori Williams, DSN, RN, OCN, AOCN

Title: Insurance coverage for clinical trials: Patient and ethical perspectives

Field experience in recruiting patients can be considered a form of qualitative research. From that perspective, the following factors have been observed to influence patient decisions to participate in a trial: one's perception of the importance of clinical trials; whether or not one believes that the treatment will be as effective as or more effective than the standard of care; one's willingness to accept potential side effects; and one's concerns about the extra burden of cost, whether direct or indirect, that may be associated with trial participation. Offering insurance coverage only available in the context of a clinical trial raises questions about coercion versus voluntary participation. This payment structure can complicate enrollment (e.g., patients may withdraw if they don't get randomized according to their preference), skew results (e.g., participants may not report side effects for fear of being removed from the trial and thus from treatment), and make treatment preferentially available to only those patients who meet study eligibility criteria, which may serve to increase disparities.

Speaker #4: Lance Dworkin, MD

Title: Challenges in the conduct of clinical trials: Lessons from the CORAL trial

Enrollment of patients to clinical trials is typically the Achilles heel of research. The CORAL (Cardiovascular Outcomes in Renal Atherosclerosis Disease) trial is designed to compare the medical therapy alone medical therapy plus renal stenting and angioplasty for treatment of atherosclerotic renal artery stenosis. This condition affects about up to 4 million patients in the US, including 7% of the elderly population.⁶⁰ CORAL is a major NIH-funded trial with an expected budget exceeding \$30 million. Approximately 35,000 renal stenosis procedures are performed annually, but CORAL attracted only 180 patients over the course of a year, representing only 0.5% (1 out of 200) of all procedures. The recruitment rate falls far short of the targeted number of 1,100 participants.

One reason for slow enrollment may be that renal stenting, despite lack of evidence regarding its efficacy, is currently reimbursed outside of clinical trials. Requiring trial participation for coverage may encourage enrollment.

However, current Medicare policy complicates matters in that it allows registries to satisfy the requirement for clinical trial participation; registries, however, do not generate rigorous scientific evidence that allows determination of the relative utility of a particular therapy (all registry patients receive treatment, with no control group). Registries create important repositories of data for observational studies, but they cannot substitute for well-designed RCTs, and they may hinder enrollment in RCTs. If patients can get coverage for a procedure by signing for a registry, this option may be preferable to participating in an RCT because registries do not require long-term participation, and they guarantee that the patient receives the procedure. Physicians have a financial disincentive for referring patients to RCTs: they receive reimbursement only 50% of the time (when the patient is randomized to the procedure under study, assuming 1:1 randomization), whereas they receive payment for every patient they direct toward a registry.

The FDA currently mandates registries for renal artery stenting devices for which companies are seeking approval. The typical endpoint in these registries is restenosis rate; by contrast, RCTs seek to establish whether a stent is associated with a lower restenosis rate than historical controls or patients receiving medical therapy, with an acceptable complication rate. Registries have enabled development of Clinical Practice Guidelines even in settings where there is a lack of convincing evidence from RCTs⁶¹; but, Clinical Practice Guidelines based on observational data may increase cost without improving patient outcomes⁶², further impede the implementation of RCTs, and result in turmoil when subsequent RCTs contradict the guidelines.⁶³ NIH, CMS, and the FDA should therefore work collaboratively to encourage, at the policy level, the performance of RCTs for investigating unproven therapies.

Speaker #5: Daniel Martin, MD

Title: Comparison of AMD Treatment Trials (CATT): Lucentis-Avastin trial

In July 2005, the monoclonal antibodies Lucentis (ranibizumab) and Avastin (bevacizumab) caught the attention of researchers and clinicians, both drugs having demonstrated unprecedented efficacy in the treatment of age-related macular degeneration (AMD). In June, 2006, the FDA approved Lucentis for AMD, while evidence for Avastin remained observational. Clinicians faced a dilemma: Avastin appeared to be superior in effect, faster-acting, feasible on an as-needed basis, and less costly. Anecdotal evidence suggested that Lucentis might also be effective and require less-frequent dosing in some populations; FDA approval was based on trial data derived from a specific dosing protocol that involved intravitreal injections every four weeks for two years. The NIH-funded CATT (Comparison of Age-Related Macular Degeneration Treatment Trials) was designed to determine the efficacy and safety of Avastin versus Lucentis; it had a \$50 million budget. The sponsor covered costs of Avastin, but not the \$22-25 million cost of Lucentis. CMS could not legally pay 80% of those costs without changes to the Medicare CTP. Despite the fact that Lucentis was already approved for AMD and that existing policy mandated coverage for routine costs of care, Lucentis was nevertheless deemed investigational in this context. This trial thus became an important stimulus for the Proposed CRP, anticipating that the changes would allow the CATT trial to proceed, with the Avastin budget covered by NIH and the Lucentis budget covered by third-party payers including CMS.

Billing practices posed a threat to double masking (a.k.a. double-blinding; hiding which intervention that the patient received from both the patient and researchers in order to reduce biased measurements in the study). Billing could unmask patients in three ways: Patients might notice differing co-pay amounts (\$400 for Lucentis vs. \$10 for Avastin); Medicare patients might see their drug billed and named on the Medicare Summary Notice; and, 85% of Medicare beneficiaries have a supplemental policy, and these patients receive a statement that identifies the drug and amount paid. To preserve masking, an initial cash outlay of \$25 million was needed to centrally purchase drug. A demonstration design was proposed, in which CMS payment would mimic a research grant, paying up front for purchase and distribution of study drugs, enabling central record keeping of drugs distributed in the trial, and eliminating patient billing for drug injections. This process would support head-to-head comparisons of covered drugs.

Despite full CMS support and full funding, HHS did not approve the project because “it was so obvious that the demonstration project would improve the quality of the clinical trial and Medicare beneficiaries participation in it that we did not need to do the project to prove it.” Dr. Martin offered his view that CMS is limited by an inflexible and inefficient system, with no culture of communication with outside investigative groups, and with OGC/HHS making unilateral decisions and offering no opportunity for discussion. He suggests that CMS provide up-front funding for drugs in a clinical trial if it is cost-neutral to CMS and if CMS deems it is in the public’s best interest to do so.

Speaker #6: Neil Bressler, MD

Title: Payment policies' impact on clinical trials participation

The Submacular Surgery Trials comprised three different trials that, given median ages that ranged from 48 to 79, involved a variety of payers. The investigators assumed that subjects and their third-party payers would cover the costs of standard care, which included the surgical procedures involved in each of the subtrials. To ensure inclusion of uninsured and underinsured patients, the study specified that investigators would manage such patients as they would any patient with financial hardship, usually, by waiving patient liability for most or all standard-care costs. Prior to study initiation, the National Eye Institute and each clinical center agreed to share the expense of covering these patients. This system introduced certain challenges, including how to handle changes of insurance that might take place during the trial and/or disproportionately affect certain centers, and how to address costs that might be out of the investigator's control (e.g., anesthesia, facilities).

The Diabetic Retinopathy Clinical Research Network, established to facilitate investigations in the field, has carried forward these efforts to proactively and rationally address payment issues in clinical trials. Issues include: the variety of payer policies, the large number of uninsured patients, unmasking due to billing practices, and different combinations of therapies administered – all of which add up to strikingly inconsistent per-patient costs, uneven cost-sharing with clinical centers, and an unwieldy process for securing coverage. The Network recommends the provision of clear payment schedules (study budget vs. standard care) at study onset, as well as the provision of central case management with consistent guidelines and policies.

Speaker #7: Walter Koroshetz, MD

Title: Third-party payment: Effect on clinical trials and evidence base

Gaps in the available medical evidence can have profound systemic consequences. For example, extracranial-intracranial bypass surgery, an unproven and extremely dangerous procedure, became common practice to address ischemic cerebrovascular disease of the carotid artery; this surgery was performed on thousands of patients and received Medicare coverage for years before research demonstrated no benefit.^{64,65} Coverage made it extremely difficult to enroll patients in the research studies necessary to examine benefit vs. harm.

Mechanical closure of the patent foramen ovale (PFO), an opening between the left and the right side of the heart, has been considered attractive but controversial as a preventative measure for stroke. Until recently, clinical trials encountered prohibitive recruitment problems because the PFO procedure was eligible for reimbursement since the FDA had granted a Humanitarian Device Exemption (HDE; an Humanitarian Use Device is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the U.S. annually; the HDE application, submitted to FDA, is similar in both form and content to a premarket approval application, but is exempt from the effectiveness requirements of a premarket approval application). Rather than accept the possibility of being randomized to a control arm, most patients opted to simply undergo the procedure off-trial, despite the lack of evidence. Eventually, to address the research conduct conundrum, the FDA nullified the exemption.

Another example is carotid artery stenting (CAS), which has gained attention as an attractive alternative to carotid endarterectomy (CEA), a risky but approved surgical procedure whose effectiveness is unknown due to its spread outside of the trial setting. CAS is a non-invasive procedure that early research shows to be at least equivalent to CEA in treating symptomatic patients. Evidence that CAS benefits asymptomatic patients is lacking; in fact, for these patients, risks associated with CAS may exceed recommended limits. CMS has been under tremendous pressure to approve the procedure for both symptomatic and asymptomatic patients. The situation involves unusually intense competition for patients, as CAS can be performed by non-surgical specialists. The NIH-funded CREST trial, which compares CEA to CAS, has been hindered by the registry mechanism for obtaining coverage. Premature CMS approval would further preclude successful recruitment.

Dr. Koroshetz suggested that CMS, FDA, and NIH should coordinate processes to prevent major public health hazard due to premature approval of devices and drugs. NIH clinical trials should be responsive to the needs of public as reflected by proposals in front of CMS and FDA; the FDA and CMS should be responsive to the recruitment needs of NIH trials.

Dr. Koroshetz also noted other concerns: coverage for registry participants is slowing enrollment in clinical trials; potential regional differences in coverage for trials negate the goal of a national CRP and complicate larger trials; and the self-certification requirement creates an imbalance between self-certified trials and NIH-funded trials, increases trial burden by requiring duplicate certification for both NIH and CMS, and may have a significant impact on the CMS budget by funneling funds into trials of low medical value.

Speaker #8: Armin Weinberg, PhD

Title: Eliminating Disparities in Clinical Trials (EDICT) Project

EDICT's goal is to develop practical and implementable policy solutions to recruiting and retaining populations that are underrepresented in clinical trials. The elderly, in particular, account for nearly 2/3 of all cancer patients, but less than 1/3 of clinical trial enrollees. The data obtained from clinical trials enrolling younger patients may fail to reflect the diverse effects of aging, co-morbidities, and pharmacokinetic differences in metabolism and treatment efficacy. Although the NIH Revitalization Act requires and FDA guidelines recommend inclusion of underrepresented populations, federal initiatives have failed to prevent widespread disparities in clinical trials.⁶⁶ More than a decade after the passage of the Revitalization Act, one group of researchers concluded that "certain populations are still underrepresented in cancer-related trials, including minorities, older adults, adolescents, rural populations and individuals of low SES."⁶⁷

Reasons for uneven enrollment and retention include the following:

- The NIH Revitalization Act applies only to federally funded studies, but 80% of trials are industry-funded.
- NIH does not require investigators to report rates of retention.
- It is difficult for CMS to see a return on investment if retention is unknown.
- IRBs spend most the predominance of their resources on initial, not continuing, reviews.
- FDA guidelines are not compulsory.

