INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

LARGE SIMPLE TRIALS AND KNOWLEDGE GENERATION IN A LEARNING HEALTH SYSTEM

An Institute of Medicine Workshop

November 26-27, 2012
Keck Center, The National Academies
500 5th St, NW
Washington, DC 20001

Workshop Framing Materials

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- Gulliford, Martin et al. Cluster randomised trial in the General Practice Research Database: 1. Electronic decision support to reduce antibiotic prescribing in primary care (eCRT study). *Trials*. 2011.

SECTION 7: POLICY NEEDS – MEDICAL PRODUCT REGULATORY ISSUES

- Getz, Kenneth et al. Measuring the Incidence, Causes, and Repercussions of Protocol Amendments. *Drug Information Journal*. 2011.
- Tufts Center for the Study of Drug Development. One in five procedures generates extraneous clinical trials data. *Tufts University*. 2012.
- Eisenstein, Eric et al. Sensible approaches for reducing clinical trial costs. *Clinical Trials*. 2008.

SECTION 8: BIOGRAPHIES AND MEETING LOGISTICS

- Planning Committee Biographies
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- Location, Hotel, and Travel

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An Institute of Medicine Workshop

NOVEMBER 26 & 27, 2012

ROOM 100
KECK CENTER
500 FIFTH ST NW, WASHINGTON DC

ROUNDTABLE ON VALUE & SCIENCE-DRIVEN HEALTH CARE
FORUM ON DRUG DISCOVERY, DEVELOPMENT, AND TRANSLATION

Meeting objectives

1. Explore accelerating the use of large simple trials (LSTs) to improve the speed and practicality of knowledge generation for medical decision making and medical product development;
2. Consider the concepts of LST design, examples of successful LSTs, the relative advantages of LSTs, and the infrastructure needed to build LST capacity as a routine function of care;
3. Identify structural, cultural, and regulatory barriers hindering the development of an enhanced LST capacity; and discuss needs and strategies in building public demand for, and participation in, LSTs; and
4. Suggest near-term strategies for accelerating progress in the uptake of LSTs in the United States.

Agenda

Monday, November 26th

1:00 pm	**Welcome, introductions, and overview**

Welcome, framing of the meeting, and agenda overview
- Michael McGinnis (Institute of Medicine)
- Richard Kuntz (Planning Committee co-Chair, Medtronic)
- David DeMets (Planning Committee co-Chair, University of Wisconsin)

1:15pm	**Introduction to Large Simple Trials**

Session chair: David DeMets (Planning Committee co-Chair, University of Wisconsin)

- **Session objectives:**
  - Set vision for LSTs as part of learning health system
  - Discuss advantages of LSTs over current trial approaches
  - Discuss opportunities for LSTs as way to embed trials in growing digital infrastructure

- **Presentations:**
  - **A vision for LSTs in the learning health system**
    Michael Lauer (National Heart Lung and Blood Institute)
  - **Opportunities and challenges for LSTs**
    Ralph Horwitz (GlaxoSmithKline)

- **Session Questions:**
  1. What is a LST?
  2. How would these trials fit into the larger clinical research ecosystem in a learning health system?
  3. What need would this approach to clinical trials fill? (RCT cost, efficiency, generalizability)
  4. What are the advantages/disadvantages to this approach? (Heterogeneity, sub group analysis)
  5. How does the increased adoption of EHRs provide an opportunity for LSTs?
  6. Are there modifications to current design and conduct of LSTs that would enhance their value to a LHS?
  7. What are some examples of the areas still in need of work in order to realize this vision? (eg. Culture shift needed to adopt potentially disruptive technologies)

Q&A and Open Discussion

1:55pm	**Highlighted examples of LSTs**

Session chair: James Young (Cleveland Clinic)

- **Session objectives:**
  - Highlight 4 examples of LSTs that each exemplify a different defining characteristic of LSTs
  - Emphasize tradeoffs in trial design by discussing pros and cons, giving examples of how these play out, and suggesting alternative approaches
  - Foreshadow rest of workshop by asking LST example speakers to address their experiences (successes and failures) with stakeholder engagement, infrastructure, and policy.

- **Presentations:**
  - Very large, population-based trial with broad inclusion criteria, high cost-efficiency, and hybrid design (mail-based plus in-clinic component)
    - **VITamin D/ OmegA 3 triaL (VITAL)**
      JoAnn Manson (Harvard University)
  - Trial assessing role of waiving medication copayments for improving drug adherence and health outcomes, collaboration with health insurance company (Aetna)
    - **Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MIFREE) trial**
      Niteesh Choudhry (Brigham and Women's Hospital)

- Cluster randomized trial involving pediatric practices, utilization of EHR and decision support tools for obesity interventions
  - **High Five for Kids Trial/ Study of Technology to Accelerate Research (STAR)**
    Elsie Taveras (Harvard Pilgrim Health Care Institute)
- Industry trial for regulatory approval with global component
  - **Heart Outcomes Prevention Evaluation (HOPE) trial**
    PJ Deveraux (McMaster University)

➢ **Session questions:**

1. Please give a very brief introduction on the specifics of the trial and why it is considered a LST.
2. How does the trial address the issues of generalizability of evidence produced, simplification of research processes, and cost effectiveness?
3. In retrospect, what were the risks and tradeoffs associated with the choice of an LST design? (eg. Risk of not collecting data that could be subsequently requested) Please discuss pros and cons, giving examples of how these play out and suggesting alternative approaches, and any design changes you would make based on lessons learned.
4. What were your team's experiences (successes and failures) with the following issues, which will be discussed in further detail during the course of the workshop:
   a. Stakeholder engagement – health system leaders, clinicians, patients
   b. Infrastructure – research infrastructure, health IT
   c. Policy – privacy, consent, IRB issues, regulatory

Q&A and Open Discussion

3:15pm	**Break**

3:30pm	**Partners perspectives on LST uptake**

Session chair: Joe Selby (Patient-Centered Outcomes Research Institute)

➢ **Session objectives:**

- Identification of stakeholders relevant to the increased use of LSTs—focusing on patients, clinicians/health care systems, and payers—and incentives they face that could impede or advance uptake
- Engage issues of most importance to stakeholders and deliberate on what it will take from each of their respective points of view

➢ **Presentations:**

- **Patient perspective**- Nancy Roach (Fight Colorectal Cancer)
- **Health systems/ Clinician perspective**- Alan Go (Kaiser Permanente)
- **Payer perspective**- Lew Sandy (UnitedHealth)

➢ **Session questions:**

1. What are the top three issues for patients/clinicians/payers in *considering the use* of an LST approach to generate clinical evidence?
2. What are the top three considerations for patients and clinicians in contemplating the greater *integration of trials into routine care* settings?
3. What are the top three priorities for *raising awareness and participation* of patients and clinicians in trials integrated into routine care?
4. What are your priorities regarding the types of evidence that can be generated through LSTs?
5. What are the roles for health systems and payers in a) setting priorities, b) dedicating staff support, and c) providing funding for LSTs in routine care settings?

Q&A and Open Discussion

4:30pm	**Summary and preview of next day**

5:00pm	**Adjourn**

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Tuesday, November 27th

8:00 am Coffee and light breakfast available

8:30 am	**Welcome, brief agenda overview**

Welcome, framing of the meeting, and agenda overview
- David DeMets (Planning Committee co-Chair, University of Wisconsin)
- Richard Kuntz (Planning Committee co-Chair, Medtronic)

8:45 am	**Infrastructure needs**

Session chair: John Orloff (Novartis)

- **Session objectives:**
  - Highlight infrastructure needs and barriers to greater performance of LSTs
  - Discuss needs and potential approaches to merge goals of care system with research, focusing on the current state and future potential of the use of EHRs as platform for LSTs
  - Discuss establishment and sustainability of trial networks as an infrastructure to host and facilitate LSTs

- **Presentations:**
  - **Aligning care and research to reduce burdens and improve integration** – Rich Platt (Harvard Pilgrim Health Care Institute)
  - **Point-of-care trials using EHR platforms**- Ryan Ferguson (VA Boston Healthcare System)

- **Getting to comparable, computable data**- Rebecca Kush (Clinical Data Interchange Standards Consortium)
- **Building reusable research networks**- Carole Lannon (Cincinnati Children's)

➢ **Session questions:**

1. What are the current infrastructure needs for more widespread performance of LSTs? Would you consider conducting LSTs on your network?
2. What opportunities and challenges currently exist in using EHRs as a platform for LSTs? What are the priorities for change to maximize this potential going forward? How can we minimize disruption to delivery of healthcare in order to incentivize more practicing physicians to engage in knowledge generation?
3. What is the current state of the use of routinely collected clinical data for trials? What role will data standards play in facilitating LSTs? What are the priorities for change to maximize this potential going forward?
4. What is the current state of reusable research networks in the US? What is their role in LSTs? What are the major opportunities and barriers to the reusable network approach? Are there alternative community-based settings with lower infrastructure costs and greater access to patients that should be considered? Are existing research networks (including perhaps CTSA institutions, or PBRNs) fit for purpose? What business models (e.g. "hub and spoke") would be most effective?

Q&A and Open Discussion

10:45am	**Break**

11:00am	**Policy needs: Ethics, trial processes**

Session chair: Rob Califf (Duke University)

➢ **Session objectives:**

- Spotlight and differentiate real and perceived policy barriers to greater use of LSTs
- Highlight examples of ways these have been dealt with (or overcome)
- Anticipate potential policy issues as trials move to leverage electronic systems
- Suggest components of a policy framework that would facilitate LSTs

➢ **Presentations:**

- **Policy overview-** Robert Califf (Duke University)
- **Ethical issues of bringing research and care closer together-** Ruth Faden (Johns Hopkins University)
- **Trial process challenges (privacy, IRBs)-** Deven McGraw (Center for Democracy and Technology)

➢ **Session questions:**

1. What are the major policy barriers to the more widespread performance of LSTs? How have these barriers been overcome in the past? What are the priorities for change going forward?
2. What are the important ethical issues to consider in bringing research and care closer together? What are the components of a new ethical framework to support a learning health system?
3. What are the major privacy and human subjects research policy-associated considerations for LSTs? How have these challenges been overcome? What are the priorities for change going forward?
4. What are the relevant ethical and policy considerations associated with randomization without additional consent in situations of equipoise?

Q&A and Open Discussion

12:00pm	**Lunch keynote**

- Randomized evaluations of accepted choices in treatment (REACT) trials
  Tjeerd-Pieter van Staa (Clinical Practice Research Datalink (UK))

- **Session questions:**
  1. What are the REACT trials? What was the impetus for these trials? How do they compare to LSTs?
  2. What are the stakeholder engagement-related challenges you have faced in setting up/running these trials? How have the relevant stakeholder groups responded?
  3. What are the infrastructure-related challenges and opportunities you have faced? What role has the level of EHR adoption placed in facilitating or inhibiting them? What are the most crucial non-IT infrastructure resources?
  4. How have you addressed concerns about the accuracy and validity of data in the electronic medical record?
  5. What are the policy-related challenges you have faced? What are the differences between the UK and US systems that have facilitated or impeded these challenges?
  6. What lessons learned and/or best practices would you pass along to LST investigators? What would you do differently?

Q&A and Open Discussion

1:00pm	**Policy needs: Medical product regulatory issues**

Session chair: Rick Kuntz (Planning Committee co-chair, Medtronic Inc.)

- **Presentations:**
  - **Trial complexity**- Ken Getz (Tufts University)
  - **Simplifying clinical trials**– Christopher Granger (Duke University)
  - **FDA perspective**- Rachel Sherman (FDA/CDER)

- **Session questions:**

1. Generally speaking, what is the optimal role of LSTs in the medical products regulatory approval pathway? Are there areas of medical product development in which LSTs are not useful?
2. How can an understanding of those policy/regulatory issues that drive complexity in traditional RCTs, and the strategies to counteract them, be applied to the adoption and use of LSTs in medical products regulatory contexts?
3. What are the real and perceived regulatory barriers hindering the development of an enhanced LST capacity?
4. What are some near-term strategies for accelerating progress in the uptake of LSTs in the United States?
5. What is the current thinking from the FDA in terms of how and when LSTs might be used without jeopardizing the medical products development process?

Q&A and Open Discussion

2:00pm	**Break**

2:15pm	**Strategies going forward**

Session chair: David DeMets (Planning Committee co-Chair, University of Wisconsin)

- **Session Objectives:**
  - Identify and discuss issues and key themes from the workshop
  - Consider strategies and priorities for accelerating progress in the uptake of LSTs in the United States

- **Brief summaries and key stakeholder perspectives from workshop:**
  - Representatives from key stakeholders groups will provide an overview of key themes and issues identified from their perspectives

    - Federal funders – Michael Lauer (NHLBI)
    - Non-governmental funders – Robert Ratner (American Diabetes Association)
    - Food and Drug Administration – Bram Zuckerman (FDA/CDRH)
    - Centers for Medicare & Medicaid Services – Rosemarie Hakim (CMS)
    - Private payers – William Crown (Optum)
    - Industry – Peter Held (AstraZeneca)
    - Patients – Kate Ryan (National Women's Health Network)
    - Clinical researchers – Elizabeth Chrischilles (University of Iowa)

- **Panel questions:**
  1. What are the themes of today's presentations and discussions that have resonated most strongly with you?

2. Where do you see the most opportunity for the application of LSTs? What do you see as the biggest barriers?
3. What will it take to seize these opportunities and overcome the barriers?
4. Based on the presentations and discussions, can you identify issues that need to be resolved by others before progress can be made? For example, as lead of the Ethics and Processes section, can you identify critical needs in infrastructure or regulatory issues that need to be resolved before you can achieve your goals?
5. If you were granted one wish to move LSTs forward, what would that wish be?

Q&A and Open Discussion

4:15 pm	**Next steps**

- **Session Description:** Workshop will conclude with a brief discussion and summary of next steps.

5:00pm	**Adjourn**

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November 26-27, 2012

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Institute of Medicine Background

FORUM ON DRUG DISCOVERY, DEVELOPMENT, AND TRANSLATION

The Institute of Medicine's Forum on Drug Discovery, Development, and Translation was created in 2005 by the IOM's Board on Health Sciences Policy to provide a unique platform for dialogue and collaboration among thought leaders and stakeholders in government, academia, industry, foundations and patient advocacy. The Forum brings together leaders from private sector sponsors of biomedical and clinical research, federal agencies sponsoring and regulating biomedical and clinical research, the academic community, and consumers, and in doing so serves to educate the policy community about issues where science and policy intersect.

The Forum convenes several times each year to identify and discuss key problems and strategies in the discovery, development, and translation of drugs. To supplement the perspectives and expertise of its members, the Drug Forum also holds public workshops to engage a wide range of experts, members of the public, and the policy community in discussing areas of concern in the science and policy of drug development. The Forum's public meetings focus substantial public attention on critical areas of drug development, focusing on the major themes outlined below.

The Approach to Drug Development

Despite exciting scientific advances, the pathway from basic science to new therapeutics faces challenges on many fronts. New paradigms for discovering and developing drugs are being sought to bridge the ever-widening gap between scientific discoveries and translation of those discoveries into life-changing medications. The Forum has explored these issues from many perspectives—emerging technology platforms, regulatory efficiency, intellectual property concerns, the potential for precompetitive collaboration, and innovative business models that address the "valley of death."

Strengthening the Scientific Basis of Drug Regulation

Over the past several years, the Forum has focused its attention on the scientific basis for the regulation of drugs. In February 2010, the Forum held a workshop that examined the state of the science of drug regulation and considered approaches for enhancing the scientific basis of regulatory decision making.