To directly address disparities, EDICT has proposed revisions to the CMS CTP that address widespread coverage and reimbursement concerns among underrepresented populations which may discourage clinical trial participation. EDICT recommends that study protocols be required (1) to explicitly discuss subpopulations affected by the treatment under investigation; (2) to address how inclusion and exclusion criteria may affect enrollment of these populations; (3) to provide a plan for the retention and reporting of said populations; and (4) to explain, if the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, why these criteria are necessary.

Question-and-answer sessions. Individuals participating via telephone were invited to use a central call line to pose questions. Questions were fielded at the end of each block of presentations, i.e., after speakers 1-3, 4 and 5, and 6-8.

The question-and-answer sessions elicited a variety of concerns and recommendations. The most frequently raised concern surrounded the clinical trial policy and proposed revision. Callers generally agreed that, although there is little quantitative data available to evaluate whether payment policies affect clinical trial enrollment, observational and qualitative data nonetheless provide important background to consideration of this issue. There was also general agreement on the perception that when a treatment is reimbursed prior to evidence development, trial enrollment becomes more difficult and delivery of unwarranted therapies may result. Ethical concerns associated with CED were raised.

The discussion suggested that consideration of the impact of payment policy on clinical trials should take into account an array of related factors: the role of the physician; disparities; timing of reimbursement; interaction of policies of multiple regulatory agencies; and differential effects

of different trial structures, diseases, patient populations, and therapeutic categories. Additionally, participants noted the following issues as important to future discussions surrounding payment policy for clinical trials:

- Definitions of standard of care versus experimental care or investigational procedures;
- Conflicts arising when funds are requested from sources other than the trial sponsor;
- Ways to minimize the institutional burden of implementing viable cost structures;
- Standardization of levels of evidence across HHS agencies, which is especially important when two or more federal agencies share responsibility for costs of a study;
- Difficulty in determining what adverse events are attributable to the trial, and thus to assign liability for subsequent healthcare costs.

Overall, town-hall participants emphasized the need for better coordination between the various regulatory agencies and for simplification, standardization, and/or centralization of payment policies and structures, but they remained uncertain about how to cultivate these changes.

Specific points made through in-person or call-in participation were the following:

- Physicians hesitate to suggest trial participation to patients who have Medicare Advantage coverage, which they know will not cover routine costs of care in the context of a trial.
- Medicare Advantage penetration is particularly high in disparity communities, which leads to a disproportionately low rate of accrual among patients in those communities.
- The degree of success in recruiting any individual patient seems to be directly proportional to how much time the physician invests in explaining the purpose and benefits of the trial.
- Physicians play a key role in influencing patients with regard to trial participation. But physicians who have a substantial investment in an FDA-approved technology and who receive CMS reimbursement for approved therapies may therefore have a strong disincentive, perhaps unknown to their patients, from encouraging participation in clinical trials evaluating those treatments. This conflict of interest may also be intensified when physicians receive better payment for using their preferred technology.
- When a treatment is available outside a trial that studies it, that trial is likely to falter. In the meantime, many patients may receive a treatment that later proves to be of no benefit.
- Contrary to the study mentioned by Dr. Gross, a study by Joseph Unger and colleagues demonstrated that Medicare's 2000 CTP had a positive impact on enrollment of elderly patients.⁴³ That increase was most notable among those who had supplemental insurance coverage, which suggests that patient costs associated with participation do affect a patient's ability to participate in a trial.
- Simple before-and-after enrollment statistics may fail to reflect complexities, such as differences between types of cancer or the timing of study onset, and thus to give a full picture of policy impact. Payment policy may indeed have a role to play along these lines, but there is no evidence that Medicare's coverage policy, as it is currently written, has had a meaningful positive effect on eliminating disparities.

- As CMS considers the issue of third-party payment policies, it should take into account how to coordinate with the FDA's 2006 proposed rule regarding the criteria for charging for investigational drugs.
- Patient decisions on whether or not to participate in a clinical trial are often made before the consent process begins; research must therefore incorporate information gathered during the stage when the patient is being evaluated by the healthcare provider.
- Rifts can occur when funding must be provided by an entity that does not play a sponsoring role for a study and had no role in design of the study.
- In areas such as stenting, the practice behavior and opinions of the physician often determine whether referral, recruitment, and enrollment occur, and/or influence the patient's decision-making regarding clinical trial participation.
- Difficulty in differentiating standard of care (covered by third-party payers) from experimental care (covered by the study) must be done on a case-by-case basis, incurs huge institutional costs, and adds to burden and pressure on investigators. Automation of these cost structures, particularly by agencies like CMS, could eliminate the structural and cost inefficiencies of manual, case-by-case decision making.
- To fully ameliorate patient concerns regarding coverage, even liability for adverse events must be clearly defined for patients entering a trial.
- Although coercion has been raised as a potential ethical conflict associated with restricting coverage to trial participants, patients seeking access to the therapy via a clinical trial do sign a consent form that explains randomization. If such a conflict does exist, it may be a lesser ethical concern than that of coverage without evidence, which could encourage the propagation of ineffective or even harmful treatments.
- Over the last 18 months, two separate publications, including one by the NIH, addressed the ethics of requiring trial participation for coverage. Both concluded that no ethical issue existed.

One email was received in follow-up to the Public Forum. This email raised the issue of Medicare HMOs charging a 20% co-payment for beneficiaries who choose to participate in clinical trials, whereas co-pays are not charged to patients who opt for "standard" treatment. "NCI grantees tell us that as a consequence patients are still declining in droves to enroll in clinical trials." This policy significantly inhibits overall enrollment, and also tends to promote disparities, as HMOs are especially popular among minorities and the less affluent.

Discussion. The September 20, 2007, Public Forum was successful in generating public comment from interested parties with relevant experience, provided insights into the locus of impact, and engaged participants in discussion of how this impact has played out in actual research settings. It was clear from this event that a valid issue does exist surrounding the impact of payment policy on clinical trials participation, but that the magnitude and extent of this impact are difficult to quantify. Several trials present case studies in this impact, but cannot elucidate whether or to what degree other, less prominent, clinical trials have encountered similar difficulties. Public Forum participants also helped to flesh out the complexity of this issue with considerations such as the ethics of restricting coverage to those on clinical trials, the challenge of differentiating standard of care from investigational treatment in order to determine

reimbursable costs, the impact of payment policies on physicians and thereafter indirectly on patients whose decisions they influence, and the role of payment policies in disparities in clinical trial participation.

Limitations. As a mechanism for soliciting information from a broad array of perspectives on this topic, the Public Forum had both strengths and weaknesses. More, and broader, participation might have been generated by earlier announcement of the event, and through use of additional informational channels to advertise it. Although participants were self-selected, bias nonetheless may have existed in that individuals motivated to engage in the Public Forum disproportionately represented certain interests, disciplines, and disease areas (see below). The call-in mechanism did elicit some participation, but could perhaps have been more widely promoted in order to obtain input from, for example, clinical trials coordinators who might not have the work flexibility or resources to travel to Baltimore but might, nonetheless, have valuable on-the-ground experiences to contribute.

Although the CMS facility was very adequate for this event, and the conference audio technology worked fairly smoothly, the setting may have served as a deterrent to broad public participation. The location and tight security measures on the CMS campus could conceivably have functioned as a barrier to engagement, for those not familiar or comfortable with CMS itself and its procedures.

Among presenters and call-in participants, there was a skew toward experience of clinical trials in the areas of cardiovascular disease, ophthalmology, and cancer, and with a subset having a strong interest in macular degeneration; this is likely representative of Medicare beneficiaries' healthcare concerns and of where the preponderance of payment policies' impact has been felt. Small and industry-sponsored trials were under-represented.

The conversational format was conducive to consideration of various viewpoints, but logistics of physical attendance and gaps in awareness of the event may limit participation. This framework was best for gathering input in the form of reports on experiences, rather than for stimulating on-the-spot discussion. The relatively short timeframe meant that unfiltered input with minimal response to that input allowed a maximum volume of experiences to be heard.

Strategy 4: Key Informant Teleconferences

Purpose. A series of teleconferences was conducted to solicit input from diverse participants who represented various perspectives and levels of involvement with clinical trials: investigators, study coordinators, administrators, government agencies, private sector third-party payers, NIH, industry, and patient advocates.

Methods.

Participants. The original study design called for approximately eight teleconferences, each of which convened a small group of nine or fewer key informants, grouped according to category of affiliation. Participants within each of the following five categories of affiliation were selected:

- 1) Decision-makers/policy-makers who influence the level and timing of payment at the national level. This category included representatives from the CMS, and other third-party payers.
- 2) Decision-makers/policy-makers who have observed the impact of payment decisions on specific clinical trials. This category included representatives from the FDA and NIH as well as industries that produce devices and agents involved in studies identified as actually or potentially impacted by, or vulnerable to the impact of, payment policy.
- 3) Patient advocates who can comment on the impact of payment or coverage decisions at the patient level, including patient decision-making to remain in or enroll in clinical trials.
- 4) Clinical research investigators whose studies may have been impacted by payment or coverage decisions, including studies where third party reimbursement occurred for use of a drug or device for an off-labeled indication outside of the clinical trials setting.
- 5) Clinical trial coordinators and administrators who are responsible for the day-to-day conduct of studies. Individuals comprising this category occupy a position from which to directly observe the impact of payment or coverage decisions on trial participants' decisions and, in the case of study coordinators, on the conduct of clinical trials.

Through consultation with the Advisory Panel, CMS, and AHRQ, we prepared a preliminary list of clinical trials whose enrollment may have been impacted by payment policies (see Appendix D: Preliminary List of Clinical Trials). We sought to identify clinical trials that either terminated early or ran into conduct-of-trial issues when third-party payment became an option for participants or potential participants, and clinical trials that were recruiting participants to a study in which the drugs and/or devices being studied were already covered by third-party payers outside of the clinical trial. The Principal Investigators and study personnel of these clinical trials, representing potential key informants, were contacted to ascertain their willingness to participate in a study teleconference.

The original proposal described a process in which a first round of teleconferences would provide further information, identify potential key informants, and define avenues of discussion that would help to refine the agenda for a second round of teleconferences. We expected that participants in the first round of teleconferences would direct us toward clinical trials that faced

challenges in accrual, experienced delays in study conduct, or terminated early due to payment policy issues. Information gathered from first-round participants was intended to be used in targeting and approaching second-round participants.

Original format. Teleconferences were planned to last approximately one hour, and were audiotaped. Participants provided verbal consent at the outset of each session, and answered a question as to whether or not they wished to remain anonymous or to be identified in this final report. According to the originally proposed format, a total of 40 key informants were to attend these teleconferences: 20 in round one and 20 in round two. Round one participants, drawn from Categories 1-3, were to comprise four participants from each of the following main affiliations: CMS, FDA, NIH, pharmaceutical and device industries, other (non-CMS) third-party payers, and patient advocacy. Round two participants were to comprise approximately 10 participants who were principal investigators (Category 4) and approximately ten who were clinical trial coordinators (Category 5). If numbers permitted, participants in the teleconferences were to be divided by medical discipline (e.g., cardiology, cancer, surgical procedures) to ensure that conversations held relevance for all participants. This methodology was designed to ensure that each participant was provided adequate opportunity to participate, and to facilitate cross-fertilization in the course of the discussion.