Transforming Research and Fostering Collaborative Research

The Forum has established an initiative to examine the state of clinical trials in the U.S., identify areas of strength and weakness in our current clinical trial enterprise, and consider transformative strategies for enhancing the ways in which clinical research is organized and conducted. Workshops and meetings held in 2009 and 2010 considered case studies in four disease areas; and included discussions around issues of management of conflict of interest, and addressing regulatory and administrative impediments to the conduct of clinical trials. Meetings in 2011 addressed how to move toward greater public engagement in and understanding of the clinical trial enterprise, and establishing a framework for a transformed national clinical trial enterprise.

Developing Drugs for Rare and Neglected Diseases and Addressing Urgent Global Health Problems

The Forum is sponsoring a series of workshops on the global problem of MDR TB. The Forum held a foundational workshop in Washington, DC in 2008, for which it commissioned a paper from Partners In Health. Additional workshops are being held in the four countries with the highest MDR TB burden—South Africa and Russia (held 2010), and India (held 2011) and China (January 2013). Also in 2012, the Forum convened a focused initiative to consider the global drug supply chain for quality-assured second-line drugs for tuberculosis.

Promoting Public Understanding of Drug Development

Successful introduction of new therapeutic entities requires testing in an informed and motivated public. The Forum has spent concerted effort to understand what limits public participation and how to enhance more widespread acceptance of the importance of advancing therapeutic development through public participation in the drug development process. Forum meetings held in the spring and fall of 2010 addressed these issues. The Forum plans to continue to work with multiple stakeholders to improve public understanding of and participation in the drug development process.

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The Roundtable

The Institute of Medicine's **Roundtable on Value & Science-Driven Health Care** provides a trusted venue for national leaders in health care to work cooperatively toward their common commitment to effective, innovative health care that consistently adds value to patients and society. A common motivation among Members is their shared concern that, despite being the world's best on various dimensions, health care in America falls far short of the possible on important measures of health outcomes and value. In 2011, about $2.7 trillion was spent in the United States on health care—nearly 50% higher per capita than that spent by the next highest country—yet performance on issues such as infant mortality, life expectancy, and the prevalence, control, and treatment of chronic diseases, ranks far down the list in international comparisons. Members working together to address these problems represent the leadership from core stakeholder communities, including clinicians, patients, health care organizations, employers, manufacturers, insurers, health information technology, researchers, and policy makers.

Vision: Development of a continuously **learning health system** in which science, informatics, incentives, and culture are aligned for constant improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience.

Mission: Identify and address those matters of greatest need in achieving continuously improving care at lower costs, and for which the trusted venue of the IOM offers particular advantage in fostering the necessary level of cooperative and collaborative discussions, strategies and activities.

Goal: "By the year 2020, ninety percent of clinical decisions will be supported by accurate, timely, and up-to-date clinical information and will reflect the best available evidence." **(Charter, 2006)**

Approach: As leaders in their fields, Roundtable members work with their colleagues to marshal the energy and resources of their respective sectors to work for sustained public-private cooperation in fostering the changes possible. The work of the Roundtable has five elements, initiated in a phased and overlapping fashion:

1. *Making the case*—analysis of the limitations in the evidence for clinical decisions, and approaches to the challenges presented
2. *Describing the possible*—vision and path to a continuously learning health system, through alignment of science, technology, culture, and incentives
3. *Stewarding the action*—Innovation Collaboratives in which stakeholder organizations work together on projects requiring cooperative solutions
4. *Getting the word out*—IOM publication channels for expert consideration of core challenges and opinion leader comments on solutions in progress
5. *Assessing the progress*—metrics for monitoring national, state, and local progress on better care, lower costs, better health

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Highlighted Examples of Large Simple Trials

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The *VIT*amin D and Omeg*A*-3 Tria*L* (VITAL): Rationale and design of a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease

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ABSTRACT

Data from laboratory studies, observational research, and/or secondary prevention trials suggest that vitamin D and marine omega-3 fatty acids may reduce risk for cancer or cardiovascular disease (CVD), but primary prevention trials with adequate dosing in general populations (i.e., unselected for disease risk) are lacking. The ongoing *VIT*amin D and Omeg*A*-3 Tria*L* (VITAL) is a large randomized, double-blind, placebo-controlled, 2x2 factorial trial of vitamin D (in the form of vitamin D_3 [cholecalciferol], 2000 IU/day) and marine omega-3 fatty acid (Omacor® fish oil, eicosapentaenoic acid [EPA] + docosahexaenoic acid [DHA], 1 g/day) supplements in the primary prevention of cancer and CVD among a multi-ethnic population of 20,000 U.S. men aged ≥50 and women aged ≥55. The mean treatment period will be 5 years. Baseline blood samples will be collected in at least 16,000 participants, with follow-up blood collection in about 6000 participants. Yearly follow-up questionnaires will assess treatment compliance (plasma biomarker measures will also assess compliance in a random sample of participants), use of non-study drugs or supplements, occurrence of endpoints, and cancer and vascular risk factors. Self-reported endpoints will be confirmed by medical record review by physicians blinded to treatment assignment, and deaths will be ascertained through national registries and other sources. Ancillary studies will investigate whether these agents affect risk for diabetes and glucose intolerance; hypertension; cognitive decline; depression; osteoporosis and fracture; physical disability and falls; asthma and other respiratory diseases; infections; and rheumatoid arthritis, systemic lupus erythematosus, thyroid diseases, and other autoimmune disorders.

1. Introduction

Although there have been marked advances in our understanding of the potential role of vitamin D and omega-3 fatty acids in the prevention of cancer and cardiovascular disease (CVD) in recent years, clear gaps in knowledge remain. Data from laboratory studies [1–3], ecologic studies [4–7], epidemiologic investigations [8–19], and secondary analyses of small randomized trials [20–23] suggest a protective effect for vitamin D against cancer and CVD. Mechanisms by which vitamin

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D may prevent these diseases [1–3] are shown in Fig. 1. The vitamin D receptor is expressed in most tissues. Vitamin D may promote cell differentiation, inhibit cancer-cell proliferation, and exhibit anti-inflammatory, proapototic, and antiangiogenic properties; it may also inhibit vascular smooth muscle proliferation and vascular calcification and control blood pressure and glucose metabolism. One large trial – the Women's Health Initiative calcium-vitamin D trial, in which 36,282 postmenopausal women were randomly assigned to a daily combination of calcium (1000 mg) and low-dose vitamin D_3 (400 IU) or to placebo and followed for a mean of 7 years – found that the intervention did not reduce risk for cancer, CHD, or stroke [24,25], but its effect on blood levels of 25-hydroxyvitamin D [25(OH)D], the major circulating vitamin D metabolite, was small [8]. However, there are no large randomized trials of supplemental vitamin D in doses adequate to produce meaningful changes in 25(OH)D levels or designed to assess cancer or CVD as primary prespecified outcomes. Although there is a lack of consensus on the definition and prevalence of vitamin D insufficiency in the United States [26,27], it is concerning that some estimates suggest that >1/2 of middle-aged and older women and >1/3 of similarly aged men have such insufficiency [28,29]. African-American (black) individuals are particularly vulnerable, in part because darkly pigmented skin is less able to synthesize vitamin D in response to solar radiation and because blacks tend to have lower dietary and supplemental vitamin D intakes than whites [30,31]. Obese individuals are also at above-average risk, presumably because of decreased bioavailability of this fat-soluble vitamin [32,33]. Given the aging population and soaring obesity prevalence [34], low vitamin D status is an increasingly important public health issue.

The marine omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are found in fish and fish-oil supplements, have shown considerable promise for the prevention of CVD in laboratory [35–41] and observational studies [42–46]; large randomized trials in secondary prevention [47] or high-risk settings [48] have also found benefit. Data on marine omega-3 fatty acids for cancer prevention have been suggestive but inconsistent [48–53]. Mechanisms by which marine omega-3 fatty acids may reduce the risk for CVD [35–41] and cancer [54] are shown in Fig. 2. However, there are no trials of marine omega-3 fatty acid supplements for the primary prevention of these diseases in a general population that has been selected only on the basis of age and not on vascular risk factors such as diabetes or dyslipidemia. It is important to clarify these relationships.

2. Materials and methods

2.1. Overview of study design

To address the role of vitamin D and marine omega-3 fatty acids in the primary prevention of cancer and CVD, we are conducting the *VIT*amin D and Omeg*A*-3 Tria*L* (VITAL), a randomized, double-blind, placebo-controlled clinical trial among 20,000 U.S. men and women without cancer or CVD at baseline, who are selected on age only (men aged ≥50 and women aged

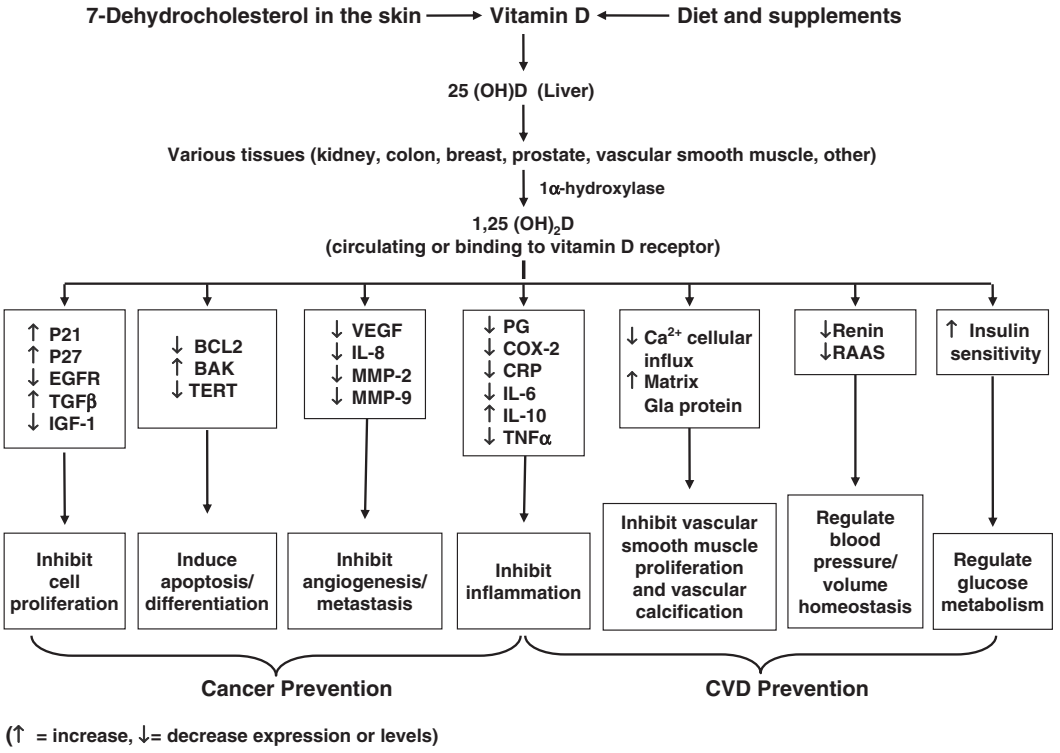

Fig. 1. Mechanisms by which vitamin D may lower cancer and cardiovascular risk. *BAK*, BCL2-antagonist/killer; *BCL2*, B-cell chronic lymphocytic leukemia/lymphoma 2; *COX-2*, cyclooxygenase-2; *CRP*, C-reactive protein; *EGFR*, epidermal growth factor receptor; *IGF-1*, insulin-like growth factor-1; *IL-6*, interleukin-6; *IL-8*, interleukin-8; *IL-10*, interleukin-10; *MMP-2*, matrix metalloproteinase-2; *MMP-9*, matrix metalloproteinase-9; *PG*, prostaglandin; *RAAS*, renin-angiotensin-aldosterone system; *TERT*, telomerase reverse transcriptase; *TGFß*, transforming growth factor-ß; *TNFα*, tumor necrosis factor-α; *VEGF*, vascular endothelial growth factor.

≥55), with an oversampling of blacks. In a 2x2 factorial design, participants will be randomized to vitamin D_3 (cholecalciferol; 2000 IU/day) and marine omega-3 fatty acid (Omacor® fish oil, EPA + DHA, 1 g/d) supplements (or placebos) independently. The mean treatment period will be 5 years. Baseline blood samples will be collected in at least 80% of participants (n = 16,000), with follow-up blood collection in about 6000 participants. Yearly follow-up questionnaires will assess treatment compliance (plasma biomarker measures will also assess compliance in a random sample of participants), use of non-study drugs or supplements, occurrence of endpoints, and cancer and vascular risk factors. Self-reported endpoints will be confirmed by medical record review by a committee of physicians blinded to treatment assignment, and deaths will be ascertained through the National Death Index-Plus and other sources. A summary of the study design is provided in Fig. 3.

2.2. Aims

The primary aims of the trial are to test whether vitamin D_3 or marine omega-3 fatty acid supplementation reduces the risk for total cancer and major CVD events (a composite endpoint of myocardial infarction [MI], stroke, and cardiovascular mortality). The secondary aims are to test whether vitamin D_3 or marine omega-3 fatty acid supplementation reduces the risk for site-specific cancers, including incident colorectal cancer, breast cancer (in women), and prostate cancer (in men); total cancer mortality; an expanded composite cardiovascular endpoint of MI, stroke, cardiovascular mortality, and coronary revascularization (coronary artery bypass grafting [CABG] or percutaneous coronary intervention [PCI]); and the individual components of the primary cardiovascular endpoint, particularly total CVD mortality. The tertiary aims are to explore whether vitamin D_3 and marine omega-3 fatty acid supplementation exhibit synergistic or additive effects on the risk for total cancer, major CVD events, and the secondary endpoints specified above, and to explore whether the effect of vitamin D_3 or marine omega-3 fatty acid supplementation on cancer and CVD risk varies by baseline blood levels of these nutrients, race/skin pigmentation (for vitamin D_3), and body mass index (BMI) (for vitamin D_3). Blacks are at higher risk of vitamin D deficiency and are also at higher risk for certain cancers (e.g., prostate cancer) [55] and cardiovascular events (e.g., stroke) [56], as well as mortality from cancer [55] and CVD [56], so it is critical to test the effect of vitamin D supplementation in this group.

2.3. Sponsors

The primary sponsor of VITAL is the National Cancer Institute, and the secondary sponsor is the National Heart, Lung and Blood Institute. The Office of Dietary Supplements, the National Institute of Neurologic Disorders and Stroke, and the National Center for Complementary and Alternative Medicine are also cosponsors of the study. Several other NIH institutes are sponsors of VITAL ancillary studies. Pharmavite LLC of Northridge, California (vitamin D_3) and Pronova BioPharma of Norway (Omacor® fish oil) are donating the agents, matching placebos, and packaging in the form of calendar packs. Because the trial (with the exception of some ancillary studies [Section 2.12]) is being conducted by mail and is utilizing a 2×2 factorial design to test the independent and synergistic effects of two promising interventions, it is extremely cost effective. VITAL has been approved by the Institutional Review Board of Partners Healthcare/Brigham and Women's Hospital, and the study agents have received Investigational New Drug Approval from the U.S. Food and Drug Administration. VITAL is registered at clinicaltrials.gov (NCT01169259), and the study website is www.vitalstudy.org.

2.4. Interventions

2.4.1. Vitamin D supplement

VITAL is testing a vitamin D_3 dose of 2000 IU/day. A careful review of the literature suggests that this dose provides the best balance of efficacy and safety.

Efficacy: We seek to obtain a large-enough difference in vitamin D status between the treatment and placebo groups to detect benefits for the primary endpoints of cancer and CVD. VITAL was designed in 2008, when the recommended dietary

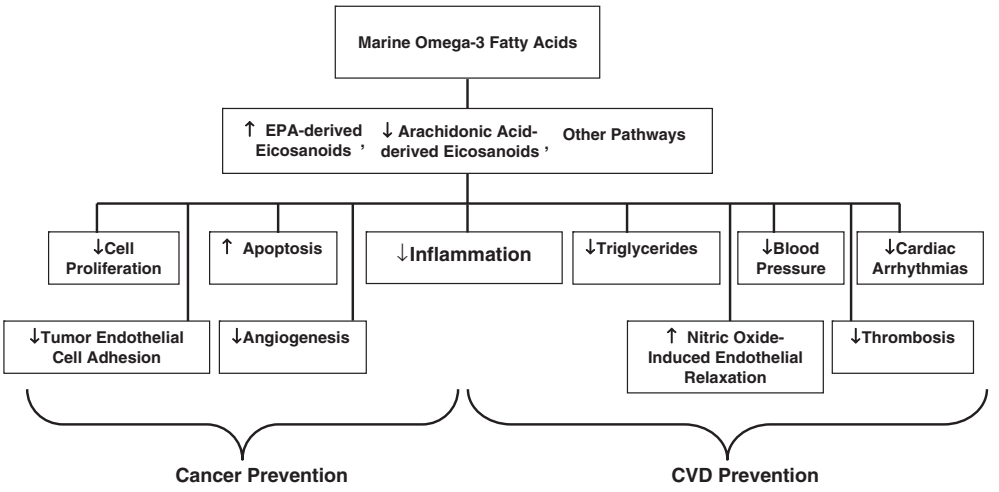

Fig. 2. Mechanisms by which marine omega-3 fatty acids may lower cancer and cardiovascular risk.

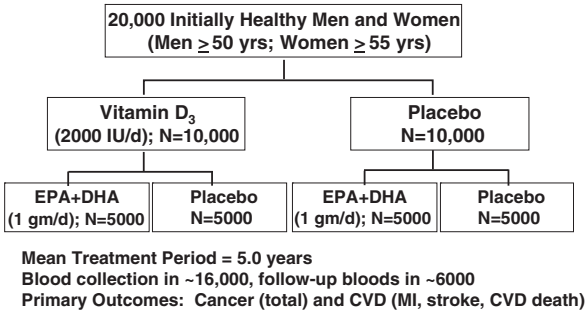

Fig. 3. The *VIT*amin D and Omeg*A*-3 Tria*L* (VITAL) design.

allowances (RDA), which are set by the Institute of Medicine (IOM), were 400 IU/day for adults aged 50–70 and 600 IU/day for adults aged >70 [57]. In 2011, the IOM raised the RDAs for these age groups to 600 IU/day and 800 IU/day, respectively [26]. These RDAs correspond to a serum 25(OH)D level of 50 nmol/L and are sufficient for the maintenance of bone health in at least 97.5% of the North American population. Nevertheless, accumulating data suggest that vitamin D intakes above these RDAs may be necessary for maximal health benefits. In a review of studies of serum 25(OH)D in relation to various outcomes, including colorectal cancer, falls, fractures, physical functioning, and dental health, Bischoff-Ferrari et al. [58] found that advantageous 25(OH)D levels began at 75 nmol/L, and optimal levels were between 90 and 100 nmol/L. The average older individual requires an oral vitamin D_3 intake of at least 800–1000 IU/day to achieve a serum 25(OH)D of 75 nmol/L [59]. Among postmenopausal women in the Women's Health Initiative (a population similar to that of VITAL), 400 IU/day of vitamin D_3 was estimated to have raised median plasma 25(OH)D from 42.3 to only 54.1 nmol/L [8,24]. Also, a study by Aloia et al. [60] showed a nonlinear dose–response relation between serum 25(OH)D and vitamin D intake, with the rate of increase in serum levels slowing at higher levels of intake. Extrapolation of the Women's Health Initiative data, along with consideration of the Aloia et al. findings, suggest that 2000 IU of vitamin D_3 would be required to reach the postulated optimal value of 90 nmol/L in the active vitamin D group in VITAL. The difference in achieved 25(OH)D levels between the active treatment and placebo groups is expected to be approximately 50 nmol/L.

Safety: The vitamin D study pills have undergone extensive quality control testing for stability of nutrient content and other parameters at a range of temperatures and humidity levels. There appear to be few safety issues associated with the selected treatment dose of 2000 IU/day. Because we are excluding from the trial persons who report supplemental vitamin D intakes of more than 800 IU/day (see Section 2.5) and we can estimate an average of 200 IU/day from diet [61], few if any participants assigned to the active vitamin D group will be consuming a dose above 3000 IU/day, which is well below the tolerable upper intake level of 4000 IU/day set by the IOM [26] and the no-observed-adverse-effect level of 4000 IU/day specified by the European Commission Scientific Committee on Food [62]. Moreover, participants assigned to the placebo group should not become vitamin D-deficient because we are allowing background intake at RDA levels. Potential side effects of vitamin D are rare and include gastrointestinal (GI) symptoms (nausea, constipation, or diarrhea), hypercalcemia, and kidney stones. To minimize risk for the latter two outcomes, we are requiring that participants limit calcium intake from supplemental sources to 1200 mg/day, and we are excluding from the trial persons with a history of hypercalcemia or sarcoidosis. As a further safety precaution, blood levels of calcium, parathyroid hormone, and kidney function will be monitored in a random subsample of participants.

Exclusion of calcium from the intervention: We have not included calcium as a component of the intervention, for several reasons. First, to test the effects of vitamin D alone, calcium alone, and calcium-plus–vitamin D would require a factorial design with a much larger sample size and a much higher cost than a trial of vitamin D alone. Second, the Women's Health Initiative calcium–vitamin D trial reported a statistically significant 17% increase in the risk for kidney stones with combined supplementation [24]. Third, supplemental calcium (calcium citrate, 1 g/day) was associated with a significant doubling in risk for MI and a borderline significant 47% increase in risk for major CVD events in a 5-year trial among 1471 initially healthy older women [63]. Fourth, the high prevalence of calcium supplement use in women [64] would reduce the pool of eligible female participants. Finally, some studies have reported a direct association between intake of calcium or milk and incidence of prostate cancer [65–67].

2.4.2. Marine omega-3 fatty acid supplement

VITAL is testing a total marine omega-3 fatty acid dose of 1 g/day (EPA + DHA, in the ratio of 1.3 to 1). A careful review of the literature suggests that a total dose of 1 g/day provides the best balance of efficacy and safety.

Efficacy: We seek to obtain a large-enough difference in omega-3 fatty acid status between the treatment and placebo groups to detect health benefits. Health authorities' recommendations vary from 400 mg to 1 g/day for cardioprotection [61]. For VITAL, we selected a total dose of marine omega-3 fatty acids of 1 g/day, which is recommended by the American Heart Association (AHA) and was demonstrated to be beneficial, with minimal side effects, in a large secondary prevention trial [47]. Because the optimal ratio of EPA to DHA is unknown [39,68], we chose an EPA-to-DHA ratio close to 1-to-1, specifically 1.3-to-1. The 1 g/day dose in a single capsule and 1.3-to-1 ratio is available in an FDA-approved product (Omacor®). On a related note, the ratio of omega-3 to omega-6 fatty acid intake may also be important for disease prevention. This ratio is between 1:10 and 1:20 in most Western countries, including the U.S., whereas the

optimal ratio has been hypothesized to be closer to 1:1 or 1:2 [69,70], although this is controversial [71]. Indeed, there is growing consensus that the absolute intake of omega-3 is a more important predictor of health than is the ratio of omega-3 to omega-6 intake, at least for cardiovascular outcomes [71–74]. However, given that the average intake of EPA + DHA is 100–200 mg/day among U.S. adults [61], the intervention of 1 g/day is expected to increase the average participant's omega-3 intake by a factor of 5 to 10. Assuming no concurrent change in omega-6 intake, the omega-3 dose would thus have the effect of achieving the purported optimal omega-3 to omega-6 ratio and providing intakes associated with benefits in previous studies.

Safety: The chosen omega-3 fatty acid supplement, Omacor® fish oil, has undergone an extensive purification process and is free of environmental toxins (e.g., methylmercury, polychlorinated biphenyls [PCBs], and dioxins) found in some fish. It has also undergone extensive quality control testing for stability of nutrient content and other parameters at a range of temperatures and humidity levels. Omacor® contains no vitamin D, ensuring that participants are not given higher vitamin D doses than intended and that VITAL has the ability to test the separate effects of the two agents (vitamin D and marine omega-3 fatty acids) under study.

There appear to be few safety issues associated with the selected treatment dose of 1 g/day. The FDA has concluded that marine omega-3 fatty acid doses of up to 3 g/day are "Generally Recognized as Safe" [75]. Although omega-3 fatty acids have potential antithrombotic effects, systematic reviews of data from small trials suggest that omega-3 fatty acid supplements at doses of up to 4 g/day do not increase the risk of clinically significant bleeding, even in combination with anticoagulant medications such as aspirin or warfarin [76,77]. One large trial [48] did report an increase in bleeding events with 1.8 g/day of EPA (1.1%) as compared with placebo (0.6%; $p = 0.0006$), but this dose is higher than that being tested in VITAL. Other concerns include a fishy aftertaste and GI disturbance (e.g., nausea or diarrhea), which may contribute to patient intolerance [35,77]. In addition, some evidence suggests that fish-oil supplements may worsen glycemia in patients with impaired glucose tolerance and increase LDL cholesterol in patients with hypertriglyceridemia [35]. However, the AHA has concluded that these risks are very low or low at doses of up to 1 g/day and low to moderate at doses of 1–3 g/day [35]. Ancillary studies will provide opportunities to assess such effects.

2.5. Trial eligibility

VITAL will be conducted among 20,000 apparently healthy adults—10,000 of whom are men aged ≥50 and 10,000 of whom are women aged ≥55, ages at which chronic disease rates increase substantially. Participants are being recruited throughout the United States, and blacks are being oversampled (our goal is a study population that is 25% black). As this is a primary prevention trial, participants are required to have no history of cancer (except non-melanoma skin cancer), MI, stroke, transient ischemic attack (TIA), angina pectoris, or coronary revascularization (CABG or PCI). In addition, participants are required to limit consumption of supplemental vitamin D to no more than 800 IU/day from all supplemental sources combined (stand-alone vitamin D supplements, calcium + vitamin D supplements, medications containing vitamin D [e.g., Fosamax Plus D] and multivitamins), to limit consumption of supplemental calcium to no more than 1200 mg/day from all supplemental sources combined, and to forego the use of fish-oil supplements during the run-in and randomized treatment periods. Safety exclusions are as follows: renal failure or dialysis, hypercalcemia, hypo- or hyperparathyroidism, severe liver disease (cirrhosis), or sarcoidosis or other granulomatous diseases such as active chronic tuberculosis or Wegener's granulomatosis; allergy to soy (which is in the vitamin D placebo pill) or fish (for the marine omega-3 fatty acid intervention); or other serious illness that would preclude participation. Participants who are willing to participate, as evidenced by signing the informed consent form and demonstrating good compliance in pill taking, defined as taking ≥2/3 of the study pills during the run-in period, are eligible for enrollment.

In a 2×2 factorial design, willing and eligible participants will be randomized to 5 years of vitamin D_3 and marine omega-3 fatty acid supplements (or placebos) independently. Participants will be instructed to discontinue their study pills if, during follow-up, they receive a diagnosis of hypercalcemia, sarcoidosis, or other safety-exclusion condition specified above. However, all participants will be included in intention-to-treat analyses.

2.6. Recruitment and randomization of the study population

2.6.1. Source of participants

We are recruiting potential participants from a master mailing tape of names and addresses assembled from commercially available U.S. mailing lists of professional organizations (e.g., those for licensed health professionals and business professionals) and other organizations (e.g., AARP), as well as subscription lists of magazines that cater or appeal to individuals likely to be eligible for the trial. The master mailing tape includes mailing lists of professional organizations and magazines for black individuals. In addition, we are recruiting potential participants via direct appeals in articles and advertisements in newspapers and magazines, and we are also inviting participants in our previously completed trials [78–80] to consider participating in VITAL. We will also employ targeted recruitment efforts in the black community, including the creation and distribution of specialized information about the study supplements and the burden of cancer and CVD in blacks, to achieve our goal of a study population that is 25% black.

2.6.2. Enrollment

Potential participants receive the following materials by postal mail: (1) an invitational letter that explains the rationale for VITAL, outlines what participation entails, and provides sources for further information on relevant scientific issues; (2) an informed consent form; (3) brief questionnaires with items on demographics (age, gender, race/ethnicity, education, occupation, income); medical history (cancer, CVD, kidney stones, hypercalcemia, kidney failure, sarcoidosis, other major illnesses); allergy to fish or soy; current use of supplements containing vitamin D or fish oil; current use of other supplements or medications; dietary intake of vitamin D and consumption of fish; cancer and vascular risk

factors (e.g., smoking, height, weight, blood pressure, cholesterol, diabetes, alcohol use, physical activity, and family history of cancer and CVD); and potential effect modifiers such as skin pigmentation and sunlight exposure; and (4) pre-paid envelopes for returning study forms. Questionnaire responses will be evaluated to determine respondents' eligibility for the trial. Our goal is to identify 40,000 individuals who are willing and eligible to enter the run-in phase of the trial.

2.6.3. Run-in

Prior experience in the conduct of large randomized trials has demonstrated the utility of a run-in period for selecting excellent compliers for long-term follow-up, which increases the trial's power [78,80–82]. In VITAL, there will be a 3-month run-in during which all participants will take one placebo vitamin D pill and one placebo fish-oil pill per day. It would not be scientifically appropriate to use active agent in the run-in and then randomize to placebo because some effects of the interventions on cancer risk may be chronic. A placebo-only run-in also permits the clearest detection of any side effects during the randomized treatment period. If the active intervention were to be used during the run-in, potential participants may drop out not only because of poor compliance but also because of side effects of treatment, and thus the true rate of side effects may be underestimated among those ultimately randomized into the trial. For ease of pill-taking, study pills will be packaged in 31-day calendar packs (2 pills per day).

2.6.4. Randomization

Initially willing and eligible participants will be randomized into the trial if they (1) demonstrate good compliance in pill taking, defined as taking ≥2/3 of the study pills during the run-in; (2) report no new history of cancer (except non-melanoma skin cancer), MI, stroke, TIA, angina pectoris, CABG, PCI, hypercalcemia, sarcoidosis, or other serious illness during the run-in; and (3) remain willing to comply with limits on non-study use of supplemental vitamin D and calcium and fish oil (Section 2.5). We estimate that 50% of the 40,000 individuals (n = 20,000) who enter the run-in will comply with pill-taking and remain willing and eligible for randomization. Within 5-year age groups, randomized treatment assignments (using a computer-generated table of random numbers) will be made in blocks of eight individuals, with two individuals in each of the four treatment combinations. The use of age stratification during randomization ensures balance and increases statistical efficiency.