This format was approved by the Duke University Health System IRB. At the beginning of each teleconference, a verbal consent form was read. The verbal consent form included a description of the project and spelled out important risks such as loss of confidentiality and personal liability for statements provided. Participants were then asked for their consent to participate and whether or not they were willing to be named in the white paper or preferred to be listed as an anonymous key informant. The entire process required approximately seven to ten minutes. Key informants were advised that the information they disclosed might become part of the public record, and that they should contribute only information which they were willing to share publicly. Participants were informed that the teleconferences were audio-taped.

Revised format. One teleconference was conducted using the format described above, but open discussion during the teleconference was minimal, with key informants providing information in a guarded manner. Participants were reluctant to openly discuss the questions raised, and were especially apprehensive with regard to mentioning specific experiences, examples, or trials. Following this teleconference, we explored what factors might have constrained participation. There was a general agreement that concerns about confidentiality and/or anonymity within the group setting, and possibly the consenting process itself, were the primary forces inhibiting first-round participants from full participation. We therefore decided to change the teleconference strategy in order to maximize the amount of information we might gather through this mechanism. We abandoned the original small-group format in favor of individual teleconferences, in which conference calls engaged one key informant per call, and in which a Duke investigator, the staff assistant responsible for audio-recording the conversation, and a medical writer were the only other persons on the call with the key informant. Individualized teleconferences maintained the same basic structure, format, and content as originally proposed. The consenting process did not change, and the IRB-approved protocol did not require modification since it covered both group and individual teleconferences.

Teleconference agenda. Each teleconference was facilitated by one of the study investigators according to a predetermined, IRB-approved agenda. To manage each teleconference, the facilitator:

1. Introduced the study and summarized its objectives and design;
2. Defined the purpose of the teleconference and its significance within the study context;
3. Described the structure and agenda of the teleconference;
4. Read the oral informed consent and obtained verbal consent (see Appendix F: Teleconference Script for Obtaining Oral Consent);
5. Initiated the conversation with an open-ended question;
6. Posed additional leading questions as warranted to gather further detail, steer the conversation back toward the specific topic when needed and explored new ideas/concepts related to the topic when they arose.

Due to the exploratory nature of this project, the teleconference format was intended to remain flexible, using open-ended questions rather than highly specific or directed ones. An agenda of initial topics was developed to catalyze the discussions, but we expected to modify and expand on this original set of topics as new information emerged and our knowledge base expanded. The content of the discussions was also to be iteratively shaped by input from the literature search, by Advisory Panel, AHRQ, and CMS suggestion, and from information gained through preceding teleconferences. We were also prepared to discuss ethical, economic, and decision-making aspects of the conduct of clinical trials during these conference calls, in the interest of identifying broader issues that bear on payment policy and clinical trial enrollment processes.

Data collection and management. Data from the teleconferences were managed as follows: (1) Each teleconference was digitally audio-recorded. Participants were informed that their input was being recorded, but that audiotapes were intended to facilitate production of the white paper only and would not become part of the public record. Digital audio files (.wav format) were stored on a confidential shared drive maintained by the Duke Center for Clinical Policy and Research and were not given to CMS or AHRQ. Files will be erased six years after study completion. (2) Teleconference input was also recorded by the Study Coordinator and Writer/Editor, and Call Facilitator in the form of typed notes, which were used in the preparation of this report. Electronic files associated with the report will be stored on the shared drive for six years, after which they will be destroyed. (3) Data collected via the teleconferences will be presented to AHRQ/CMS in a single format – a white paper – and will not be presented to additional third party payers or to the public through other written or oral channels without prior AHRQ/CMS approval. While specific statements have not been attributed to specific key informants, a list of all informants has been provided (except when informants preferred to remain anonymous). (4) Prior to the publication of this paper, all study investigators and key personnel thoroughly reviewed content for accuracy and protection of participants’ confidentiality.

Results. One hundred and one (101) individuals were identified through Advisory Panel suggestion, literature search, Public Forum, professional networks, and suggestions of

individuals who participated in teleconferences. All 101 of these persons were contacted by phone or through e-mail to participate in a teleconference. Seventy-four (73%) of these potential key informants declined to participate, or believed they were not in possession of the information we were seeking and gave us additional names to contact. The most frequent reasons cited for nonparticipation were the following:

- Because the study with which they had experienced payment policy issues took place some years ago, they expected that they would not be able to recall useful information.
- Because their institution handled all financial interactions with patients, they felt that they would not have the necessary information to substantively contribute.
- Because they, themselves, did not handle payments and consents for the study in question, they felt that they were not the appropriate person to participate.
- Because participation in this project would require managerial permission, and they preferred not to request this permission.
- Because they generally did not believe that they were "the right person" to answer the proposed questions.

A total of 20 teleconferences were conducted over a six-month period. The 26 key informants in these teleconferences represented the FDA (4), NIH (3), IOM (1), industry (5), third-party payers including CMS (3), and were patient advocates (4), principal investigators (3), and other research staff, primarily clinical trial coordinators (4). (NOTE: One individual had experience in two domains.)

Key points that emerged during the course of the teleconferences were the following:

- No method currently exists for collecting information prospectively or retrospectively on the topic of payment policies' influence on clinical trial participation.
- The impact of payment policy on completion of clinical trials is unknown. Reasons for study termination or delays in study completion are not typically collected. There are many reasons for difficulty in enrolling patients in clinical trials, and it is often not possible to tease these apart.
- The impact of payment policy may differ depending upon the insurance status of study participants/potential participants (private insurance, uninsured, Medicare, etc.).
- The impact of payment policy may differ depending on the specific policies established by third-party payers.
- The payment policy issue may be integrally related to issues of equity, particularly that of ensuring all patients have access to clinical trials if they desire to participate.
- Payment policy seems to have less impact on accrual/completion of early-phase clinical trials. Sponsors and sites appear to be attempting to better delineate costs associated with research up front.
- For later-phase research – notably comparative effectiveness of existing therapies and studies of off-label uses of approved therapies – the impact of payment policy may be greater, but is not well defined. No entity assumes full responsibility for research costs, and plans to co-share expenses are in their infancy. Thus, in areas lacking sufficient evidence, especially regarding products that are already on the market, there is currently no consensus on who should pay for the evidence-generating research.

- A trend in clinical trials is toward greater investment of up-front time and effort on the part of sponsors and sites to determine the economic viability of a study prior to initiation. Some research may never be undertaken because the economic prospects are not attractive. Payment policy may be a factor in these decisions, though data on the presence and extent of this issue are not available.
- In addition to potentially complicating clinical trial enrollment, third-party payment structures challenge the conduct of clinical trials in other ways. For example, unblinding of study arm assignment, to enable reimbursement of participants in one arm, can jeopardize the integrity of the study results.
- Sponsors, patient advocates, and research sites typically believe that consent forms provide sufficient information on third-party reimbursement, sponsor responsibility, and patient responsibility, and thus patients are provided with enough relevant financial information to make informed decisions.
- The impact of payment policy on clinical trial participation, and on the conduct of clinical research more generally, may vary considerably depending on the specific disease, type of treatment, demographics of the clinical population, and other variables. Therefore, the impact of payment policy on clinical trial completion may be highly variable.
- The difference in evidence requirements for devices versus drugs causes payment policy (based on evidence) to have a disproportionate impact on device trials. Essentially, since devices can secure approval with less robust evidence than is required of drugs, and since reimbursement typically hinges upon approval, device trials more than drug trials have a difficult time accruing patients because patients often can already obtain reimbursement for the device off-trial. Registries compound the problem for both device studies and drug studies, though again the burden on device trials may be heavier.
- The lack of coordination among federal agencies, and among all entities involved in payment for clinical trials may be a significant factor in the impact of payment policy on clinical trial completion. Coordination and communication is difficult due to the agencies' differing missions and views of their roles. For example, a marketed drug may receive coverage by CMS for an indication for which it does not have FDA approval.

Categories 1 through 3. This group consisted of twenty representatives of various government agencies, third-party payers, industry and patient advocacy groups. Included in this group were key informants who participated in the original small-group teleconference (Category 1 and 2 key informants) and those who participated in the subsequent individual-conference format (Category 1 through 3 key informants). For purposes of this report we will report results from the small group teleconferences separate from those obtained from the individual teleconferences.

Small Group Teleconference (Category 1 and 2 key informants). Key informants on this conference call were hesitant to openly discuss specific examples. The main items raised by this group are summarized below.

1) One example cited by the group which was thought relevant to the study topic dealt with the issue of equity in clinical research and processes to reduce disparities. One multi-center study encountered difficulties when it proposed to offer free care to uninsured participants while asking Medicare to cover the routine care costs of study participants who were Medicare beneficiaries. Study administrators were informed that this approach constitutes Medicare fraud. This policy not only impeded recruitment of uninsured patients, who were largely minorities, but did so differentially across trial centers.

2) In payment policy discussions, clinical trials and demonstration trials should be distinguished from each other, as rules and regulations governing demonstrations are more stringent than for clinical trials. Medicare demonstration studies, which are almost invariably conducted by CMS, have a broader set of purposes, are often congressionally mandated, and often lack features of a clinical trial, such as randomization and control arms.

3) Medicare's payment policy did have an impact on recruitment for one post-approval registry study. A device company had been struggling with enrollment in the registry and had hoped that a decision by CMS to provide reimbursement for participants enrolled in the registry would facilitate accrual. However, the reimbursement decision by CMS did not link reimbursement with enrollment in the registry. It was felt that this decision led to difficulties in enrollment in the registry and ultimately led to a request by the device company to lower the number of subjects enrolled in the registry.

4) CMS reimbursement policy sometimes helps to augment registries. CED stipulates coverage for patients who enroll in registries for FDA-mandated post-approval studies. This proviso has given companies an incentive to present large-scale registries to the FDA, whereas they formerly had little interest in developing registries.

5) In situations where several therapeutic options exist, including marketed devices approved for other indications, payment policy may have substantial impact on the generation of needed evidence. An example of a study to evaluate use of a device for tumor ablation where clinicians were already using the device off-label for this indication (without evidence) was cited.

At the conclusion of the teleconference, participants offered specific recommendations.

- Payment policy should make allowances to facilitate access for uninsured patients who wish to participate in clinical trials.
- Measures should be taken to allow CMS, sponsors, and other government agencies to more easily collaborate on studies that are in their mutual interest. To date, funding and sponsorship agreements between CMS and NIH have faltered on privacy issues and conflicting regulations.
- Better processes of cooperation could enable up-front, cross-agency efforts to jointly address questions of interest to more than one agency and to bridge the different institutional cultures and perspectives on research vs. regulation.
- A common understanding of what the data gaps are could facilitate discussion, wherein parties with different perspectives come together to brainstorm about how best to fill those gaps. To clarify the data gaps, however, one must assess the entire care path, rather than focusing on single treatments in single settings.