2.6.5. Ethnicity/race of study population

The anticipated racial/ethnic distribution of the randomized study population is as follows: 5000 (25%) non-Hispanic black, 1400 (7%) Hispanic, 500 (2.5%) Asian, 400 (2%) American Indian, 80 (0.4%) Pacific Islander, and 12,620 (63.1%) non-Hispanic white participants.

2.7. Blood collection and assays

2.7.1. Blood collection

We will collect fasting blood samples at baseline (i.e., during the run-in, prior to randomization) from as many participants as are willing to provide them (expected response rate is 80%, or n = 16,000). Fasting blood samples will also be collected at trial years 1, 2, and 4 from a randomly selected subset of about 6000 participants who provide baseline samples. The main reason for the baseline blood collection is to assess whether treatment effects are modified by baseline blood levels of 25(OH)D (for vitamin D) and EPA + DHA (for the marine omega-3 fatty acids). The main reasons for the follow-up blood collection are to assess (a) pill-taking compliance, (b) changes in biomarkers with treatment, and (c) in the placebo group, the effect of changing trends in background intakes of vitamin D and marine omega-3 fatty acids. The follow-up blood samples will be particularly important for determining how 25(OH)D levels change in response to vitamin D supplementation in black individuals, an understudied area of investigation [83]. In addition, changes in blood calcium and parathyroid hormone levels will be measured to assess possible hypercalcemia, a potential side effect of high vitamin D intake. The blood samples will also be used to evaluate whether the interventions affect biomarkers related to lipids, glucose tolerance, inflammation, endothelial dysfunction, thrombosis, insulin, and insulin-like growth factor pathways. Finally, the samples will allow for future explorations of other biochemical and genetic hypotheses in a well-characterized cohort.

During the run-in period, participants will be mailed a blood collection kit, including a gel-filled freezer pack and overnight courier air bill. We anticipate that most participants will have their blood drawn by their own healthcare provider or at a local blood-drawing facility. Some participants will have their blood drawn in their homes by a company that provides phlebotomy services. Participants will be instructed to return the fasting blood sample to our blood laboratory in the freezer pack within 24 h of venipuncture. Upon receipt, the samples will be centrifuged to separate plasma, serum, red blood cells, and buffy coat; these components will be stored in nitrogen freezers (−170 °C) within 30–36 h of venipuncture. Identical procedures will be used for the follow-up blood collection.

2.7.2. Blood assays

Baseline and follow-up blood levels of 25(OH)D and EPA + DHA, as well as calcium and parathyroid hormone, will be assayed in a subset of participants who provide a sample at baseline and all participants who provide a blood sample at follow-up. The biochemical assays will be performed by established laboratories with extensive experience in clinical chemistry and the conduct of these assays.

Serum 25(OH)D: Measurement of serum 25(OH)D will be performed at the Clinical and Translational Science Center (CTSC) laboratory at Harvard. Circulating 25(OH)D will be determined by radioimmunoassay [84,85], using reagents from the DiaSorin Corporation (Stillwater, NM) that recognize and quantify $25(OH)D_2$ and $25(OH)D_3$ equally. The intra- and inter-assay coefficients of variation (CV) in the ranges expected are <10%. The VITAL study will participate in the National Institute of Standards and Technology/Office of Dietary Supplements quality assurance program for measurement of $25(OH)D_2$ and $25(OH)D_3$ in human blood samples [86].

Omega-3 fatty acids (EPA and DHA) in red blood cells: Measurement of omega-3 fatty acids in red blood cells (RBC) will be performed by Dr. William Harris at the University of South

Dakota. RBC samples will be analyzed by gas chromatography. The CV for EPA + DHA as a percent of total RBC fatty acids (our metric of primary interest) is 5.0% for a mean value of 10.9% (SD 0.5%) and 5.3% for a mean value of 3.8% (SD 0.2%).

Calcium, parathyroid hormone, phosphorus: Measurement of calcium, parathyroid hormone, and phosphorus will be performed in the Harvard CTSC laboratory. All CVs are <10%.

2.8. Assessment of dietary and non-study supplemental intakes of vitamin D and marine omega-3 fatty acids

Classifying participants by background intakes – at baseline and during the course of the trial – of vitamin D, marine omega-3 fatty acids, and other nutrients will allow an evaluation of whether the study agents' effects are influenced by these variables. For example, it may be that partipants with the lowest baseline intakes of vitamin D will benefit the most from the vitamin D intervention. Participants will be asked to complete a self-administered semi-quantitative food frequency questionnaire (FFQ) at baseline, 2 years, and at trial's end. This questionnaire is an efficient, reliable, and accurate instrument for categorizing individuals' nutrient intake, including intake of vitamin D and marine omega-3 fatty acids [87–92]. Respondents estimate their average intake over the past year of various foods, beverages, and supplements that contain vitamin D, marine omega-3 fatty acids, and other nutrients. Additional questions on use of non-study supplements or drugs containing vitamin D or marine omega-3 fatty acids will be asked at baseline, 6 months, and on yearly follow-up questionnaires. We will ascertain and analyze nutrient intakes from food alone, supplements alone, and the two sources combined, to determine whether the interventions' effects vary according to these variables.

2.9. Follow-up and endpoint determination procedures

The primary method of follow-up will be mailed questionnaires and review of medical records to confirm study endpoints. Participants will receive follow-up questionnaires at 6 months and 1 year after randomization and annually thereafter. The questionnaires include items on compliance with randomized treatments, use of nonstudy supplements of vitamin D and marine omega-3 fatty acids, dietary intakes of vitamin D and fish, development of major illnesses, risk factors for cancer and CVD, and potential side effects of the study agents. For vitamin D, side effects include GI symptoms and physician diagnosis of hypercalcemia or kidney stones. For marine omega-3 fatty acids, side effects include GI upset or bleeding, skin eruptions, and physician diagnosis of atrial fibrillation or other irregular rhythms. Non-responders will receive two additional requests by mail and then be telephoned to collect study data. At a minimum, vital status will be ascertained. At 6-month intervals between the annual follow-ups, participants will receive a short questionnaire limited to items on the development of primary endpoints (cancer, MI, and stroke), difficulties with pill compliance, and address changes. This will allow us to address compliance issues and collect medical records for endpoint confirmation in a timely fashion.

Participants who report a cancer or cardiovascular endpoint of interest will be asked to sign a medical release for relevant hospital and physician records. An Endpoints Committee of physicians who are blinded to the randomized treatment assignment will review the records to confirm or disconfirm the case by applying a defined protocol. Cancer diagnoses will be confirmed with histologic or cytologic data, or, if these are unavailable, strong clinical evidence accompanied by radiologic evidence or laboratory markers; the histologic type, grade, and stage of cancer will also be recorded [93]. MI will be confirmed using Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force for the Redefinition of Myocardial Infarction criteria [94]. Stroke will be confirmed and categorized according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [95]. Cardiovascular deaths will be confirmed by convincing evidence of a CVD event from all available sources, including death certificates, hospital records, autopsy reports, and, for deaths outside the hospital, observer accounts.

For deaths reported by family members, the next-of-kin will be asked to provide medical records and a copy of the death certificate. If the latter is not provided, a copy will be obtained from the state vital records bureau where the participant died. The Endpoints Committee will review the records and assign a cause of death. If records are not available (or if participants are lost to follow-up), we will search the National Death Index Plus (NDI-Plus) to obtain an International Classification of Disease-coded cause of death based on death-certificate information.

2.10. Assessment of compliance

The primary measure of compliance with pill-taking will be participants' responses to questionnaire items asking about adherence. Our experience with large trials indicates that although most participants strive to take their pills as assigned, those who do not willingly admit not doing so. Thus, blood levels and self-reported adherence data have been strongly correlated in previous trials [96]. Nevertheless, to obtain an objective measure of compliance, we will visit a group of randomly sampled local participants (50 per year, or a total of 250 participants during the course of the trial) to draw an on-the-spot blood sample for determination of 25(OH)D and EPA + DHA levels. (A separate consent form, to be administered by the phlebotomist at the time of the draw, will be used for these blood collections.) The distribution of these values will be compared between the active treatment and placebo groups, and compared with the questionnaire data on adherence, as a check on the validity of the latter. In addition, during years 1, 2, and 4 of the trial, about 6000 participants will provide follow-up blood samples to allow an assessment of changes in levels of 25(OH)D, EPA + DHA, and other biomarkers in the treatment group, as well as changes in the placebo group that may result from changes in background intakes (Section 2.8).

2.11. Analysis plan and statistical power

2.11.1. Analysis plan

Analyses of treatment effects will be based on the intention-to-treat principle. An initial analysis will compare baseline demographic, medical, and lifestyle characteristics of the study population by randomized treatment assignment

to ensure that balance was achieved by the randomization. The large sample size and successful balance of known potential confounders will provide assurance that unmeasured or unknown potential confounders are also equally distributed across randomized treatment groups.

The primary analyses will compare the main effects of intention-to-treat with vitamin D and with marine omega-3 fatty acids (assigned independently in a 2×2 factorial design) on the cancer and CVD endpoints specified in Aims (Section 2.2). Use of the Cox proportional hazards model will allow for variable follow-up lengths [97] and estimation of hazard ratios for each intervention while adjusting for the second intervention, age, and gender. Because the cohort will consist of older individuals, competing risks due to deaths from other causes will be considered. This will be done by estimating the cause-specific hazard and the hazard ratio comparing intervention groups for each outcome of interest by censoring individuals with deaths due to competing causes. To estimate the cumulative incidence function, the subdistribution of each endpoint will be plotted over time [98,99]. Although we will consider the alternative Fine and Gray model [100], the proportional hazards approach will be our primary analysis.

We will also explore interactions between the vitamin D and the omega-3 fatty acid intervention; between the vitamin D intervention and baseline serum levels of 25(OH)D; and between the marine omega-3 fatty acid intervention and baseline RBC levels of EPA + DHA. We hypothesize that the intervention effects may be larger among those with below-median baseline levels; we will examine treatment effects by quartiles of these biomarkers. Blood levels of 25(OH)D and EPA + DHA will be assayed in the final 2 years of the study in a case-cohort design on a subset of participants who provide a blood sample at baseline and all participants who provide one at follow-up. A case-cohort design allows an efficient and unbiased estimation of hazard ratios as well as absolute risks for individuals [101]. With this design, a common subcohort sample can serve as the reference risk set for more than one outcome—in this instance, total cancer and total CVD. Cancer and CVD cases will accrue during 5 years of follow-up; a subcohort sample that is approximately twice the size of the case sample for each outcome will be selected, stratifying by gender and baseline age (within 5-year groups) to frequency-match the distribution in the total case group. The biomarker data will be analyzed using proportional hazards regression [102] using appropriate age and gender stratum-specific weighting of the observations [103]. We will also examine effects of the vitamin D intervention on cancer and CVD outcomes within groups defined by race/skin pigmentation and by BMI. In exploratory analyses, we will evaluate effect modification by age, gender, sunlight exposure, calcium and phosphorus intakes estimated from the FFQ (as these nutrients affect vitamin D bioavailability [104]); and baseline risk factors for cancer and CVD. The latter interaction effects will be interpreted cautiously, as hypothesis generating. Finally, we will examine whether treatment effects of the two interventions vary over time and duration of treatment by examining survival plots and interactions with time. There may be a latent effect on cancer incidence, depending on the stage of carcinogenesis during which these agents act.

We will also compare the incidence of potential side effects in the active *v*. placebo groups for each agent, including the incidence of kidney stones with vitamin D assignment and the incidence of GI symptoms and bleeding with marine omega-3 fatty acid assignment.

2.11.2. Statistical power

Careful attention to issues of statistical power is necessary to ensure the success of a large clinical trial—i.e., achieve definitive results. VITAL was designed to have excellent statistical power to test the primary hypotheses and adequate statistical power to test the secondary hypotheses. The following assumptions were made for the power calculations: (1) a 2×2 factorial trial in 10,000 men aged ≥50 and 10,000 women aged ≥55 at baseline; (2) independent and equal allocation of participants to each treatment (achieved by randomization); (3) an age distribution based on that observed at baseline in our past trials for men aged ≥50 and women aged ≥55, but limited to 30% in the youngest age groups (50–59 years in men and 55–64 years in women); (4) age-specific event rates based on the observed rates in the first 5 years of follow-up in our trials with similarly aged populations; (5) a target of 25% blacks, with a corresponding increase in rates of CVD [105] and cancer [106]; (6) a trial follow-up period of 5 years, with little loss to follow-up as achieved in our past trials; and (7) compliance (80%) similar to that in published trials upon which our estimated rate ratio (RR) reductions are based. The cited reductions are thus the observed effects we would see in the trial. The corresponding 'true' RR is given assuming an average compliance of 80%. Power was computed for a two-sided test using a logrank analysis [107] with a significance level of 0.05.

Assuming that only one agent is effective, there will be 86% power to detect an observed rate ratio (RR) of 0.85 for the primary cancer endpoint of total cancer incidence (Table 1) and 89% power to detect an observed RR of 0.80 for the primary cardiovascular endpoint—a composite of MI, stroke, and cardiovascular mortality (Table 2). With regard to secondary endpoints, there will be adequate power to detect risk reductions of 25–40%. If both agents are effective in reducing risk for disease but act independently, power would be reduced slightly due to a smaller number of endpoints. If the agents interact to influence risk for disease, power will be affected to the extent of the interaction. Should the agents act synergistically, power would increase, as illustrated in Table 3 for the endpoint of total cancer. For example, if the effect of each agent alone is a risk reduction of 10%, but the effect is stronger in combination, with an additional 10% decrease, the RR comparing the group assigned to active vitamin D plus active marine omega-3 fatty acids with the group assigned to vitamin D placebo and marine omega-3 fatty acid placebo would be 0.73, as opposed to 0.81 with additive effects (on the multiplicative scale). Power for the main effect of each agent would then increase to 81% (or higher with greater synergy). Should the agents interact in a subadditive fashion, power would be reduced.

2.12. Ancillary studies and the Clinical and Translational Science Center

Although the primary goal of VITAL is to test whether vitamin D or omega-3 fatty acids reduce the risk for cancer and CVD, the trial will also advance our understanding of the role of these agents in other major health outcomes through the integration of ancillary studies. These studies will examine whether the interventions can prevent diabetes and glucose

Table 1
Power for effects of a single agent on cancer in VITAL, a 2×2 factorial trial of 10,000 men aged ≥50 and 10,000 women aged ≥55, with 5 years of follow-up.

Observed RR[a]	True RR[b]	Total cancer	Cancer mortality	Colorectal cancer	Breast cancer (women)	Prostate cancer (men)
0.90	0.875	52.1	–	–	–	–
0.85	0.812	86.3	–	–	–	–
0.80	0.750	98.5	42.3	26.3	32.8	67.5
0.75	0.687	99.9	60.9	39.0	48.4	86.4
0.70	0.625	>99.9	77.7	53.4	64.7	96.1
0.65	0.560	>99.9	89.7	67.8	79.0	99.3
0.60	0.500	>99.9	96.2	80.3	89.4	99.9

RR, rate ratio.
[a] Observed RR = intent-to-treat RR, including noncompliant participants. Compliance is assumed to be 80%.
[b] True RR = that with perfect compliance.

intolerance; hypertension; age-related cognitive decline; late-life depression; osteoporosis and fracture; physical disability and falls; chronic knee pain symptoms; asthma and other respiratory diseases; infections; periodontal disease; and rheumatoid arthritis, systemic lupus erythematosus, thyroid diseases, and other autoimmune disorders. Other ancillary studies using non-invasive imaging techniques are planned among participants available for in-person visits (see next paragraph), including dual energy x-ray absorptiometry scans to measure bone density and body composition; mammography to assess breast tissue density, a predictor of breast cancer risk; and vascular imaging – ultrasound to assess carotid intima-media thickness and Doppler echocardiography to assess left ventricular function – to clarify mechanisms by which the interventions may influence CVD risk.

A key feature of VITAL is the establishment of a subcohort of 1000 participants who will be evaluated at Clinical and Translational Science Centers (CTSCs) in Boston. The CTSC subcohort will be identified toward the end of the placebo run-in, prior to randomization. In addition to fulfilling eligibility criteria for the main trial, CTSC participants must live within driving distance of the Boston CTSC sites and be able to provide informed consent for the CTSC evaluation. The CTSC subcohort is expected to reflect the diverse racial/ethnic composition of the VITAL study population and will be randomized equally into the four treatment groups created by the factorial design (i.e., 250 participants per treatment group).

CTSC participants will visit the CTSC sites for detailed health assessments prior to randomization and again two years later. The two visits will use the same protocol to gather basic clinical data (e.g., medical history and physical exam, including measurement of height, weight, other anthropometric indices, and blood pressure) and data on variables related to aims of the ancillary studies (e.g., glucose tolerance testing, physical performance batteries, lung function exams, cognitive assessments, and structured interviews to diagnose mood disorders and depression). Blood samples will be drawn not only for glucose tolerance testing but also for assays of 25 (OH)D and EPA + DHA levels. The timing of the second CTSC visit will be matched by month to the initial visit to minimize variability in seasonal sun exposure, a major source of within-person variation in 25(OH)D levels. The CTSC visits provide a valuable opportunity for face-to-face contact with a subset of the VITAL study population, allowing for in-depth phenotyping and in-person validation of the remote assessment methods used in the main trial and ancillary studies. For example, in-person assessments of cognitive function at the CTSC visit will be used to validate telephone-based assessments in the cognitive function ancillary study, and in-person structured diagnostic interviews for clinical depression at the CTSC visit will be used to validate clinical depression cases identified by screening checklists in the depression ancillary study.

2.13. Trial monitoring

An independent Data and Safety Monitoring Board (DSMB) consisting of representatives from the National Institutes of Health (NIH) and other experts in clinical trials, epidemiology, biostatistics, and relevant clinical areas of cancer and CVD meets annually to review the progress of VITAL and the unblinded data on study endpoints and possible adverse effects in order to recommend continuation, modifications to the

Table 2
Power for effects of a single agent on CVD in VITAL, a 2×2 factorial trial of 10,000 men aged ≥50 and 10,000 women aged ≥55, with 5 years of follow-up.

Observed RR[a]	True RR[b]	Major CVD[c]	Total CVD[d]	CVD mortality	MI	Stroke
0.90	0.875	34.6	52.8	–	–	–
0.85	0.812	66.1	86.9	–	–	–
0.80	0.750	89.4	98.6	45.1	50.9	51.0
0.75	0.687	98.2	>99.9	64.4	71.0	71.1
0.70	0.625	99.9	>99.9	80.9	86.4	86.5
0.65	0.560	>99.9	>99.9	91.9	95.2	95.2
0.60	0.500	>99.9	>99.9	97.3	98.8	98.8

CVD, cardiovascular disease; *MI*, myocardial infarction; *RR*, rate ratio.
[a] Observed RR = intent-to-treat RR, including noncompliant participants. Compliance is assumed to be 80%.
[b] True RR = that with perfect compliance.
[c] Major CVD = myocardial infarction, stroke, and CVD mortality
[d] Total CVD = myocardial infarction, stroke, CVD mortality, and coronary revascularization (coronary artery bypass grafting or percutaneous coronary intervention)

Table 3
Power for interaction effects on total cancer in VITAL, a 2×2 factorial trial of 10,000 men aged ≥50 and 10,000 women aged ≥55, with 5 years of follow-up.

RR single agent[a]	RR interaction[b]	RR both agents	Power main effect	interaction
0.90	1.0	0.81	49.9	
	0.9	0.73	80.6	
	0.8	0.65	95.9	51.5
	0.7	0.57	99.6	87.6
0.85	1.0	0.72	83.4	
	0.9	0.65	96.2	
	0.8	0.58	99.5	48.8
	0.7	0.51	>99.9	85.2
0.80	1.0	0.64	97.4	
	0.9	0.58	99.6	
	0.8	0.51	>99.9	46.0
	0.7	0.45	>99.9	82.5

RR, rate ratio.
[a] RR = intent-to-treat RR, including noncompliant participants (assuming 80% compliance). Represents the effect among those not assigned to the other intervention and assumes the same effect for both agents.
[b] The interaction is the RR for the combined group divided by the product of risks for the two separate groups—i.e., RRint = RRboth/(RR vitamin D alone*RR omega-3 fatty acids alone). An interaction = 1 implies additive effects (no interaction).

study design, or early termination of the trial. Evaluation of interim results will be guided by Haybittle-Peto rules [108,109], which appropriately require strong evidence for early stopping and allow for assessments at convenient intervals without inducing statistical complexity [110]. These rules apply to the main endpoints of cancer and CVD. However, because VITAL will also assess the overall balance of benefits and risks of the interventions in the primary prevention of these diseases, other outcomes that may critically affect the benefit-risk balance will be considered. Decisions regarding the trial's continuation will also be informed by relevant scientific data (e.g., from other trials of the study agents) that may become available during the planned 5-year treatment period.

3. Discussion

VITAL has many strengths. This study is testing two very promising nutritional agents (vitamin D and marine omega-3 fatty acids) for the prevention of two major chronic diseases (cancer and CVD) in a multi-ethnic population in an extremely cost-effective fashion—i.e., utilizing a mail-based, large simple trial design. The trial has excellent power to detect small to moderate effects of the interventions on the primary endpoints of interest. The trial will include the collection and storage of baseline blood samples in the majority of the cohort to allow assessment of effect modification by baseline 25(OH)D and EPA + DHA levels, and the collection and storage of follow-up samples in a subgroup of participants to allow assessment of pill-taking compliance; changes in biomarkers with treatment; and, in the placebo group, the effect of food fortification and changing background intakes of vitamin D and marine omega-3 fatty acids. VITAL will also further our understanding of the role of the interventions in relation to many other major health outcomes through well-integrated ancillary studies, including currently funded and future investigations of multiple clinical, biochemical, and genetic hypotheses. The study also has some limitations. It will test only one dose of each agent rather than examining multiple doses to determine the dose–response relationship. However, the dose for each agent was chosen on the basis of an extensive and careful review of available evidence, with the goal of optimizing the balance of safety and efficacy. Because the trial population is older, the results may not be generalizable to younger individuals. However, older populations have higher disease rates, allowing the trial to be completed in a shorter time period, at greater cost efficiency. Finally, latency of effect may be an issue, especially for cancer outcomes. However, several lines of evidence suggest that the agents of interest, particularly vitamin D [2,20,111], may act at later stages of carcinogenesis (including effects on tumor invasion and metastasis), suggesting that benefits could be observed with 5 years of treatment.

The purported health benefits of vitamin D and marine omega-3 fatty acids are receiving increasing attention in both the medical literature and the popular press. Sales of fish-oil supplements are rising, and an increasing number of foods are omega-3 fortified [112]. Many clinicians now include vitamin D blood tests as part of routine lab work and recommend vitamin D supplements to patients. Indeed, sales of such supplements have skyrocketed in recent years [113]. However, in a report published earlier this year, the IOM critically reviewed nearly 1000 studies of vitamin D in relation to a wide variety of health outcomes and concluded that although there is clear evidence that vitamin D – at doses of 600 to 800 IU/day – confers bone benefits, current data are inconclusive as to whether higher vitamin D intakes reduce risk for cancer, CVD, and other chronic diseases [26]. Because of this uncertainty, the IOM called for more research – especially large randomized clinical trials – to determine whether high-dose vitamin D supplements can lower the risk for nonskeletal illnesses and whether they pose any health risks. Similarly, the conclusion from a 2004 NIH workshop [114] was that "… the body of evidence is consistent with the hypothesis that intake of omega-3 fatty acids reduces CVD but … a definitive trial is needed." Rigorous trials of many other single-agent nutritional interventions – such as certain antioxidant vitamins, selenium, B-vitamins, and calcium – have disproved some health claims and even uncovered health risks that may not have otherwise been detected [115–119]. Indeed, recent observational data suggest that not only very low but also very high 25(OH)D levels may contribute to the development of CVD [9,16] and certain cancers [120]. The growing enthusiasm for vitamin D and marine omega-3 fatty acid supplements underscores the need for a timely initiation of a large randomized trial such as VITAL to test these agents rigorously, before their use becomes so prevalent as to render participant recruitment and hypothesis testing impossible. The results of VITAL are expected to inform individual decisions, clinical recommendations, and public health guidelines regarding the use of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and CVD.

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Rationale and design of the Post-MI FREEE trial: A randomized evaluation of first-dollar drug coverage for post–myocardial infarction secondary preventive therapies

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Background Medication nonadherence is a major public health problem, especially for patients with coronary artery disease. The cost of prescription drugs is a central reason for nonadherence, even for patients with drug insurance. Removing patient out-of-pocket drug costs may increase adherence, improve clinical outcomes, and even reduce overall health costs for high-risk patients. The existing data are inadequate to assess whether this strategy is effective.

Trial Design The Post-Myocardial Infarction Free Rx and Economic Evaluation (Post-MI FREEE) trial aims to evaluate the effect of providing full prescription drug coverage (ie, no copays, coinsurance, or deductibles) for statins, β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers to patients after being recently discharged from the hospital. Potentially eligible patients will be those individuals who receive their health and pharmacy benefits through Aetna, Inc. Patients enrolled in a Health Savings Account plan, who are ≥65 years of age, whose plan sponsor (ie, the employer, union, government, or association that sponsors the particular benefits package) has opted out of participating in the study, and who do not receive both medical services and pharmacy coverage through Aetna will be excluded. The plan sponsor of each eligible patient will be block randomized to either full drug coverage or current levels of pharmacy benefit, and all subsequently eligible patients of that same plan sponsor will be assigned to the same benefits group. The primary outcome of the trial is a composite clinical outcome of readmission for acute MI, unstable angina, stroke, congestive heart failure, revascularization, or inhospital cardiovascular death. Secondary outcomes include medication adherence and health care costs. All patients will be followed up for a minimum of 1 year.

Conclusion The Post-MI FREEE trial will be the first randomized study to evaluate the impact of reducing cost-sharing for essential cardiac medications in high-risk patients on clinical and economic outcomes. (Am Heart J 2008;156:31-6.)

Coronary heart disease (CHD) remains the leading cause of death in the United States and other developed countries[1]; >1 million Americans have acute myocardial infarctions (MI) every year.[2] In 2008, CHD is estimated to account for >$156 billion in direct and indirect health care costs.[2] Large-scale randomized trials have identified medications that are highly effective at reducing the risk of CHD-related events.[3-8] Accordingly, practice guidelines recommend that all patients with acute MI receive treatment with a β-blocker, a statin, an angiotensin-converting enzyme (ACE) inhibitor, or an angiotensin II receptor blocker (ARB), and aspirin,[9,10] unless a contraindication exists.

Although rates of prescribing these medications at hospital discharge after acute MI have improved substantially,[11] subsequent long-term adherence to therapy continues to be poor.[12] Only 46% of patients with CHD report consistent β-blocker use within 1 year of an acute MI,[13] and only 50% of patients are adherent with their prescribed statin.[14] Less than 20% of acute MI patients use all 4 of the recommended agents.[13,15] Not surprisingly, nonadherent patients are at substantially higher risk of death.[16,17] Patients with MI who discontinue all of their medications are >3 times as likely to die than patients who remain adherent.[16] Therefore, the burden

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of CHD may be reduced further by improving medication adherence.

Contribution of cost to the underuse of prescription medications

Of the many factors that contribute to poor adherence, the cost borne by patients is central.[18-21] In the past year, one third of Americans said that they or a family member has had difficulty paying for medications,[22] and a similar proportion have not filled a prescription or have reduced a prescribed dosage because of high out-of-pocket costs.[23] Even among individuals with insurance, medication utilization varies by the comprehensiveness of coverage.[24,25] For example, hypertensive Medicare beneficiaries covered by plans with higher cost-sharing and no catastrophic coverage were less likely to use medication than patients with more generous coverage.[26] The amount of cost-sharing faced by younger managed care enrollees also influences their use of essential medications; a doubling of copayments is estimated to reduce statin utilization by 34%.[20]

Eliminating patient cost-sharing may improve both adherence and clinical outcomes. Moreover, because the cost of preventable CHD events far exceeds medication costs, providing more comprehensive drug benefits may simultaneously save lives and money.[27] In 2 recent cost-effectiveness analyses, we predicted that the small changes in adherence that will result from providing full prescription drug coverage (ie, without patient cost-sharing) for statins, aspirin, ACE inhibitors, and β-blockers to patients after acute MI will reduce mortality and rates of nonfatal reinfarction, stroke, and congestive heart failure readmission and will save substantial amounts of money as compared with usual levels of prescription drug coverage.[28,29]

Limitations of the existing data and need for a randomized policy trial

No studies have adequately evaluated the impact of improving drug coverage on medication use and health outcomes for any disease. Cross-sectional studies evaluating the effects of coverage on medication adherence are inherently subject to bias. Individuals enrolled in plans with generous pharmacy benefits differ in important ways from individuals with less generous benefits, and the ability of statistical models to adjust adequately for these differences is limited. Longitudinal studies evaluating the changes in outcomes from restrictions in health benefits are not subject to selection bias, but expanding pharmacy benefits may not merely be the reciprocal of restricting coverage.[30] The studies that have evaluated selective copay reductions have been uncontrolled or inadequately powered to measure clinically important outcomes.[31,32] Even the RAND Health Insurance Experiment, which is the only truly randomized intervention of different levels of patient cost-sharing for prescription drugs to date, did not measure adherence and had a relatively small sample size.[33]

One way to adequately evaluate the impact of expanding coverage for essential medications of proven efficacy is to conduct a prospective trial in which patients are randomized to receive full (first-dollar) or usual drug coverage. Patients who have recently been discharged from hospital after acute MI are an ideal population in which to study this question. These individuals have high cardiovascular event rates, and secondary prevention medications for acute MI are clearly efficacious, are substantially underused in part because of cost, and are inexpensive relative to the cost of the events that they are intended to prevent.

Overall study design

The Post-Myocardial Infarction Free Rx and Economic Evaluation (Post-MI FREEE) trial will assess the clinical and economic impact of first-dollar coverage for post-MI medications. The trial will enroll patients discharged from hospital after acute MI. Randomization will occur at the level of the plan sponsor (ie, the employer, union, government, or association that sponsors the particular benefits package) so that all eligible employees of a given plan sponsor will receive the same coverage plan after randomization. This design strategy prevents the contamination of patients within a given plan sponsor and avoids the equity problems that may arise should 1 employee of a given plan sponsor be randomized to receive full drug coverage whereas another gets the usual level of pharmacy benefit.

Subjects

Eligible subjects will be patients discharged alive from hospital after MI who received health services and prescription drug benefits through Aetna, Inc. Aetna is one of the largest health insurers in the United States providing medical coverage to 15.7 million beneficiaries and pharmacy benefits to 10.5 million beneficiaries, through numerous small, midsized, and large multisite national plan sponsors.