Following the group teleconference, the study design was altered such that input from remaining key informants was gathered through individual teleconferences rather than group teleconferences. As described above, this change was instituted in order to provide a more confidential environment in which participants could offer opinions, personal experiences, and potentially sensitive information. Main points from these teleconferences are summarized for Categories 1-3 and for Categories 4-5 in the tables below. Affiliations of key informants appear in Appendix G: Key Informants. All key informants were given the option to remain anonymous; names are listed only for those key informants who explicitly agreed to have their identity disclosed.

Table 4: Key Informants – Category 1-3

MAIN POINTS

- Sites and patients both consider reimbursement factors when deciding whether to run, or to participate in, a clinical trial. With sites, this is increasingly the case in oncology.
- Study sites do not all have a sound understanding of Medicare policies for reimbursement when patients are enrolled in clinical trials. Education on this topic for both sites and patients would help.
- Physicians may be gate-keeping for their patients, i.e., considering what participation in a clinical trial would cost the patient, and then presenting or not presenting the option to the patient based on that assessment.
- Difficulties with recruitment increasingly cause trials to need multiple sites to reach enrollment targets. The number of sites per trial has increased for trials at all phases. Sponsors hear more and more sites raising reimbursement as an issue impeding enrollment.
- Sponsors first assess a study in terms of scientific design, and then in terms of financial viability. An increasing number of studies are not being started due to concerns about the latter.
- Sponsors may not have a mechanism for tracking the extent of trial enrollment problems and whether or not they are related to issues with payment policy.
- Financial challenges are complicating the conduct of studies at US sites. These challenges include lack of funding for adequate staff at study sites, resulting in reluctance of some sites to participate in clinical trials and allowing their patients access to the study.
- Many sponsors will not even start a study if there is an anticipated barrier to reimbursement/funding for that study, but there are no data as to how many studies fail to happen for this reason. Trial design process now involves a “reimbursement analysis.”
- Within a government funded research facility, the issue surrounding third-party payment for clinical trial expenses was explored. In a survey, 23% of patients said that they would not participate in a clinical trial at this center if standard of care or non-research related expenses incurred in the course of trial participation were submitted to a third party for payment and 34% of the center’s faculty expressed that this type of change would impact their willingness to remain at the center.
- The number of studies being done is not declining, but the studies are taking longer to complete.
- Slower rates of enrollment mean slower rates of clinical trial completion, and correspondingly, generation of evidence is proceeding at a slower pace. This is more the case with government-funded studies, where a flat budget makes NIH less concerned about the timing of trial completion, than with industry-funded studies, where the sponsor is anxious to learn the result of the trial as soon as possible.
- Data resources, such as data from CMS are a rich resource for research and hypothesis generation and might provide an alternative to expensive clinical trials that are having difficulty with completion/recruitment.
- Reimbursement/payment policy issues may be very different for studies enrolling children than for studies enrolling adults.
- The processes for how health plans handle issues related to research need to be simplified; the current system is confusing and antiquated.
- One consideration is a “learning health care system” in which evidence of benefit is a prerequisite for payment. In this model, drugs may come to market sooner, but require that research data be collected as a contingency for use/marketing. Use in these situations could be “co-sponsored” by industry sponsors and third-party payers.
- Plans to establish “categories” of research for which coverage by Medicare and third-party payers would be provided (e.g., CED and research in areas where data are urgently needed) were mostly

halted by legal challenges.

- There are several ways in which a third-party payer can discern that a patient is participating in a clinical trial: provider may call for pre-authorization, identification through early claim that doesn't match standard therapy, or patient may call customer service with an inquiry about research participation.
- For many trials that are properly randomized and study an intervention that doesn't differ substantially from standard of care, a third-party payer may not know whether or not the patient is participating in a clinical trial.
- Specific policies on coverage, even within large national health insurance companies, may differ state-by-state and between companies.
- Insurers may not cover any "ancillary" services associated with a treatment provided as part of a research study, in part because it would be extremely difficult to go through the line-by-line costs in an attempt to separate these costs, even if they may be for standard of care, from the research study costs.
- Coverage decisions are made on the basis of efficacy and safety data. Third-party payers look for peer-reviewed, well-designed studies with sufficient sample size to show efficacy.
- Research studies evaluating treatments that are covered off-trial by third-party payers are difficult. In one example, a trial was expected to require three months to accrue subjects, but actually took two years. It was suggested that had access/coverage to the off-label treatment been limited to those patients who participated in the trial, accrual would presumably have occurred much more rapidly.
- There are substantial concerns regarding patient access to clinical trials, and the impact that reimbursement structures may have on that access. Unequal access to clinical trials leads to disparities in medical care.
- Patients have difficulty understanding what the costs to them will be if they participate in a trial; including uncertainties of whether they will be hit with unexpected bills at the end of the trial.
- Financial considerations add an additional access barrier, atop an already large burden of emotional distress and logistical stress, for patients considering participating in a trial.
- Better, more inclusive and/or higher paying, insurance policies will make individuals more willing to participate in clinical trials; more affluent individuals are more likely to have these sorts of policies; therefore, differential reimbursement across insurance policy types will potentially skew the demographics of clinical trial populations.
- There is a lack of clear, available resources for patients on issues related to payment/reimbursement when participating in clinical trials.
- Different reimbursement structures across third-party payers make it very difficult to determine what exactly will be paid when a patient is enrolled in a clinical trial.
- Payment policy is one among many factors influencing patients' participation in clinical trials.
- Many patients don't consider clinical trials because they are unaware of outside resources that can help them with the financial implications.
- Patient advocates can help patients to understand which costs, if they participate in a clinical trial, will be reimbursed and which ones will not be covered.
- Many patients follow the lead of their physicians, and will enroll in a clinical trial if their physician suggests it. However, many physicians do not talk with their patients about clinical trials at all.
- Third-party payment issues arise mostly in the context of federally-funded trials.
- Physicians often do not offer a clinical trial to a patient because they do not want to lose the patient to an academic center where the trial is being conducted, thus losing a portion of their revenue stream.
- Routine care for patients enrolled in clinical trials should be covered by third-party payers.
- The policy question is: if insurance barriers to clinical trial participation were removed, would

access to clinical trials improve and hence participation rise?

- A 1999 ASCO study found that cost to insurance carriers did not differ much when patients received standard of care vs. when they received care in the context of a clinical trial. [NOTE: the authors of this report could not verify this statement.]
- Physicians sometimes do not tell their patients about available clinical trials, if they know, or suspect, that the costs will not be covered.
- The lack of a definition of “standard of care” is a major problem. In the absence of such a definition, payers can pick and choose what they are going to reimburse.

Table 5: Key Informants – Categories 4-5.

MAIN POINTS

- Patients and study staff do not typically discuss reimbursement issues in detail, perhaps feeling that extensive discussions would “scare” the patient.
- One issue that is often unclear regarding payment policy for clinical trial participation is that of coverage for adverse effects incurred due to study participation. If the sponsor does not pay for this care, it is unclear whether or not third-party payers will cover it if the adverse effects resulted from study participation.
- There is a movement in the industry toward addressing reimbursement issues prior to accepting a study for conduct at the site.
- Difficulty in separating what is standard clinical care from what is research within a study makes it difficult to address the question of payment policy and clinical trial conduct.
- It is more likely that a payment policy issue would be addressed for trials involving a very expensive intervention (drug or device). For example, it would be more reasonable for sponsor, site, and patient to explore reimbursement of a single “big ticket” expense rather than smaller ones.
- Although there is much confusion and misunderstanding about what third-party payers or Medicare will and will not reimburse, many sites/investigators don’t focus on this.
- Within some therapeutic areas (e.g., neuroscience), completion of studies has not been impeded because of payment/reimbursement issues. If anything, the opposite is true; patients are more willing to participate in trials when insurance does not cover a therapy, therapies are not commercially available, or the patient is uninsured (and would get free care on-trial).
- There did not seem to be a demonstrable difference in the importance of issues related to payment policy and clinical trial completion in community/private practice and in academic medical centers.
- Sites are now carefully selecting the trials they accept because of reimbursement issues and the desire not to lose money on the study. They have instituted new processes to evaluate reimbursement issues in each trial prior to accepting to do the study.
- Sites are taking these precautions (*see statement above*) largely due to concern with inadvertently committing Medicare fraud.
- The process of negotiation between site and sponsor now includes delineation of the sponsor’s vs. the third-party payer’s responsibility for clinical trial-related costs.
- Clinical trials still encounter problems with billing to the sponsor vs. third-party payer vs. patient. Many additional resources have been added to facilitate the process.
- Billing mishaps may have led to patient withdrawal from clinical trials, but this type of information is not collected.
- Overall, new processes surrounding fiscal responsibility, reimbursement, and billing result in a longer time before the study can begin. However, the hope is that this will lead to fewer problems during the course of the study.
- Specific examples where reimbursement issues have arisen include specific tests/procedures for which staff struggle to clarify responsibility surrounding payment, such as heart catheterization and echocardiogram needed for a research study but also a part of routine clinical care for the participant..
- One example of a study that encountered accrual problems due to third-party payment issues was a trial in which one arm involved a marketed procedure/device being used for an off-label indication. The procedure/device was covered by CMS off-trial despite a recognized lack of available evidence for its use in this setting and made recruitment to the trial very difficult.

- To attempt to complete the trial listed in bullet above, investigators are trying to educate referring clinicians about the importance of completing this trial, in order to gain a definitive answer about the benefit of the procedure. Physicians are necessary partners in the recruitment process.
- In the study mentioned above, insurance companies were not involved in a discussion surrounding payment on- versus off-trial.
- Patients may prefer to know which treatments work and which do not. It is conceivable that patients would choose not to undergo a procedure if they knew that it offered no additional benefits compared to regular medical treatment.
- Lack of coordination between government agencies, even competition between them, makes it harder for investigators to work with government to overcome challenges in clinical trials.
- The option of registries poses a real threat to clinical trials, and especially challenges the ability to enroll patients in clinical trials.
- A financial incentive makes enrollment in clinical trials much easier; for example, indigent patients enrolling in clinical trials at an adult psychiatric free care hospital.
- One health care system essentially offers universal coverage and access; all care is free regardless of the patient's insurance status. Here the incentive is to not enroll, because the financial impact on the patient will be the same, but if the patient enrolls in an RCT, he/she faces the possibility of being randomized to an arm in which participants do not receive the most cutting edge treatment.
- Patients might be more willing to participate in research if trials were not randomized, and were open-label rather than placebo-controlled.
- It is felt that studies cannot offer incentives for enrollment because those would constitute coercion.
- An example of a study impacted by third-party payment issues was an aging study, in which Medicare coverage of many of the services provided by the study reduced patients' interests in participating. As this is a longitudinal observational study, it does not involve randomization. The issue instead is participant burden. Patients are declining to enroll because of the additional tests it would require, which are covered outside of the trial by Medicare as needed. Investigators expect that healthy individuals will be more likely to enroll, and that this will skew the data.
- The Women's Health Initiative encountered a retention issue related to payment policy. Some women on the study were asked to have a mammogram, but the study did not cover it. Participants were disgruntled that they needed to file an insurance claim for this procedure, which they expected the study to cover. The WHI eventually began covering the cost of the mammograms in order to keep the participants in the study.
- In general, if patients can get services for free in the clinical trial setting, and would not be able to get these services at all, or not to get them for free off-trial, then they are likely willing to enroll.
- There are examples where participants enrolled willingly at the trial outset because the intervention was not available off-trial, but when coverage for the intervention off-trial became available mid-way through the study, the study had great difficulty recruiting additional participants. They ultimately closed down the study due to inability to recruit enough participants.
- When studies are slowed due to recruitment challenges, the evidence generating process slows as well, and vital answers are not found for clinical questions.
- Insurance does not cover routine follow-up visits for children without medical needs, once they go off-trial, but does cover these visits for children with further needs. This skews the data collected for longitudinal analysis and retrospective studies.