Patients will be identified on the basis of hospital claims submitted to Aetna with a discharge diagnosis of *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) 410.xx (except 410.x2) as the principal or secondary diagnosis and a length of stay ≥3 and ≤180 days. This algorithm has a positive predictive value, sensitivity, and specificity of 96.9%, 96%, and 99%, respectively, for the diagnosis of acute MI.[34] Exclusion criteria include the following: (1) enrollment in a Health Savings Account plan, as patients in these plans already receive first-dollar coverage for the study

medications; (2) age ≥65 years at the time of hospital discharge, as Medicare is the primary health insurer for such patients; (3) plan sponsor has opted out of participating in the study; and (4) patients who receive only medical services or pharmacy coverage but not both through Aetna.

Patients will be recruited over a 1.5-year period and followed up for a minimum of 1 year.

Intervention

Patients will be randomized to first-dollar drug coverage or usual pharmacy benefits based on the group to which their plan sponsor is randomized (see below for details). Patients whose sponsor is randomized to first-dollar coverage will have their pharmacy benefits changed so that they have no out-of-pocket costs for any brand-name or generic β-blocker, angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), and statin for every subsequent prescription after randomization. All copays and coinsurance will be waived at the point of care (ie, pharmacy) as will any contribution that the cost of these drugs makes to a patient's deductible. We anticipate that 80% of randomized patients will be contacted within 2 months of hospital discharge; thus, first-dollar coverage will begin before patients fill their second prescription for most individuals randomized to this group and will continue for the duration of the study. Patients randomized to usual coverage will have no change in their existing benefits.

Randomization and patient recruitment

All plan sponsors will be contacted by mail before the study starts and given the opportunity to opt-out of study participation. Because plan sponsors may differ from each other in important ways, simple cluster randomization may result in plan sponsors with larger numbers of patients or those with particular prognostic factors being unequally distributed between the 2 randomized groups. Therefore, we will categorize plan sponsors into 1 of 6 blocks based on characteristics that were found to predict cluster size or health status in preliminary analyses: (1) whether the plan sponsor is nationally based (defined as being a Fortune 500 company with >3,000 employees or a governmental plan sponsor) and (2) the generosity of the existing levels of prescription-drug insurance coverage that each of the plan sponsor offers (3 levels). Insurance generosity was calculated by averaging the copayments for all statins, ACEI/ARBs, and β-blockers filled by patients of eligible plan sponsors between January 1 and June 30, 2007.

When a newly eligible post-MI patient is identified, an investigator blinded to the identity of the plan sponsor will determine whether that patient's plan sponsor has previously been randomized, and if not, the plan sponsor's block assignment. Plan sponsors will be randomly assigned in a 1:1 ratio to intervention or control using a random number generator. All subsequent patients of that plan sponsor will be assigned to the same group.

Patients in both groups will be contacted by mail and telephone by Aetna and will be told, very briefly, of the importance of taking their medications as prescribed. In addition, patients in the intervention group will be informed of their benefit change. Medication choices and treatment decisions will be left entirely to the discretion of patients' treating physicians. Although patients in the intervention group will be given the option to opt-out of receiving their medications without cost-sharing, no specific patient-level informed consent will be sought because all patients, at a minimum, will receive their usual level of prescription drug coverage. This study was approved by the institutional review board of Brigham and Women's Hospital and is registered with clinicaltrials.gov (NCT00566774).

Table I. Outcomes under study and their measurements

Outcome	Description
Primary	First occurrence of fatal or nonfatal acute MI, unstable angina, stroke, congestive heart failure, or revascularization (coronary bypass, stent insertion, or angioplasty)
Secondary	First occurrence of fatal or nonfatal acute MI, unstable angina, stroke, or congestive heart failure
	First occurrence of fatal or nonfatal acute MI, unstable angina, stroke, congestive heart failure or out-of-hospital cardiac death
	Rate of fatal or nonfatal acute MI, unstable angina, stroke, or congestive heart failure, or revascularization (coronary bypass, stent insertion, or angioplasty)
	Medication adherence (ie, the mean medication possession ratio and the proportion of patients fully adherent to each and all 3 of the study medications) *
	Health care utilization (ie, use of physician visits, emergency department admissions, hospitalizations or other resources) *
	Total pharmacy and health care costs during follow-up *

*See text for more details.

Outcomes

The primary outcome for this study will be the first admission after the initial hospital discharge for fatal or nonfatal acute MI, unstable angina, stroke, congestive heart failure, or coronary revascularization (coronary bypass, stenting, or angioplasty) (see Table I). All patients will be followed-up for a minimum of 1 year; patients recruited at the beginning of the study may contribute up to 2.5 years follow-up time. We chose a minimum of 1-year follow-up based on results of cost-effectiveness models that suggest that a meaningful difference in outcomes should be observable within this time frame.[28,29]

Outcomes will be assessed by applying validated diagnostic algorithms with specificities of at least 95%

Table II. Criteria for identifying patients with clinical outcomes

Outcome	Criteria *	Specificity of criteria (%)
Acute MI	*ICD-9* 410.x (except 410.x2) as the principal or secondary diagnosis and a length of stay of >3 and <180 days	99[34]
Unstable angina	*ICD-9* 411 as the principal diagnosis	96[35]
Stroke	*ICD-9* 433.x1, 434 (excluding 434.x0), 435.xx, 436.xx, 437.1x or 437.9x in any diagnosis position	99[36]
Congestive heart failure	*ICD-9* 428.x as the principal diagnosis	97[35]

*Based on hospital discharge codes during follow-up time.

(see Table II) to Aetna's health care utilization databases. This source contains data for all filled prescriptions, procedures, physician encounters, hospitalizations, and inpatient deaths for the patients in this cohort.

The secondary clinical outcomes will be include the following: (1) the primary outcome, but patients will not be censored at the time of their first event (ie, patients may experience multiple events); (2) the primary outcome excluding revascularization; and (3) the primary outcome including rates of outpatient cardiac death as assessed with the Center for Disease Control's National Death Index.

Other secondary outcomes will include measures of medication adherence, health care utilization, and health care costs. Medication adherence will be assessed by calculating the mean medication possession ratio (ie, the proportion of days for which patients have medication) and the mean proportion of patients fully adherent (defined as a medication possession ratio ≥80%) to each and all of the 3 study medications (β-blockers, statins, ACEI/ARB) throughout follow-up. Days in acute care during follow-up will be subtracted from the denominator of the medication possession ratio, and patients who die or lose insurance eligibility during follow-up will be censored at that point. Utilization will be assessed with annual rates of physician visits, emergency department admissions, hospitalizations, and other health care services (eg, revascularization). The cost of cardiovascular and overall health care will be estimated by summing total expenditures for medications, physician and professional fees, hospitalizations, other health care services, and long-term care facility admissions throughout follow-up.

Analytic plan

We will report means and frequencies of prerandomization variables separately for intervention and control subjects. The primary outcome will be compared based on intention-to-treat principles using proportional hazards regression. The model will adjust for clustering using a robust sandwich estimate for the covariance matrix[37] and the blocking factors used for sample stratification, as well as differences in baseline characteristics between study groups. Patients will be censored after they experience an event, if they lose insurance eligibility (eg, if they change employers), at age 65 years, or administratively at the study end.

Medication adherence and health care costs for both treatment groups will be compared. Generalized estimating equations will be used to adjust for the cluster and block randomized design.

Table III. Statistical power based on expected event rates in control patients and relative risk reductions from full drug coverage

Proportion of control patients experiencing primary outcome	Relative risk reduction from full drug coverage				
	0.15	0.2	0.25	0.3	0.35
0.2	0.70	0.92	0.99	1.0	1.0
0.25	0.79	0.96	1.0	1.0	1.0
0.3	0.85	0.98	1.0	1.0	1.0
0.35	0.89	0.99	1.0	1.0	1.0
0.4	0.92	1.0	1.0	1.0	1.0

Sample size considerations

Our study should be sufficiently powered to detect relatively small changes in the primary outcome. Using data from our published economic models[28,29] and pilot data from Aetna, we estimate that 35% of our control population will experience the primary study end point. We estimate that eliminating cost-sharing will increase adherence by 13%.[25,38] Using efficacy data from randomized trials, we estimate that this improvement in adherence will reduce the relative risk of the primary end point by 20%.

Pilot data indicate that approximately 5,000 Aetna beneficiaries per year will be eligible for randomization, and therefore, we will recruit 7,500 patients during the 1.5 years of planned recruitment. We assume that 15% of subjects will be noninformatively lost to follow-up annually (eg, because of change in employment or benefit program). With this sample, we should have sufficient power to detect plausible changes in event rates that are expected from full drug coverage (see Table III).

Data-monitoring committee

An independent data-monitoring committee (DMC) will meet twice a year to review unblinded data including the number of patients randomized, baseline characteristics, and patterns of medication filling. The DMC will also monitor the overall event rate and whether the assumptions underlying the study's size and expected duration are being met. At appropriate time points, the DMC will

also consider unblinded data with respect to study efficacy and make recommendations on whether to continue the study using the Haybittle-Peto stopping rule.[39,40] This group-sequential method maintains an overall α of .05 by applying a very stringent level of significance for interim analyses (ie, $P < .001$). The DMC will include a cardiologist, an internist, and a statistician.

Funding and responsibilities

The trial was designed as an investigator-initiated protocol from the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School. The study is sponsored by Aetna, Inc. Aetna staff have been involved in refining the study design and assessing its feasibility and will be responsible for the day-to-day operations of the trial, as described above. All data analysis and outcome assessment will be performed independent of the trial sponsor.

Limitations

There are several limitations to this trial that must be acknowledged. First, this trial will only evaluate the impact of cost-sharing on adherence to post-MI medications based on the hypothesis that even small improvements in adherence that are likely to result will be sufficient to improve clinical outcomes and reduce overall health care costs. As such, we will not assess other reasons for nonadherence, such as medication complexity and patient comprehension. Interventions to address these reasons for nonadherence have been evaluated.[41]

Second, patients will be enrolled using hospital discharge claims. Although this will enhance the generalizability of our findings to other insurers who seek to institute similar copayment reduction plans, there will be a lag between hospital discharge and randomization, during which some patients may not fill newly prescribed medications or may become nonadherent to the medications they have filled. This may diminish the effect of eliminating cost-sharing on medication use and clinical outcomes should one exist. Because we anticipate that 80% of patients will be contacted within 2 months of hospital discharge and therefore that first-dollar coverage will begin before patients fill their second prescription for most individuals randomized to this group, the magnitude of this bias should be small.

Third, patients randomized to the intervention group will not receive full coverage for clopidogrel, and thus, our results will only be generalizable to the medications being studied. Clopidogrel is costly, and rates of adherence to clopidogrel are fairly high[42]; thus, the trade-off between reduced cost-sharing for this drug and averted clinical events is likely less favorable than for the other post-MI medications. Accordingly, if clopidogrel was included among the covered medications and if ultimately this study shows no benefit from full coverage, it will be unclear whether the concept of eliminating cost-sharing for effective medications is itself flawed or more simply whether the cost of clopidogrel has extinguished the cost-savings derived from the other drugs being studied. In addition, clopidogrel is not intended for indefinite use after MI unlike other secondary prevention medications. As such, for the insurance coverage being evaluated to be truly evidence based, we would have to provide intervention group patients with full coverage for 1 year only and then return their coverage to usual levels. Doing so would influence clinical decision making and would confound our assessment of the relationship between selective copay reduction and improvements in medication adherence.

Summary

The Post-MI FREEE trial will be the first randomized study to rigorously evaluate the impact of reducing patient cost-sharing for essential cardiac medications in high-risk patients on clinical and economic outcomes. The study is powered to detect differences in clinically important outcomes in addition to medication adherence and health care costs. A positive finding from this trial will dramatically influence the nature of prescription drug coverage for essential cardiac medications. The results will also inform the nature and structure of coverage for many other chronic medications for which the cost of full drug coverage may be more than offset by the clinical and economic savings resulting from better adherence to these therapies.

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SPECIAL ARTICLE

Full Coverage for Preventive Medications after Myocardial Infarction

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ABSTRACT

BACKGROUND

Adherence to medications that are prescribed after myocardial infarction is poor. Eliminating out-of-pocket costs may increase adherence and improve outcomes.

METHODS

We enrolled patients discharged after myocardial infarction and randomly assigned their insurance-plan sponsors to full prescription coverage (1494 plan sponsors with 2845 patients) or usual prescription coverage (1486 plan sponsors with 3010 patients) for all statins, beta-blockers, angiotensin-converting–enzyme inhibitors, or angiotensin-receptor blockers. The primary outcome was the first major vascular event or revascularization. Secondary outcomes were rates of medication adherence, total major vascular events or revascularization, the first major vascular event, and health expenditures.

RESULTS

Rates of adherence ranged from 35.9 to 49.0% in the usual-coverage group and were 4 to 6 percentage points higher in the full-coverage group ($P<0.001$ for all comparisons). There was no significant between-group difference in the primary outcome (17.6 per 100 person-years in the full-coverage group vs. 18.8 in the usual-coverage group; hazard ratio, 0.93; 95% confidence interval [CI], 0.82 to 1.04; $P=0.21$). The rates of total major vascular events or revascularization were significantly reduced in the full-coverage group (21.5 vs. 23.3; hazard ratio, 0.89; 95% CI, 0.90 to 0.99; $P=0.03$), as was the rate of the first major vascular event (11.0 vs. 12.8; hazard ratio, 0.86; 95% CI, 0.74 to 0.99; $P=0.03$). The elimination of copayments did not increase total spending ($66,008 for the full-coverage group and $71,778 for the usual-coverage group; relative spending, 0.89; 95% CI, 0.50 to 1.56; $P=0.68$). Patient costs were reduced for drugs and other services (relative spending, 0.74; 95% CI, 0.68 to 0.80; $P<0.001$).

CONCLUSIONS

The elimination of copayments for drugs prescribed after myocardial infarction did not significantly reduce rates of the trial's primary outcome. Enhanced prescription coverage improved medication adherence and rates of first major vascular events and decreased patient spending without increasing overall health costs. (Funded by Aetna and the Commonwealth Fund; MI FREEE ClinicalTrials.gov number, NCT00566774.)

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The use of medications based on solid clinical evidence has contributed substantially to reductions in cardiovascular morbidity and mortality.[1,2] For patients with acute myocardial infarction, prescribing of these highly effective therapies is now nearly universal at the time of hospital discharge in the United States,[3,4] but important gaps in care persist thereafter. Some patients never fill their first prescriptions,[5] and most have poor adherence to medication regimens over time.[6]

Drug costs are central among the many factors that contribute to medication underuse.[7,8] A third of Americans report that they did not fill a prescription or reduced the dose in the past year because of out-of-pocket costs.[9] Even among those with insurance, medication utilization varies according to the comprehensiveness of patients' insurance coverage.[8,10] Accordingly, the elimination of out-of-pocket costs for evidence-based therapies may promote the appropriate use of medication[11] and reduce rates of preventable events.[12] Observational studies suggest that this strategy increases targeted medication use,[13,14] but its effect on actual health outcomes and spending has not been rigorously assessed.

Methods

Study Design

The Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) trial was an investigator-initiated, cluster-randomized, controlled policy study. Details of the study design have been published previously.[15] The trial protocol was designed and written by the academic investigators and conducted in collaboration with the sponsor, Aetna, which administered the changes in study-benefit design. The academic authors analyzed the trial data using an independent copy of the study database and vouch for analytic accuracy and completeness as well as the fidelity of the report to the study protocol. The study was monitored by an independent data and safety monitoring committee.