DISCUSSION

This project was designed to describe the impact of payment policy on participant enrollment and retention in clinical trials. It utilized four primary strategies to elucidate this potential problem for which data are largely non-existent. A literature search was conducted to cull from the published medical literature any relevant articles and information that might inform the study. An Advisory Panel, comprised of national experts, was convened to provide guidance to the inquiry as well as to point out specific articles and studies for inclusion. A Public Forum was held on the CMS campus in Baltimore, MD, to solicit public input. A series of teleconference with key informants was held to gather the observations and perceptions of individuals with relevant experiences related to clinical trial recruitment and enrollment, payment policy for costs associated with clinical trials, and the impact of payment policies on patients' decisions to participate or not participate in clinical trials. And, a draft version of the summary White Paper was presented for public review and comment, with appropriate resulting modifications presented in the final White Paper.

A discussion section under each of the four Strategies (Advisory Panel, Literature Search, Public Forum, Key Informant Teleconferences) comprising this project addresses the key findings from each respective Strategy. Listed below are the main points that have emerged through conduct of this study as a whole.

1. Payment policy does impact clinical trial participation, but data on the extent and magnitude of this influence are difficult to find. There are, however, a few examples of high-profile, high-budget, clinical trials which have encountered problems with enrollment or retention due to payment policies. The impact of payment policies on participation in less visible clinical trials is unclear, as information regarding termination of clinical trials, or delays in their completion, is generally not published. No mechanism exists for collecting data on reasons why patients choose not to participate in clinical trials.
2. The impact of payment policy on clinical trial participation is not uniform across study types, study phases, disease areas, and clinical populations. There is more evidence of this impact on clinical trials studying medical devices than on those investigating new drug treatments, partly reflecting the earlier timing of the FDA policy on IDE exemption and the implications for third-party payment for exempted Category B devices. Studies of the comparative effectiveness of existing therapies, especially in head-on trials, have had particular difficulty when one or both therapy(ies) has been available and reimbursable off-trial. Studies of off-label indications, which are not typically reimbursable outside of the clinical trial setting (except for off-label anticancer therapies), are also especially susceptible to the influence of payment policy. Studies seeking to enroll adults face different challenges than do those enrolling children, with decisions to participate in adult studies being more influenced by payment policy than studies involving children. Finally, studies of interventions for which there is policy of no reimbursement (e.g., obesity interventions) face particular challenges because, since treatment both on and off trial is out-of-pocket, patients have no incentive to enroll in a randomized trial where they might receive placebo.

3. Lack of clarity surrounding responsibility for specific expenses exacerbates the impact of payment policy on clinical trial participation. There is no consensus on which party should pay for which costs when a patient is enrolled in a clinical trial. While “standard of care” costs are commonly assigned to the third-party payer, the definitions of standard of care versus research-related costs remain unclear. This lack of clarity complicates the task of assigning costs to a sponsor or third-party payer, and resulting uncertainty about cost implications may inhibit patients from participating in a study or providers from referring a patient to a study. There is a trend among sponsors and sites to clarify, in advance of opening a study, the locus of responsibility for specific patient care and research-related costs.
4. To circumvent the impedance of payment policy on accrual and retention, investigators are implementing creative solutions to enable them to enroll enough patients to complete their clinical trials. Examples of such strategies include paying for participants’ travel and lodging while on a trial, and appealing to insurance carriers on a case-by-case basis. These sorts of strategies are personnel intensive and/or budgetarily burdensome, make conduct of the trial more cumbersome, and add an unnecessary layer of inefficiency to the research enterprise.
5. Payment policy can impact the evidence base in several ways. When enrollment proceeds slowly because payment policies reduce patients’ willingness to participate in clinical trials, or diminish providers’ interest in directing patients toward clinical trials, the pace of evidence generation slows correspondingly. The evidence base fails to grow in areas where research-derived answers are needed to guide clinical care. When payment policy makes a clinical trial economically infeasible, that trial may be terminated early or never initiated. In either case, evidence fails to be generated in that area. When payment policy steers patients toward registries rather than clinical trials, the quality of evidence may suffer as the preponderance of research results will come from uncontrolled observational studies rather than from rigorously designed RCTs. When payment policy initiates coverage for a device or drug before proof of efficacy has been established, the “cart is put before the horse.” It becomes challenging or impossible to recruit patients to trials of those interventions, and thus very difficult to arrive at a definitive determination of efficacy.
6. Payment policy, through its impact on clinical trials participation, has an impact on disparities in and access to care. Different subsets of the general population – minorities, the uninsured, those with adequate insurance, children, the elderly – are likely to have differing insurance scenarios. Payment policies related to clinical trial participation will therefore affect these groups differently, resulting in different rates of accrual in different subpopulations. If clinical trials cannot enroll representative samples large enough to allow power to detect statistically significant differences in outcomes, the evidence they generate may not be robust, generalizable, or applicable to the relevant population.
7. Payment policies, or policies that are related to payment and clinical trial participation, are developed by various entities including the NIH, CMS, FDA, state legislatures, and

third-party payers. Cutting-edge science and meritorious clinical trials are developed through NIH, industry, academia, and others. All of these entities have an interest in the successful conduct of clinical trials, the development of a robust evidence base, and the quality of scientific research and resulting data. Their policies related to reimbursement and financial aspects of clinical trials impact participants and studies in sometimes deleterious ways. Moreover, these policies are not always clear or transparent across agencies and between agencies, industry/sponsors, providers, and the public. Improved communication and coordination among these agencies and organizations would help facilitate the conduct of research, ensure that vital evidence is generated, and thereby uphold the safety and quality of medical care. For example, Medicare Advantage (MA) plans currently do not have access to clinical trial participation information involving MA enrollees, particularly with respect to providers and patients involved in Investigational Device Exemptions; this information resides with CMS, and lack of accessibility may negatively impact MA plans' ability to effectively manage clinical trial activities and participants. Alignment of payer (including MA plan) policies and local/national coverage determinations is necessary to ensure both access to care and appropriate assignment of costs.

8. Competition between registries and clinical trials appears to be a major concern in the research community. By participating in a registry, a patient can satisfy CED requirements, receive the same coverage as he/she would in the context of a randomized clinical trial, and be assured that the intervention received is the actual treatment. On a clinical trial, by contrast, the individual runs the risk of being randomized to a non-treatment (e.g., placebo) arm. Policy allowing registry participation to substitute for clinical trial participation creates head-on competition for participants, and is likely to slow or impede the development of an evidence base built on data from high-quality randomized controlled trials (RCTs). Instead, the research environment could benefit from a coordinated program of research that articulates a role for both registries and RCTs; such a program would capture the results from both experimental and observational studies, thus building a more completely understanding of the impact of interventions against the backdrop of the disease's natural history.
9. Blinding, as well as randomization, is threatened by current changes and practices in payment policy. Unblinding in order to facilitate reimbursement by third-party payers was noted as a problem for clinical trials, one that jeopardizes the quality of research results.

Suggested future directions

Given this backdrop – common agreement that payment policy impacts clinical trials participation, clarity that new approaches are needed to ameliorate these problems, but little data to quantify or describe the phenomenon – there are several areas of action that CMS might consider. Of paramount importance is greater coordination between CMS, the FDA, and the NIH around the common mission of improving the quality of clinical trials and the resulting evidence base, while honoring these agencies' distinct purposes and roles. It is critical to determine, first, whether a payment policy is in fact interfering with the conduct of clinical trials, and secondly to describe that impact in terms of locus and extent.

A mechanism to collect information on impact, including differential impact by variables such as socioeconomic status and age, will need to be implemented. An efficient vehicle for such a mechanism already exists in ClinicalTrials.gov; here, trials could be required to provide information on their plans for managing reimbursement-related issues, as part of the standard registry process; initial effort would need to be devoted to development of standard definitions, to ensure consistency of reporting and to minimize burden on trial sponsors or investigators. Ideally, this mechanism – collecting information on reimbursement-related plans in advance of studies and information on impact domains during/after conduct of studies – would be created as part of an “intelligent system,” in that data could be regularly queried to identify potential problems and report on them. These reports should be delivered to CMS, FDA, and NIH for joint development of appropriate solutions; data-sharing arrangements should be fully transparent to allow for stakeholder input and to ensure that data-driven policy decisions are fully informed. The system should also store data to enable monitoring of payment policy-related issues in clinical trial participation over time; this system will enable tracking of progress to overcome the identified problems, and will allow payers to manage and plan for costs associated with their enrollees’ participation in clinical trials.

It is important to note that payment policy, though perhaps a significant influence on patients’ decisions to participate in clinical trials, is not the only factor operative in these decisions. Any further inquiry would benefit from complementary exploration of other barriers to enrollment including patients’ perceptions of research, socioeconomic and educational factors, cultural factors, access, provider behavior, physician incentives, and health care performance metrics.

Tension between registries and clinical trials, and the discrepancies between evidence requirements for drugs versus devices, should be addressed in the context of an integrated, carefully constructed, plan for research that incorporates both observational and experimental studies, pursues a goal of obtaining the highest level evidence within practical constraints, acknowledges a valid place for different types of study (RCT, observational/registry) to address different types of research question, and generates a solid long-term understanding of toxicity and impact. Registry requirements, including definition of data to be collected and data-related methodology, will need to be articulated with sufficient oversight to ensure sound quality of data residing in registries. Requirements of clinical trials, legitimately based upon the need for research evidence, should not impair access to innovative technology; rather, policy should be designed so as to facilitate both access to therapies and research in a coherent manner that is safe, respects privacy, and contributes to the care of future generations. Because device trials encounter the preponderance of recruitment difficulties due to payment policy, a coordinated strategy to facilitate conduct of these studies is warranted.

There are several additional actions that CMS could take to minimize the impact of payment policies on clinical trials. At present, the shifting definition of standard of care (SOC) for any given condition allows for interested parties to define SOC to their own advantage; sponsors and health systems disagree on what cost items constitute SOC, and on which costs should be the responsibility of either party. Clearer methods should be developed for assignment of SOC costs, beginning with articulation of what SOC encompasses for the condition at hand. One approach might be to pilot a process of co-sharing SOC costs, report on results of that pilot, and iteratively improve the process based on results. Additionally, to protect the research community’s ability to generate evidence through appropriately designed trials – RCTs as well as observational studies – it is imperative that the financial incentives to participate in a registry

rather than a randomized trial (when they exist) do not place RCTs in competition with registries for participants. Instead, a rational approach should be developed to ensure that evidence is generated through studies designed as appropriate to answer the research question at hand. Finally, background structures need to be created to facilitate blinding throughout the duration of a study, perhaps by use of pooled funds that can be accessed, to even out costs in two study arms with differently costed treatments, until the study is complete.