Study Population

Patients were eligible for inclusion in the study if they received both medical and prescription drug benefits through Aetna, a large commercial insurer in the United States, and if they had been discharged from the hospital with a principal or secondary diagnosis code of *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) 410 (except when the fifth digit was 2) and a length of stay of 3 to 180 days. This algorithm had a positive predictive value of 97%, a sensitivity of 96%, and a specificity of 99% for myocardial infarction.[15,16] Patients were excluded if they were enrolled in a health savings account, since these plans already offered full coverage for the study medications, or if they were 65 years of age or older at the time of hospital discharge, since Medicare was the primary health insurer for such patients.

Randomization and Study Procedures

Randomization occurred at the level of plan sponsor (i.e., the employer, union, government, or association that sponsors a particular benefits package) so that all eligible employees of a given plan sponsor received the same coverage after randomization. Plan sponsors were categorized into blocks on the basis of whether they were nationally based (a Fortune 500 company with more than 3000 employees or a governmental plan sponsor) and the baseline average copayments required for study medications. All plan sponsors were contacted by mail before the initiation of the study or as soon as they began providing benefits through Aetna and were given the opportunity to opt out of study participation. Plans that did not opt out were randomly assigned to full coverage (full-coverage group) or usual pharmacy benefits (usual-coverage group) with the use of a random-number generator, and all subsequently eligible patients of that plan sponsor were assigned to the same group.

Pharmacy benefits for patients in the full-coverage group were changed so that they had no cost sharing for any brand-name or generic statin, beta-blocker, angiotensin-converting–enzyme (ACE) inhibitor, or angiotensin-receptor blocker (ARB) for every prescription after randomization. All copayments and coinsurance were waived at the point of care (i.e., the pharmacy), as was any contribution to a patient's deductible. The date on which a patient was assigned to a study group was defined as the randomization date. Because the identification of patients was based on claims submitted by hospitals to Aetna, there was a lag between hospital discharge and randomization.

Upon ascertainment of eligibility, all patients were contacted by mail and phone and told of the importance of taking their medications as prescribed (see Appendix A in the Supplementary Ap-

pendix, available with the full text of this article at NEJM.org). Patients in the full-coverage group were also informed of the change in their pharmacy benefits. Medication choices and treatment decisions were left entirely to the discretion of the treating physicians and their patients. Because all patients, at a minimum, received their usual level of prescription-drug coverage, no specific patient-level written informed consent was sought. This study was approved by the institutional review board at Brigham and Women's Hospital.

STUDY OUTCOMES

We evaluated medication adherence by calculating the mean medication possession ratio (i.e., the number of days a patient had a supply of each medication class available, divided by the number of days of eligibility for that medication). Ratios were multiplied by 100 to generate absolute adherence percentages. We also calculated the proportion of patients who had full adherence (defined as a medication possession of ≥80%) to each and to all three study medication classes throughout follow-up.[17] Different agents within a therapeutic class were considered interchangeable. Patients who did not fill a particular prescription after randomization were considered to be nonadherent. In addition, we evaluated adherence among patients who filled at least one prescription during follow-up. In post hoc analyses, we measured adherence to drugs for which copayments were unchanged (i.e., clopidogrel, oral hypoglycemics, inhaled bronchodilators, proton-pump inhibitors, and antidepressants).

The primary clinical outcome was a composite of the first readmission for a major vascular event (fatal or nonfatal acute myocardial infarction, unstable angina, stroke, or congestive heart failure) or coronary revascularization (coronary bypass, stenting, or angioplasty). Prespecified secondary clinical outcomes included the rate of total major vascular events or revascularization, allowing for the occurrence of more than one event per patient and the time to the first major vascular event (i.e., the primary composite outcome excluding revascularization). In the recurrent events analysis, we excluded transfers between institutions (defined as readmission ≤2 days after the previous discharge), counted only one diagnosis per treatment episode, and counted each specific outcome (e.g., stroke) only one time per patient. All outcomes were assessed by applying validated algorithms with specificities of at least 95% to Aetna's databases of health care utilization.[15] This source contains complete data for filled prescriptions, procedures, physician encounters, hospitalizations, and inpatient deaths.

We evaluated the effect of the intervention on health care spending by patients and insurers using the allowed amounts appearing in the insurers' claims data for prescription medications, nondrug medical services (i.e., physician visits, emergency room admissions, hospitalizations, and outpatient procedures), and the combination of these two factors after the assignment of the patient to a study group. We evaluated cardiac-specific spending on the basis of relevant codes for coronary artery disease, congestive heart failure, stroke, hypertension, hyperlipidemia, arrhythmia, and other diseases of the heart and circulatory system.

STATISTICAL ANALYSIS

We planned to recruit 7500 patients over a 1.5-year period and to follow them for a minimum of 1 year in order to achieve a power of 90% to detect a between-group difference of 20% in the relative risk of the primary outcome. Because of slower-than-anticipated enrollment, the trial steering committee accepted a recommendation from the independent data and safety monitoring committee that equivalent power could be obtained if a total of 1000 primary outcome events were to occur. The steering committee then adapted the trial by extending enrollment by 15 months and reducing minimum follow-up to 3 months.

All analyses were performed on the basis of the intention-to-treat principle. We used generalized estimating equations with adjustment for the cluster and block-randomized design to compare rates of medication adherence and health spending. We used an identity link function with normally distributed errors to compare medication possession ratios and used a logit link function with binary distributed errors to compare rates of full adherence. Health spending was evaluated with the use of a log-link function with variances proportional to the mean.[18] In these analyses, data from patients were censored on the date of death or loss of insurance eligibility or at the end of the study period on November 30, 2010, whichever came first.

The primary clinical outcome and rates of major vascular events were evaluated as the time to the first event after randomization. The exposure

time was calculated as the time from randomization to the date of an outcome event, loss of insurance eligibility, or the end of the study period. We used Cox proportional-hazards models to estimate hazard ratios and 95% confidence intervals. We adjusted for clustering using a robust sandwich estimator for the covariance matrix.[19] The rate of total major vascular events or revascularization was compared with the Cox model extension, which allows for the estimation of multiple correlated failure times, as described by Wei and colleagues.[20] In additional analyses, we adjusted for age, sex, and differences in rates of coexisting illnesses between the study groups.[21] Subgroup analyses were performed according to age, sex, baseline copayment levels, presence or absence of coexisting illnesses, and patterns of medication use before randomization.

RESULTS

PATIENTS

Of the 6768 potentially eligible patients, 913 (13.5%) were excluded because their plan sponsors declined to participate. Thus, 5855 patients from 2980 plan sponsors were enrolled (Appendix B in the Supplementary Appendix). Plan sponsors had a median enrollment of 1 patient (range, 1 to 340). The plan sponsor with the largest number of enrolled patients was assigned to the usual-coverage group; 325 plan sponsors (10.9%) were nationally based.

Assignment to a study group occurred a median of 49 days after hospital discharge; 95% of patients were assigned within 100 days after discharge. A total of 133 patients (4.7%) in the full-coverage group and 151 (5.0%) in the usual-coverage group lost insurance eligibility between the time of hospital discharge and randomization, so data from these patients were not included in the follow-up analyses. The median duration of follow-up after randomization was 394 days (interquartile range, 201 to 663).

The baseline characteristics of the patients were well balanced between the two study groups (Table 1). The average age was 54 years, and three quarters of the patients were men. More than half the patients had filled prescriptions for the study drugs before their index hospitalization. Among patients who filled prescriptions between the time of hospital discharge and randomization, average copayments were similar in the two study groups.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Full Prescription Coverage (N=2845)	Usual Prescription Coverage (N=3010)
Age — yr	53.6±7.6	53.7±7.6
Male sex — no. (%)	2152 (75.6)	2248 (74.7)
Medication use before hospitalization — no. (%)†		
ACE inhibitor or ARB	1541 (54.2)	1588 (52.8)
Beta-blocker	1841 (64.7)	1965 (65.3)
Clopidogrel	1541 (54.2)	1637 (54.4)
Statin	1735 (61.0)	1828 (60.7)
Warfarin	180 (6.3)	178 (5.9)
Coexisting illness — no. (%)†		
Congestive heart failure	769 (27.0)	876 (29.1)
Chronic obstructive pulmonary disease	446 (15.7)	495 (16.4)
Diabetes	976 (34.3)	1047 (34.8)
Hypertension	2027 (71.2)	2178 (72.4)
Previous myocardial infarction	445 (15.6)	523 (17.4)
Stroke	164 (5.8)	201 (6.7)
Procedure on index hospitalization — no. (%)		
Angiography	2695 (94.7)	2819 (93.7)
Percutaneous coronary intervention	1915 (67.3)	1988 (66.0)
Coronary-artery bypass grafting	508 (17.9)	544 (18.1)
Comorbidity score‡	0.22±0.39	0.23±0.39
No. of days from hospital discharge to randomization	48.9±23.0	48.4±22.2
Copayment before randomization — U.S. $§		
ACE inhibitor or ARB	13.48±11.74	13.35±10.82
Beta-blocker	12.64±11.15	12.83±12.97
Statin	24.98±22.06	24.92±20.80

* Plus–minus values are means ±SD. There was no significant between-group difference in any category. ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.

† Medication use before hospitalization and coexisting illnesses were assessed on the basis of all filled prescriptions and available diagnoses during the 12-month period preceding the index hospitalization. Medication use was defined as the filling of at least one prescription during this period.

‡ The comorbidity score ranges from 0 to 3.4, with higher scores indicating an increased risk of death. The score was calculated with the use of the Ontario acute myocardial infarction mortality prediction rules, which predict 30-day and 1-year mortality.[21] Each patient's score is calculated on the basis of published weights according to sex and the characteristics observed on the index hospitalization: shock, diabetes with complications, congestive heart failure, cancer, cerebrovascular disease, pulmonary edema, acute renal failure, chronic renal failure, and cardiac dysrhythmias. Because all patients in the trial were under the age of 65 years, weights according to age were not included in our calculations.

§ Included in this category are all patients who filled prescriptions after the index hospitalization and before randomization. Amounts represent average copayments for a 1-month supply of medication.

Table 2. Medication Adherence during Follow-up.*

Variable	Absolute Adherence†				Full Adherence‡			
	Full Prescription Coverage	Usual Prescription Coverage	Absolute Difference (95% CI)	P Value	Full Prescription Coverage	Usual Prescription Coverage	Odds Ratio (95% CI)	P Value
		percentage points			*no./total no. (%)*			
All patients§								
ACE inhibitor or ARB	41.1±39.8	35.9±38.1	5.6 (3.4–7.7)	<0.001	789/2845 (27.7)	689/3010 (22.9)	1.31 (1.14–1.49)	<0.001
Beta-blocker	49.3±37.5	45.0±36.6	4.4 (2.3–6.5)	<0.001	873/2845 (30.7)	758/3010 (25.2)	1.32 (1.16–1.49)	<0.001
Statin	55.1±37.7	49.0±37.3	6.2 (3.9–8.5)	<0.001	1097/2845 (38.6)	950/3010 (31.6)	1.37 (1.20–1.56)	<0.001
All three medication classes	43.9±33.7	38.9±32.7	5.4 (3.6–7.2)	<0.001	344/2845 (12.1)	268/3010 (8.9)	1.41 (1.18–1.67)	<0.001
Patients who filled at least one prescription								
ACE inhibitor or ARB	66.5±29.6	60.8±30.7	5.8 (3.6–8.1)	<0.001	789/1759 (44.9)	689/1775 (38.8)	1.28 (1.10–1.49)	0.002
Beta-blocker	65.0±28.9	61.0±28.9	4.0 (2.1–5.9)	<0.001	873/2159 (40.4)	758/2224 (34.1)	1.31 (1.14–1.50)	<0.001
Statin	70.5±27.0	65.0±28.4	5.5 (3.6–7.5)	<0.001	1097/2223 (49.3)	950/2267 (41.9)	1.36 (1.18–1.56)	<0.001
All three medication classes	67.4±15.5	62.9±26.3	4.5 (2.5–6.4)	<0.001	344/1385 (24.8)	268/1389 (19.3)	1.36 (1.12–1.65)	0.002

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.
† Absolute adherence was calculated with the use of a medication possession ratio (i.e., the number of days for which patients had a supply of each medication class available divided by the number of days they were eligible for that medication). Ratios were multiplied by 100 to generate absolute adherence percentages. Values are for mean medication possession.
‡ Full adherence was defined as having a supply of medications available on at least 80% of days during follow-up. Patients who did not fill a particular prescription after randomization were considered to be nonadherent.
§ Patients who lost eligibility before randomization or who did not fill a prescription after randomization were considered to be nonadherent.

MEDICATION ADHERENCE

In the usual-coverage group, rates of adherence were 35.9% for ACE inhibitors or ARBs, 45.0% for beta-blockers, 49.0% for statins, and 38.9% for all three medication classes (Table 2). In the full-coverage group, rates of adherence were increased by 5.6 percentage points (95% confidence interval [CI], 3.4 to 7.7) for ACE inhibitors or ARBs, by 4.4 percentage points (95% CI, 2.3 to 6.5) for beta-blockers, by 6.2 percentage points (95% CI, 3.9 to 8.5) for statins, and by 5.4 percentage points (95% CI, 3.6 to 7.2) for all three medication classes ($P<0.001$ for all comparisons). The odds of full adherence to the study medications increased by 31 to 41% ($P<0.001$) (Table 2). Rates of adherence to other medications for which copayments were not altered did not differ significantly between the two study groups (Appendix C in the Supplementary Appendix).

CLINICAL OUTCOMES

The primary outcome of a fatal or nonfatal vascular event or revascularization occurred in 562 patients in the usual-coverage group (rate per 100 person-years, 18.8), as compared with 493 patients in the full-coverage group (rate per 100 person-years, 17.6), a nonsignificant reduction (hazard ratio, 0.93; 95% CI, 0.82 to 1.04; $P=0.21$) (Table 3 and Fig. 1A). After adjustment for age and baseline coexisting illnesses, the results were similar (hazard ratio, 0.94; 95% CI, 0.83 to 1.06; $P=0.29$).

Prespecified secondary outcomes occurred in significantly fewer patients in the full-coverage group than in the usual-coverage group. Rates of total major vascular events or revascularization, which included all outcome events that occurred in each patient during the study, were reduced by 11% (hazard ratio, 0.89; 95% CI, 0.80 to 0.99; $P=0.03$) (Table 3). The hazard ratio for the first major vascular event was reduced by 14% (hazard ratio, 0.86; 95% CI, 0.74 to 0.99; $P=0.03$) (Table 3 and Fig. 1B). Among individual components of the composite outcomes, the elimination of copayments led to significant reductions in the rate of stroke (hazard ratio, 0.69; 95% CI, 0.50 to 0.96; $P=0.03$) (Appendix D in the Supplementary Appendix) and nonsignificant reductions in the rates of myocardial infarction or unstable angina (hazard ratio, 0.84; 95% CI, 0.70 to 1.02; $P=0.08$) (Appendix D in the Supplementary Appendix) and congestive heart failure (hazard ratio, 0.87; 95% CI, 0.70 to 1.08; $P=0.21$). The elimination of copay-

Table 3. Clinical Outcomes.