Limitations. The first limitation of this strategy lay in recruitment of key informants. It was initially challenging to identify individuals with relevant background and experiences who might be willing to participate. Upon identifying and contacting potential key informants, we frequently met with reluctance and/or refusal to participate. Principal investigators and clinicians, in particular, were well-buffered by their assistants; a strategy of having one of the study investigators (a physician) contact the potential key informant proved more successful.

A second limitation was met in the group teleconference, as described above. Because of reluctance of the participants to fully participate, the teleconference format was changed to one in which each teleconference included only one key informant. After this change was instituted, individuals who agreed to participate were more open to discussion.

Perhaps the principal limitation of this strategy was noted by key informants themselves. While individuals mentioned that they would like to be able to provide more solid evidence, they spoke from personal experience and mostly provided anecdotes and observations rather than data. Many provided encouragement in the face of what they saw as a difficult task, given the lack of data on this topic and the absence of any clear way to go about gathering information on this topic.

PERSONNEL

Amy P. Abernethy, MD, Principal Investigator. Dr. Abernethy, a practicing oncologist and health outcomes researcher, is Assistant Professor of Medicine at Duke University School of Medicine, Assistant Professor of Nursing at Duke University School of Nursing, and Associate Lecturer at Flinders University in South Adelaide, Australia. She is a Senior Fellow of the Duke Center for Clinical Health Policy Research, and a faculty member of the Duke Clinical Research Institute and the Duke Comprehensive Cancer Center Cancer Control Program. Her research has focused on conducting high quality clinical trials that generate evidence-based solutions for common problems in cancer and other chronic life-limiting illnesses, such as pain, dyspnea, and fatigues; a significant portion of her research agenda involves the study of health service delivery models. Dr. Abernethy is PI of an AHRQ-funded technology assessment (TA) of targeted cancer drugs, and has served as a lead investigator on TAs of oral cancer drugs, use of compendia for off-label listing of pharmaceutical products, and psychological interventions for cancer pain. She has held responsibility for all aspects of this project, including study design, convening of the Advisory Panel, the literature search, the Public Forum, key informant teleconferences, synthesis of data, and preparation of the report.

Meenal Patwardhan, MD, MHSA, Co-Investigator. Dr. Patwardhan is a health services researcher and adjunct member of the Duke Center of Clinical Health Policy Research, as well as an Adjunct Assistant Professor of Medicine in Duke University School of Medicine. She has recently moved to a new role at Abbott Laboratories; this transition took place in the middle of this project and she did not have any input into the research or its interpretation after moving to industry. Her work ranges from evidence compilation to implementing best evidence in practice. She has served as the PI of a chronic kidney disease guideline implementation project that involved interviewing several physicians and patients. Dr. Patwardhan has also been the PI of the AHRQ-funded evidence report on Cancer Care Quality Measures: Diagnosis and Treatment of Colorectal Cancer, and has served as a co-investigator for use of compendia for off-label listing (the methodology of which was similar to the current proposal). She participated integrally in design of the study, convening of the Advisory Panel, the Public Forum, preparation for key informant teleconferences.

David B. Matchar, MD, FACP, Co-Investigator and Task Order Director. Dr. Matchar is Director of the Duke Center for Clinical Health Policy Research and Professor of Medicine at Duke University School of Medicine. In addition to clinical expertise, Dr. Matchar will provide methodological expertise in evidence-based medicine, decision analysis, and guideline development. Dr. Matchar has worked with the project team as they interfaced with AHRQ, CMS, and the Advisory Panel, conducted key informant teleconferences, and synthesized and interpreted the data.

Nancy M. Allen LaPointe, PharmD, Co-Investigator. Dr. Allen LaPointe is an Associate Professor of Medicine at Duke University Medical Center and Clinical Associate Professor in Pharmacy at University of North Carolina-Chapel Hill. After ten years of clinical practice and teaching as a Cardiovascular Clinical Pharmacist at Duke University Medical Center, Dr. Allen LaPointe moved to the Duke Clinical Research Institute (DCRI) as the Project Manager for the

Duke Center for Education and Research on Therapeutics (CERTs) program, in which she developed and managed all clinical research projects for the research center. From 2002-2007, she was the Program Director for the Duke CERTs. During her eight years at the DCRI, Dr. Allen LaPointe has worked as a member of the DCRI faculty in developing both government and non-government funded clinical research projects and as part of the DCRI clinical operations leadership. Dr. Allen LaPointe's research has focused on evaluating and improving the use of evidence-based therapies in clinical practice, medication safety and adherence, and risk communication and management. She participated in leading key informant teleconferences, and interpreting the data.

Jane L. Wheeler, MS, Writer. Ms. Wheeler has played a central role in gathering the evidence, and compiling and presenting study results, with responsibility for summarizing key informant input solicited during conference calls, intercalating results, and writing, compiling, and editing the final evidence report. Ms. Wheeler has extensive experience in these tasks; she has been involved in a similar capacity on several concurrent studies including the AHRQ-sponsored evidence report, "Targeted Therapies for Cancer."

R. Julian Irvine, MS, Project Coordinator. Mr. Irvine held responsibility for supervising day-to-day operations, scheduling, setting meeting agendas, organizing results of the literature search, creating and maintaining the database, coordinating the Public Forum, and facilitating communication between the investigators and Public Forum participants, key informants, Advisory Panel members, and officers at AHRQ and CMS. Mr. Irvine is currently project coordinator for several other EPC projects.

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Appendix A: Introduction of study to the public and questions for public comment

[This summary was posted on the AHRQ or CMS website, along with a study plan document, to provide the public with a lay description of the project and potential items on which the public may want to comment.]

Funded by the Agency for Healthcare Research and Quality (AHRQ), this project is examining what impact, if any, changes in insurance coverage for new treatments – such as drugs and procedures – have on patients’ interest in participating in clinical research studies evaluating those treatments. Patients often participate in a research study in order to gain access to a new treatment option that is not available outside of the study. Sometimes the study provides an opportunity to have the new treatment paid for, and other times it does not. Many research studies are “randomized”, meaning that the participant has an equal random chance of receiving the new treatment under study or the current standard of care, and cannot specify which treatment is received.

Sometimes, either before or during the course of the research study, health funders such as Medicare or private insurance will decide to cover the treatment for patients who are not involved in the research study – but will not reimburse patients who are on the study. In these situations, it is possible that the change in payment policy will affect patients’ willingness to enroll in, or to stay in, the research study. As a result, it is possible that there will never be adequate descriptive information about benefits or harms of the new treatment, and how it compares to older treatments.

Together with the Center for Medicare and Medicaid Services (CMS) and the AHRQ, we are conducting this public policy project to understand how decisions regarding healthcare payment for these new treatments impact participation in clinical research studies about the new treatments. We will convene in small groups opinion leaders from CMS, the National Institutes of Health, the Food and Drug Administration, industry, other healthcare funders, and patient advocacy groups, as well as clinical researchers and clinical research staff.

Your input can help us shape these discussions, and therefore the outcome of this policy project. We seek your input on the extent to which insurance coverage for a treatment would affect your interest in participating in a clinical research study. We also need to know what factors should be considered as we develop this report. We ask for your input on the following questions:

1. Would you be willing to participate in a clinical research study if that were the only way to gain access to a new, and possibly more effective, treatment?
2. Would you be willing to participate in a clinical research study of a new drug or procedure, if you would have to pay out-of-pocket for the drug/procedure when on study?
3. What if you could receive reimbursement for it off-trial, how would that influence your decision? Why or why not?
4. If you decided to enroll in a clinical research study comparing two treatments, and one of the two treatments would cost more than the other, would you be willing to be assigned to a group receiving *either* of the treatments?
5. If you *might* be assigned to a study group where you do *not* receive the new drug or procedure (but instead receive the traditional “standard care” treatment), would you still

be willing to participate in a clinical research study? Would your decision be different if you knew that you *might* get the new treatment for free by being in the trial?

6. If you have been involved in the conduct of a clinical trial (e.g., as an investigator, coordinator, manager, or administrator), have you felt that patients' decisions to enroll or continue participation in the trial were influenced by payment policy considerations? If so, please explain.
7. If you are a person who relies on the output from clinical trials to make decisions regarding healthcare (e.g., as a part of evidence-based decision making), have you felt that the output from clinical trials was influenced by payment policy considerations? If so, please explain.
8. Our research plan is included for public comment. Are there other things that we should consider when conducting this project?

Appendix B: Peer-reviewed Articles Abstracted for Literature Review

- Aaron H, Gelband H. *Extending Medicare Reimbursement in Clinical Trials* Washington DC: National Academies Press; 2000. (Medicine Io, ed.
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Appendix C: Articles from the Non-Medical Press Included in Literature Review

ARTICLE TITLE	SOURCE	DATE
Report Claims Clinical Trials Miss Many Populations	Scout News, LLC	April 1, 2008
Participants Left Uninformed in Some Halted Medical Trials	New York Times	October 30, 2007
Duke Studying Impact of Clinical Trial Coverage on Enrollment for CMS	The Gray Sheet	October 1, 2007
Medicare's Coverage With Evidence Development: A Policy-Making Tool in Evolution	Journal of Oncology Practice	November 2007
Concentric Medical stroke treatment cleared	Silicon Valley/ San Jose Business Journal	August 31, 2007
FDA Weighs Flexibility in Trials of Heart Treatment	New York Times	September 21, 2007
FDA: Panel Recommends Reduced Restrictions on Ablation Trials	New York Times	September 21, 2007
AF Ablation Devices Need Randomized Trials, Advisory Panel Tells FDA	The Gray Sheet	October 1, 2007
Patient Registries' Impact On Clinical Trials Debated At IoM, CMS Meetings	The Pink Sheet	October 15, 2007
Commercializing Clinical Trials—Risks and Benefits of the CRO Boom	New England Journal of Medicine	October 4, 2007
Reimbursement, Not Off-Label Use, May be Hindering Carotid Stent Trials	The Gray Sheet	October 22, 2007
Cardiac-Resynchronization Therapy in Heart Failure with Narrow QRS Complexes	New England Journal of Medicine	November 6, 2007
Resynchronization Misses Endpoint in St. Jude-Sponsored RethinQ Trial	Health News Daily	November 7, 2007
Multi-MERCI: Higher Recanalization, Lower Mortality With Newer MERCI Retriever	Medscape Medical News	February 15, 2007
Medical Privacy Rule May Hurt Research	Associated Press	November 13, 2007
Renal Stenting Surprise: CMS Proposes To Keep Coverage Status Quo	Health News Daily	November 26, 2007
Clinical Trial Modernization, Outsourcing Concerns Are Focus Of FDA/Duke Effort	The Pink Sheet	December 3, 2007
A Different 'Right to Life'	Wall Street Journal	January 11, 2008

Supreme Court Lets Stand Experimental-Drug Ruling	Washington Post	January 15, 2008
CREST Update: Meeting the challenges of a randomized clinical trial	Correspondence from AHRQ	January 15, 2008
Sharing a commitment to improve cardiovascular devices [Part I: Identifying holes in the safety net and Part II: Sealing holes in the safety net]	American Heart Journal	June, 2004
A Review of Prostate Cancer Leaves Men in a Muddle	New York Times	February 26, 2008
Medicare to Revisit Clinical Trial Policy, Consider New Coverage Decision, AHHA Told	Health Care Daily Report	May 9, 2008
High-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for severe systemic sclerosis: long-term follow-up of the US multicenter pilot study	Blood	August 15, 2007
Variation in Approval by Insurance Companies of Coverage for Autologous Bone Marrow Transplantation for Breast Cancer	New England Journal of Medicine	February 17, 1994
Prospective Evaluation of Cancer Clinical Trial Accrual Patterns: Identifying Potential Barriers to Enrollment	Journal of Clinical Oncology	March 15, 2001
Impact of the Year 2000 Medicare Policy Change on Older Patient Enrollment to Cancer Clinical Trials	Journal of Clinical Oncology	January 1, 2006

Appendix D: Preliminary List of Clinical Trials

TRIAL NAME	DATE	LOCATION	OBJECTIVE	PI NAME & #
CORAL Trial 1	published 2005	Multicenter (~100) sites	This study is designed to test the hypothesis that optimal medical therapy with stenting of hemodynamically significant and angiographically documented ARAS in patients with systolic hypertension reduces the incidence of adverse CV and renal events.	Christopher J. Cooper Medical Univ of Toledo, OH ccooper@mco.edu Coordinator: Holly Burtch holly.burtch@utoledo.edu
CORAL Trial 2	Sep 2003 - ???	Multicentre intergroup trial	This multicentre phase III CORAL study aims to guide choice of salvage chemotherapy in diffuse large B-cell lymphoma (DLBCL) and assess the role of rituximab maintenance after autologous stem cell transplantation (ASCT).	H. Hagberg Dept of Oncology Akadeniska sjukhuset 75185 Uppsala, Sweden +46 18 611 55 29 hans.hagberg@akademiska.se
CREST	published 2006	Multicenter sites	We sought to evaluate resource use, cost, and cost-effectiveness of cilostazol in CREST.	John S. Douglas Director, Interventional Cardiology Emory University Hospital 404-727-7040 john.douglas@emoryhealthcare.org Coordinator: Pamela Hyde 404-712-7665
CARESS	published 2005	11 centers in France, Germany, Switzerland, & UK	Asymptomatic Microembolic Signals (MES), detected by transcranial Doppler ultrasound (TCD), are markers of future stroke and transient ischemic attack (TIA) risk, offering a surrogate marker to evaluate antiplatelet therapy. This is the first multicenter study to evaluate the feasibility of this approach.	Hugh S. Markus Dept. of Clin Neuroscience St. George's Hosp Med Sch Cranner Terrace London, SW17 0RE, UK h.markus@sghms.ac.uk

SAPPHIRE	Feb 2002 - Jun 2002	29 US Centers	The SAPPHIRE trial was a randomised study comparing carotid stenting with the AngioGuard embolic protection device to CEA in patients at increased risk for carotid surgery.	Jay S. Yadav Dept. Cardiovasc. Med The Cleveland Clinic Found 9500 Euclid Ave., F25 Cleveland, OH 44195
Vertebroplasty Trial 1	published 2002	Columbus & Toledo, OH	To determine the efficacy and durability of percutaneous vertebroplasty for the treatment of back pain associated with vertebral body compression fractures.	J. Kevin McGraw Dept. Vasc & Intervent. Radiology, Riverside Methodist Hosp 3555 Olentangy River Rd Suite 2050 Columbus, OH 43214 jkmcgraw@hotmail.com Coordinator: J. Kevin McGraw 614-340-7747
Vertebroplasty Trial 2	Dec 2001 - Aug 2003	Fukuchiyama, Kyoto, Japan	To assess the immediate efficacy of percutaneous vertebroplasty (PVP) in relief of pain and improving mobility of patients with vertebral compression fractures (VCF) secondary to osteoporosis.	Kiyokazu Kobayashi Dept. of Radiology Kyoto Renaiss Hosp 1-38 Suehiro-cho, Fulushiyama Kyoto, Japan radiology@renaiss.jp +81-773-223550
Vertebroplasty Trial 3	Nov 1994 - Jun 2002	Madrid, Spain	To determine the factors affecting the outcome of percutaneous vertebroplasty for the treatment of persistent painful osteoporotic fractures.	Luis Alvarez Dept. of Orthopaedics Fundacion Jimenez Diaz, Av. Reyes Catolicos, 2, 28040 Madrid, Spain lalvarez@fjd.es
Vertebroplasty Trial 4	published 2003	Washington Univ Med Cnt, St. Louis, MO	To evaluate different types of polymethylmethacrylate (PMMA) leakage and patient-related factors in relations to clinical midterm (1-24 month) outcome after vertebroplasty.	(Corr. Author) Louis A. Gilula Inst. Of Radiology Wash Univ Med Ctr 510 S. Kingshighway Blvd. St. Louis, MO 63110-1076 gilula@mir.wustl.edu

Vertebroplasty Trial 5	1996-1999	7 hospitals in US	To describe the immediate outcome of a large cohort of patients who underwent percutaneous polymethylmethacrylate (PMMA) vertebroplasty for treatment of one or more vertebral fractures.	Avery J. Evans Radiology Assoc of Tampa 511 W. Bay St, Suite 301 Tampa, FL 33606 aevans1@tampabay.rr.com
Early ICD Trial	Jul 1998 - Feb 2003	45 centres in Italy	This multicentre prospective randomised trial was undertaken to evaluate the usefulness of an electrophysiological study (EPS) - guided/inplantable cardioverter defibrillator (ICD) strategy in patients at high risk of sudden death (SD) early after myocardial infarction (MI).	Antonio Raviele Cardiology Div. Ospedale Umberto I Via Circonvallazione, 50 - 30170 Mestre-Venezia, Italy +39 041 2607201 araviel@tin.it
MIRACLE ICD Trial	Oct 1999 - Aug 2001	Multicenter US	To examine the efficacy and safety of combined CRT and ICD therapy in patients with New York Heart Association (NYHA) class III or IV, congestive HF despite appropriate medical management.	James B. Young Cleveland Clinic Found 9500 Euclid Ave, F25 Cleveland, OH 44195 youngj@ccf.org Coordinator: MEDTRONIC
MUSTT Study	1991 - 1996	Multicenter German Trial	The multicenter unsustained tachycardia trial (MUSTT) tested the value of electrophysiologically guided antiarrhythmic drug therapy against no therapy in high risk coronary artery disease with poor left ventricle function (LV-EF<=40%) and nonsustained ventricular tachycardia.	Helmut U. Klein Div. of Cardiology University Hosp Leipziger Strasse 44, D 39120 Magdeburg, Germany ++49 391 671 32 03 Helmut.Klein@medizin.uni-magdeburg.de

B-Blocker + ICD Trial	Jun 1998 - ???	95 Centers in Italy & Germany	This trial will test the hypothesis whether, in high-risk post myocardial infarction (MI) patients already treated with B-blockers, electrophysiologic study (EPS)-guided therapy (including the prophylactic implantation of implantable cardioverter defibrillator [ICD] in inducible patients) will improve survival compared with conventional therapy.	Antonio Raviele Cardiology Div. Ospedale Umberto I Via Circonvallazione, 50 - 30170 Mestre-Venezia, Italy +39 041 2607201 araviel@tin.it
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Appendix E: Clinical Trials in Which Payment Policy has Impeded Participation

TRIAL	PURPOSE	CHALLENGE(S) ENCOUNTERED
<p>MR RESCUE (Merci Retriever and Recanalization of Stroke Clots using Embolectomy)</p>	<ul style="list-style-type: none"> • An NIH(NINDS)-funded trial of a device (MERCITM Retriever) to remove intracranial cerebrovascular clots • Purpose: To compare the effectiveness of treating acute ischemic stroke with the Merci Retriever within 8 hours of symptom onset to standard medical treatment, and to identify people who might benefit from the MR device • Enrollment goal: 120 patients in ten centers. Enrollment began in 2004; as of June 2008, the study is still recruiting. 	<ul style="list-style-type: none"> • Device is being used off-trial at a high rate (approximately 5,000 procedures in July 2007 and 6,000 in August 2007). • Availability of and coverage for the device off-trial has made it very difficult to recruit patients to the trial.
<p>CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions)</p>	<ul style="list-style-type: none"> • An NIH(NHLBI)-funded study of a device to treat renal artery stenosis • Purpose: To compare medical therapy plus stenting of hemodynamically significant renal artery stenoses to medical therapy alone in patients with systolic hypertension and renal artery stenosis • Enrollment goal: 1,080 patients. Enrollment began in 2005 at multiple sites; as of June 2008, the study is still recruiting. 	<ul style="list-style-type: none"> • While 35,000 stenting procedures are performed annually in the United States, the trial had managed to enroll only 290 patients as of September 2007. • Investigators attribute slow accrual to CMS coverage for stents off-trial.
<p>CREST (Carotid Revascularization Endarterectomy versus Stenting Trial)</p>	<ul style="list-style-type: none"> • An NIH(NINDS)-sponsored trial of a relatively new procedure to prevent stroke • Purpose: To compare stent-assisted carotid angioplasty (CAS) to the traditional and accepted surgical approach of carotid endarterectomy (CEA) for treatment of carotid artery stenosis to prevent recurrent strokes in patients who had a TIA (transient ischemic attack) or a mild stroke within the past 6 months (symptomatic) and in patients who have not had any symptoms within the past 6 months (asymptomatic). 	<ul style="list-style-type: none"> • This trial encountered initial difficulty enrolling because CMS reimbursed for one arm (CEA) but not the other (CAS). • Physicians are implanting stents in many low-risk patients off-label before RCTs have generated evidence to support this practice. • Surgeons appear reluctant to refer patients to the trial, due to potential loss of income (i.e., patient has 50% chance of being randomized to CAS and therefore not undergo surgery). • Many non-CMS payers will not cover cost of stenting for low-risk patients on clinical trial.

	<ul style="list-style-type: none"> • Enrollment goal: 2,500 patients at multiple sites. Enrollment began in 2001, and is predicted to be completed in 2008. 	
Multi MERCI™ Trial (Mechanical Embolus Removal in Cerebral Ischemia)	<ul style="list-style-type: none"> • An industry-sponsored (Concentric Medical) trial of a new generation device to restore blood flow in the neurovasculature of ischemic stroke patients by removing blood clots • Purpose: To test the safety and efficacy of newer generation (L5) MERCI™ Retriever Device • Enrolled 164 patients from 15 sites. The study has been completed. 	<ul style="list-style-type: none"> • This controlled registry study rather than an RCT. • Because the device was both available and reimbursable, radiologists and vascular surgeons rapidly adopted it despite lack of evidence from RCTs. • Patients are eager to receive this device, and may have no incentive to enroll in an RCT where they might be randomized to a non-device arm.
CATT (Comparison of Age-Related Macular Degeneration Treatments Trials: Lucentis-Avastin Trial)	<ul style="list-style-type: none"> • An NIH(NEI)-funded trial of two drug therapies for age-related macular degeneration. • Purpose: to evaluate the relative efficacy and safety of treatment of neovascular AMD with Lucentis on a fixed schedule, Avastin on a fixed schedule, Lucentis on a variable schedule, and Avastin on a variable schedule. • Enrollment goal: 1,200 patients. Enrollment began in February 2008, and is still open as of June 2008. 	<ul style="list-style-type: none"> • Cost of Avastin, but not cost of Lucentis, was covered by the sponsor. Lucentis was approved for AMD, but was nonetheless deemed investigational in this context. • CMS could not legally pay 80% of those costs without changes to the Medicare CTP. • This trial thus became an important stimulus for the Proposed CRP. • Billing practices posed a threat to blinding, but the cost implications of central purchase of drugs was prohibitive.
SCOT Trial (Scleroderma: Cyclophosphamide or Transplantation)	<ul style="list-style-type: none"> • An NIH(NIAID)-funded trial of two treatments for systemic sclerosis • Purpose: To compare high-dose immunosuppressive therapy followed by hematopoietic stem cell transplant to high-dose pulse IV cyclophosphamide for treating systemic sclerosis • Enrollment goal: 226 patients from multiple sites. Enrollment began in June 2005. As of June 2008, 113 patients had been enrolled and screened on SCOT but only 40 randomized. 	<ul style="list-style-type: none"> • This Phase randomized III trial was preceded by a pilot study which enrolled 36 patients at 4 sites. • By study design, all costs of clinical care were assigned to the insurance carriers; study budget includes no funds for clinical care costs. Research costs (e.g. blood samples) are covered by the grant. • The study had difficulty enrolling patients due to insurance coverage denials. • Primary reason for denial was the reimbursement was requested for “investigational” or “experimental” procedures or items. • The PI has engaged in “hand-to-hand combat” with individual carriers to advocate for coverage of patients wishing to enroll in the trial.

<p>NETT (National Emphysema Treatment Trial)</p>	<ul style="list-style-type: none"> • A trial funded by NIH (NHLBI), CMS, and AHRQ of interventions to treat emphysema • Purpose: To evaluate the long term efficacy, morbidity and mortality associated with medical therapy with lung volume reduction surgery (LVRS) as compared to medical therapy alone and to define patient selection criteria. • Enrollment goal: 2,500 patients. The study is ongoing but enrollment closed; 1,218 patients were randomized. 	<ul style="list-style-type: none"> • Initially (per DHHS Advisory Opinion No. 98-6), the target enrollment for the study sample was 4,700. This goal was dropped to 2,500 due, in part, to difficulties encountered by sites in recruiting patients to the study (per Advisory Opinion No. 00-5). • A waiver of Medicare copayment and deduction for participants was requested on the grounds that it would promote patient compliance with data collection and promote enrollment of additional patients. • This waiver was denied in DHHS Office of the Inspector General (OIG) Advisory Opinion No. 00-5.
<p>BARI 2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes)</p>	<ul style="list-style-type: none"> • A 2x2 factorial NIH(NHLBI)-funded trial of (1) elective revascularization, and (2) glycemic control strategies for patients with Type 2 diabetes and stable coronary artery disease. • Purpose: To compare elective revascularization with aggressive medical therapy to aggressive medical therapy alone, and simultaneously an insulin providing to an insulin sensitizing strategy of glycemic control. • Enrollment goal: 2,400 patients. As of June 2008, the study is ongoing but no longer recruiting patients. 	<ul style="list-style-type: none"> • The supplier requested a waiver of Medicare cost-sharing expenses of blood glucose self-monitoring supplies • Desire to encourage adequate enrollment in the study was cited as a reason for requesting this waiver. • OIG Advisory Opinion No. 04-01 ruled in favor of the request.
<p>Chicago Healthy Aging Study</p>	<ul style="list-style-type: none"> • An NIH(NHLBI)-funded observational study examining how risk factors for heart disease in young and middle aged people affect people's health as they age. • Purpose: To gather follow-up data on individuals who participated in the CHAS between 1967-1973. • Enrollment goal: 1,500 patients, 600 of whom formerly had low-risk of heart disease and 900 who were at high risk. 	<ul style="list-style-type: none"> • Participation entails many tests and services, including: a physical exam, blood pressure measurements, blood and urine collection, electrocardiogram, physical function tests, and computed tomography chest scan. • Many of these items are covered by Medicare. • Patients have had little incentive to enroll, because they can get the services reimbursed off-trial. Even offering services for free has not been an incentive. Recruitment has been challenging. • Patients have expressed concern that participation may impact their Medicare coverage.

<p>Women's Health Initiative (WHI)</p>	<ul style="list-style-type: none"> • An NIH(NHLBI)-funded trial studying cardiovascular disease, cancer, and osteoporosis in postmenopausal women • Purpose: To evaluate, through a randomized controlled clinical trial, three primary prevention strategies: hormone replacement therapy (HRT), dietary modification, and calcium/vitamin D supplementation • Enrollment: 68,132 patients enrolled in the RCT component. The study was terminated due to results indicating that risks of HRT outweighed benefits. 	<ul style="list-style-type: none"> • The study budget did not include funds for mammograms, which were expected to be covered by Medicare and third-party payers. • Participants were displeased that they were expected to file insurance claims. • This became a retention issue, and eventually the study began paying for mammograms in order to retain participants.
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Appendix F: Teleconference Script for Obtaining Oral Consent

Introduction to teleconferences being conducted as one component of “Horizon Scan: To what extent do changes in third-party payment affect clinical trials and the evidence base?”

NOTE: This script was designed for the teleconferences as originally proposed – in small group format. When the teleconference format was changed to include key informants individually rather than in small groups, the script was read in full but the change in format was noted.

VERBAL CONSENT

[Read to teleconference participants as a group, at the outset of each conference call. In the case of a call with only one person, read the script as if there is only one key informant on the call.]

Hello, my name is [...] and on the call with me is [...; other project personnel say hello.] We are part of a team of investigators at Duke who are gathering input for a white paper that will assist the Center for Medicare and Medicaid Services (CMS) in its decisions regarding payment policy, especially the timing of initiating coverage, for new therapeutic agents. This teleconference today is one of several mechanisms for collecting input from diverse sources with various perspectives on the payment policy issue. Our inquiry and discussion will help to answer key questions related to Medicare coverage policies; specifically:

- (a) To what extent do changes in third-party payment policies affect the conduct of clinical trials, particularly the accrual and retention of patients to participate in trials?
- (b) What impact do differing payment structures for interventions under study in clinical trials have on patients’ participation in those trials?
- (c) Do payment factors have an impact on the quality of subsequently accumulated evidence, and if so, what is the nature of that impact?

To answer these questions, we are convening, in a series of teleconferences, individuals whom we view to be “key informants” – people with on-the-ground experiences related to the topic of payment policy and its impact on clinical trials. Each of you has been specifically selected as a participant in one of these teleconferences since we anticipate that you have a critical understanding of the topic generally, or of some specific element of the topic that is a key aspect to report and/or explore within the final white paper report that will come from this project.

It is important to understand that this is a policy project, where the main output will be a white paper summary. The white paper will be delivered to CMS and the public for the purpose of informing future decision-making on the topic of third-party payment for clinical trials. However, while we call it a policy project, like preparing any report, we must conduct some background research to gather the content. This teleconference is part of that information-gathering process. The topic is compelling, and therefore there is conceivably some minor risk that disclosure of what you say -- and attribution of that input to you -- would put you at risk for personal or civil liability. Hence, we seek your oral consent to participate, after we review the details of the teleconference and the careful processes we are using to protect your confidentiality. There will be no signed documents linking you to the research.

I will first read the salient points:

- This teleconference will last approximately one hour, and will be digitally audiorecorded.
- The content of this teleconference will be used in development of a white paper, but otherwise statements provided by individuals will not become part of the public record.
- A list of key informants, i.e., teleconference participants, will be included with the white paper. At the end of this oral consent process, I will ask you if you agree to have your name included in this list of key informants. You are not required to do so.
- We will maintain confidentiality by attaching no personal identifying information to any content provided, so nothing that you say can be directly linked back to you within our report.
- Digital audiorecordings will be stored on a secure server at Duke and will only be accessible only to the investigators to prepare the report. They will not be shared with CMS or become part of the public record, although they may be made available to members of the Duke IRB in the event of an internal audit. The digital audiofiles will be destroyed 6 years after the project is complete.
- We request that members of the teleconference also maintain confidentiality by not disclosing information gained during the teleconference to others not involved in today's session, and by not disclosing the identity of any person who provided specific information.
- While we are working hard to maintain confidentiality, there is a small potential risk that specific statements may be traced back to specific informants. This risk is similar to that involved in discussions within any professional setting. We ask that all participants help to minimize this risk by remaining cognizant of the importance of confidentiality and adhering to these terms of privacy and non-disclosure.
- The Duke University Medical Center IRB (IRB reference number Pro00004165) has approved how we are handling these teleconferences.

Now I am going to go through the participants in today's call one-by-one, and ask each person individually to respond with "I consent" if these terms are agreeable. If you do not agree with these terms, please respond with "I do not consent" and you will be free to exit the teleconference; any key informant has the option to discontinue participation at any point during the conference call. I will also ask you if you are willing to have documentation linking you to this research project, in other words, if you are willing to be included in the list of key informants within our white paper. Please indicate "I agree to be in the listing of key informants" or "I do not wish to be in the listing of key informants." If you do not want to be in the list, we will count you as an anonymous key informant in the final tally of the number of teleconference participants. Are there any questions?

[If not, proceed as below.]

The statement to which you will respond with "I consent" or "I do not consent" is the following:

"I understand that the teleconference in which I am about to participate will solicit information that will be used to generate a white paper for CMS. I am being asked to describe experiences which I have had with payment policy impact on clinical trials. Any information I provide may

be used in development of the white paper, and may conceivably be inadvertently linked to me in the public domain – though careful precautions are in place to ensure confidentiality. I will participate in this call without disclosing my own identity or that of any other participant.”

The statement to which you will respond with “I agree to be in the listing of key informants” or “I do not wish to be in the listing of key informants” is the following:

“Within the final white paper there will be a list of the key informants interviewed. This will be a listing only, and no specific statements, comments, or concerns will be linked with any individual participant. You can elect to not be included in this listing, and we will count you as an anonymous key informant. Please indicate whether you agree to be in this listing.”

[Proceed to call out names individually, in alphabetical order.]

Appendix G: Key Informants

CMS	Sidney Trieiger, one anonymous participant
FDA	Dr. Wiley Chambers, Dr. Thomas Gross, two anonymous participants
NIH	Dr. David Gordon, Bryan Walker, Dr. John Gallin
Business/Employers/Insurers	Bruce Bradley (General Motors), Gwen Thompson (General Motors), Helen Darling (National Business Group on Health and Institute of Medicine Evidence-based Medicine Roundtable), Dr. Don Bradley (Blue Cross Blue Shield of North Carolina)
Pharmaceutical Industry	Lee Scheible (Eli Lilly), Linda House (Eli Lilly), one anonymous participant
Patient Advocacy Groups	Holly D'Addurno (North Carolina Leukemia and Lymphoma Society), George Dahlman (National Leukemia and Lymphoma Society), Rosemary Rosso (National Breast Cancer Coalition)
Study PI or Coordinator	Dr. Keith Sullivan (SCOT trial PI), Holly Burch (CORAL 1 trial Clinical Research Coordinator), five anonymous participants