Outcome	Full Prescription Coverage (N=2845)		Usual Prescription Coverage (N=3010)		Hazard Ratio* (95% CI)	P Value
	no.	*rate/100 person-yr*	*no.*	*rate/100 person-yr*		
Fatal or nonfatal vascular event or revascularization†						
First event	493	17.6	562	18.8	0.93 (0.82–1.04)	0.21
Total events	622	21.5	729	23.3	0.89 (0.80–0.99)	0.03
First fatal or nonfatal vascular event	329	11.0	405	12.8	0.86 (0.74–0.99)	0.03
Individual components of outcome‡						
Myocardial infarction or unstable angina	187	6.0	236	7.1	0.84 (0.70–1.02)	0.08
Stroke	60	1.8	92	2.6	0.69 (0.50–0.96)	0.03
Congestive heart failure	150	4.8	182	5.4	0.87 (0.70–1.08)	0.21
Revascularization	293	9.8	298	9.1	1.06 (0.90–1.24)	0.51
Death from cardiovascular causes	57	1.7	72	2.0	0.85 (0.60–1.21)	0.36

* Hazard ratios have been adjusted for the cluster and block randomized design.
† First events are based on the first occurrence of any of the composite outcome events. Total events include all events in patients who may have had more than one component of the composite outcome. In this analysis, we excluded transfers between institutions, counted only one diagnosis per treatment episode, and counted each specific outcome (e.g., stroke) only one time per patient.
‡ Individual components are based on the first occurrence of these outcomes.

ments was not associated with a significant difference in the rate of coronary revascularization (hazard ratio, 1.06; 95% CI, 0.90 to 1.25; P=0.51). There was no evidence of heterogeneity in the clinical outcomes (Appendix E in the Supplementary Appendix).

HEALTH SPENDING

During follow-up in the full-coverage group, there were significant reductions in patients' out-of-pocket spending both for prescription drugs (relative spending, 0.70; 95% CI, 0.65 to 0.75; P<0.001) and for nondrug medical services (relative spending, 0.82; 95% CI, 0.72 to 0.94; P=0.005) (Table 4). In contrast, there was a significant increase in pharmacy spending by insurers (relative spending, 1.32; 95% CI, 1.14 to 1.52; P<0.001) but not for nondrug medical services (relative spending, 0.90; 95% CI, 0.52 to 1.58; P=0.72). The mean total spending was $66,008 in the full-coverage group and $71,778 in the usual-coverage group, a nonsignificant difference (relative spending, 0.89; 95% CI, 0.50 to 1.56; P=0.68). Although the effect of the intervention on cardiovascular-specific spending was similar to that for total spending and was not significant, the strength of the observed association was stronger (relative spending, 0.89; 95% CI, 0.77 to 1.02; P=0.08).

DISCUSSION

In this randomized policy trial involving 5855 patients who were discharged from the hospital after myocardial infarction, the elimination of copayments for statins, beta-blockers, ACE inhibitors, and ARBs did not significantly improve the primary outcome of the first major cardiovascular event or revascularization. The intervention increased medication adherence and reduced the rates of prespecified secondary clinical outcomes (first major vascular event and total major vascular events or revascularization). The enhanced coverage reduced patients' out-of-pocket spending for drug and nondrug services and did not significantly change total spending by insurers or overall costs.

Most activities that are aimed at boosting the quality of care for patients with myocardial infarction have focused on efforts to improve prescribing practices at the time of hospital discharge.[22,23] In contrast, reducing copayments for evidence-based medications, commonly known as value-based insurance design or evidence-based plan design,[11,24]

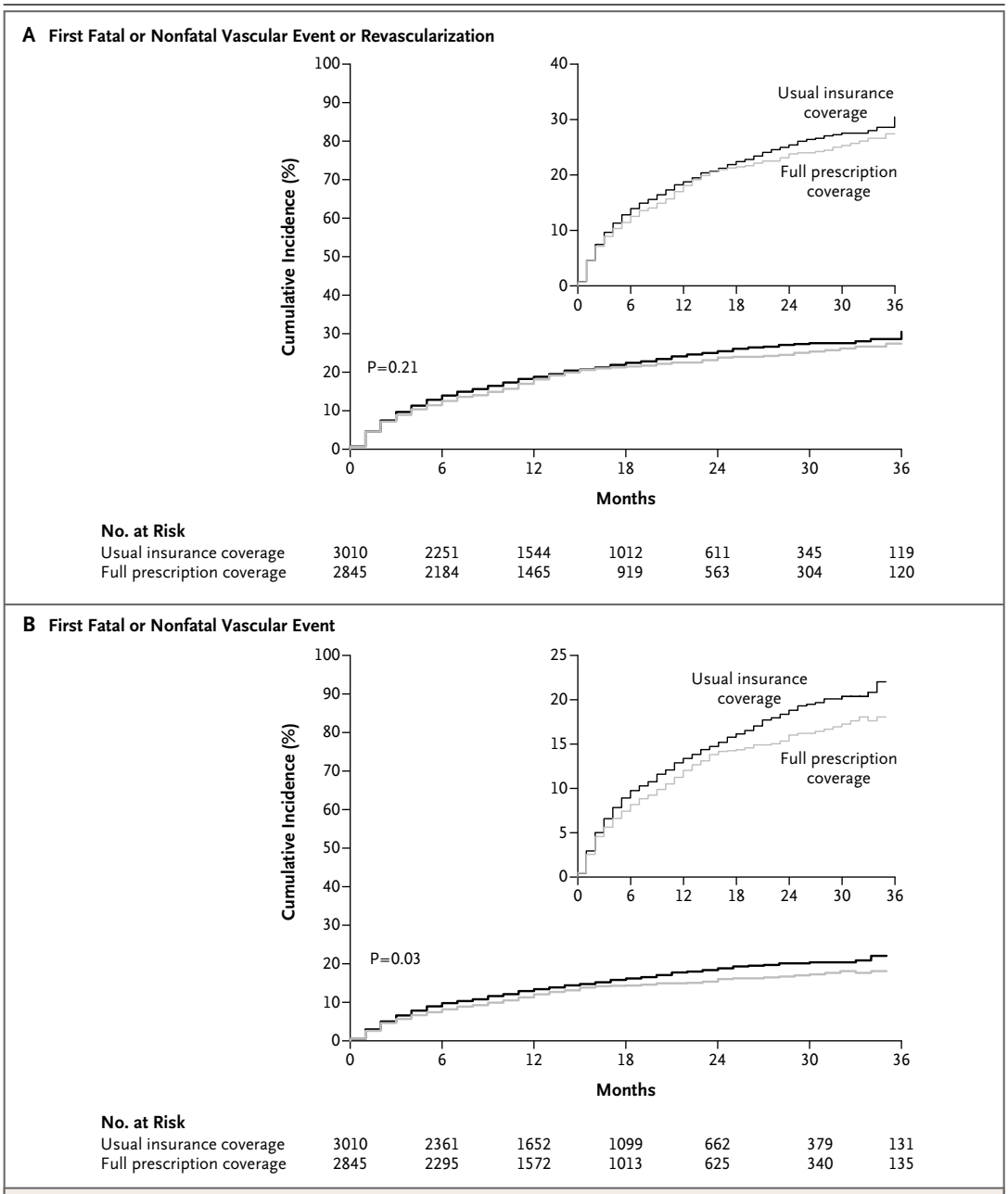

Figure 1. Cumulative Incidence of Outcomes.

Panel A shows the cumulative incidence of the primary outcome (first fatal or nonfatal acute myocardial infarction, unstable angina, stroke, congestive heart failure, or coronary revascularization). Panel B shows the cumulative incidence of the first fatal or nonfatal acute myocardial infarction, unstable angina, stroke, or congestive heart failure.

aims to increase long-term medication use. However, data are lacking from randomized, controlled studies evaluating the effectiveness of this strategy on clinically relevant outcomes for any condition.[13,14,25] Although the changes in medication use that we observed were modest, the simultaneous increases in adherence to multiple drug classes with synergistic effects may have been sufficient to reduce the rate of major vascular events and is consistent in magnitude with effects that would be expected from published economic models.[12,26] The nonsignificant reduction in the primary out-

Table 4. Drug and Nondrug Spending by Patients and Insurers during Follow-up.*

Outcome	Full Prescription Coverage (N=2845)	Usual Prescription Coverage (N=3010)	Relative Spending (95% CI)	P Value
	U.S. dollars			
Total spending				
Prescription drugs				
Insurer	4,847±15,835	3,921±6,606	1.32 (1.14–1.52)	<0.001
Patient	802±1,061	1,164±1,331	0.70 (0.65–0.75)	<0.001
Combined	5,649±16,384	5,085±7,583	1.17 (1.03–1.32)	0.02
Nondrug spending				
Insurer	59,878±634,988	66,076±617,412	0.90 (0.52–1.58)	0.72
Patient	480±815	618±1,480	0.82 (0.72–0.94)	0.005
Combined	60,358±635,098	66,693±617,756	0.90 (0.52–1.57)	0.72
Total spending				
Insurer	64,726±639,683	69,997±617,650	0.92 (0.55–1.56)	0.77
Patient	1,282±1,549	1,781±2,263	0.74 (0.68–0.80)	<0.001
Combined	66,008±639,970	71,778±618,055	0.89 (0.50–1.56)	0.68
Cardiovascular-specific spending				
Prescription drugs				
Insurer	2,271±2,408	1,822±2,058	1.31 (1.22–1.41)	<0.001
Patient	323±396	665±721	0.49 (0.46–0.53)	<0.001
Combined	2,594±2,688	2,488±2,659	1.08 (1.01–1.15)	0.02
Nondrug spending				
Insurer	15,457±39,386	17,516±52,895	0.86 (0.74–1.01)	0.06
Patient	203±316	235±349	0.91 (0.82–1.00)	0.05
Combined	15,661±39,509	17,750±52,993	0.86 (0.74–1.01)	0.06
Total spending				
Insurer	17,729±39,658	19,338±53,082	0.90 (0.78–1.04)	0.14
Patient	526±564	900±888	0.60 (0.56–0.64)	<0.001
Combined	18,254±39,839	20,238±53,250	0.89 (0.77–1.02)	0.08

* Plus–minus values are means ±SD.

come appears attributable to the lack of effect of the intervention on rates of coronary revascularization.

The intervention increased medication use for all the targeted classes, including those for which generic drugs are already commonly used. Similarly, we did not observe any modification in the effect on the basis of baseline copayment levels. Although patients with higher copayments might have been expected to benefit more, the elasticity of demand may not be linear. In addition, adherence to other medications, such as clopidogrel, for which copayments were not eliminated, was virtually identical in the two study groups.

Despite the improvements in adherence that we observed, overall adherence remained low. Consistent with previous studies,[6,27] less than half of patients in the full-coverage group were fully adherent to their prescribed therapies. Therefore, interventions to address other contributors to nonadherence (e.g., knowledge, attitudes, the complexity of prescribed regimens, and difficulties that patients have in accessing their medications) will be necessary to adequately address this problem.[28,29]

Providing more generous prescription drug coverage increased the insurer's pharmacy spending but did not significantly change spending for other

medical services, nor did it increase the insurer's total costs. An intervention that reduces patients' financial burdens without changing overall spending and with possible clinical benefits is a rarity in health care and suggests that eliminating cost sharing for secondary prevention after myocardial infarction may be cost-effective.[30]

Several limitations of our study should be acknowledged. We relied on administrative claims to identify patients and evaluate outcomes. The use of such data for the outcomes that were studied has been validated, and we did not adjudicate study events with medical records. We recruited patients with hospital discharge claims that take time to become available in administrative databases. During the resultant delay, some patients may have become nonadherent to their prescribed therapies. Although this approach increases the generalizability of our findings to other insurers that seek to institute similar plans, it may have diminished the observed effect of the intervention. We evaluated relatively young patients who had been discharged from the hospital after myocardial infarction and who were covered by a large national insurer, and our results may not be generalizable to patients with other conditions or to those who receive health benefits through other means. We do not report the effect of eliminating copayments on the rate of out-of-hospital deaths from cardiovascular causes, since such rates will be ascertained by means of data from death certificates recorded in the Centers for Disease Control and Prevention National Death Index (NDI), for which there is a lag between the date of death and its documentation in the NDI. The clinical outcomes we report include only verifiable deaths from cardiovascular causes (i.e., those that occurred during the course of a hospital admission).

In conclusion, in this randomized trial, the elimination of patient copayments for secondary prevention after myocardial infarction did not significantly reduce rates of the composite primary outcome. We did observe beneficial effects on secondary clinical outcomes, including rates of total major vascular events or revascularization procedures, as well as on rates of first major vascular events and patients' out-of-pocket spending. The intervention did not change overall health spending. This simple strategy may contribute to ongoing efforts to improve the quality of care for patients after myocardial infarction.

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ONLINE FIRST

Randomized Controlled Trial to Improve Primary Care to Prevent and Manage Childhood Obesity

The High Five for Kids Study

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Objective: To examine the effectiveness of a primary care–based obesity intervention over the first year (6 intervention contacts) of a planned 2-year study.

Design: Cluster randomized controlled trial.

Setting: Ten pediatric practices, 5 intervention and 5 usual care.

Participants: Four hundred seventy-five children aged 2 to 6 years with body mass index (BMI) in the 95th percentile or higher or 85th to less than 95th percentile if at least 1 parent was overweight; 445 (93%) had 1-year outcomes.

Intervention: Intervention practices received primary care restructuring, and families received motivational interviewing by clinicians and educational modules targeting television viewing and fast food and sugar-sweetened beverage intake.

Outcome Measures: Change in BMI and obesity-related behaviors from baseline to 1 year.

Results: Compared with usual care, intervention participants had a smaller, nonsignificant change in BMI (–0.21; 95% confidence interval [CI], –0.50 to 0.07; $P = .15$), greater decreases in television viewing (–0.36 h/d; 95% CI, –0.64 to –0.09; $P = .01$), and slightly greater decreases in fast food (–0.16 serving/wk; 95% CI, –0.33 to 0.01; $P = .07$) and sugar-sweetened beverage (–0.22 serving/d; 95% CI, –0.52 to 0.08; $P = .15$) intake. In post hoc analyses, we observed significant effects on BMI among girls (–0.38; 95% CI, –0.73 to –0.03; $P = .03$) but not boys (0.04; 95% CI, –0.55 to 0.63; $P = .89$) and among participants in households with annual incomes of $50 000 or less (–0.93; 95% CI, –1.60 to –0.25; $P = .01$) but not in higher-income households (0.02; 95% CI, –0.30 to 0.33; $P = .92$).

Conclusion: After 1 year, the High Five for Kids intervention was effective in reducing television viewing but did not significantly reduce BMI.

Trial Registration: clinicaltrials.gov Identifier: NCT00377767

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In the United States, approximately 21.2% of children aged 2 to 5 years are overweight (age- and sex-specific body mass index [BMI] in the 85th-94th percentile) and 10.4% are obese (BMI ≥ 95th percentile).[1] Preschool-aged children who are overweight, especially those with overweight parents, tend themselves to become obese as adults[2] and are at high risk of short-term[3] and long-term adverse outcomes.[4-8] The pediatric primary care team is well positioned to provide effective interventions to promote healthful behaviors among families of young children. Well-child visits occur at least annually from ages 2 through 6 years and additional problem-oriented visits provide other opportunities to develop a relationship with the child and family. The continuity of the relationship between pediatricians and families, embodied in the concept of the "medical home,"[9] promotes receptivity to suggestions for changes in health-related behaviors.[10]

Few interventions to prevent childhood obesity have been conducted in the primary care setting.[11-23] Only 1 primary care–based randomized controlled trial[23] and 2 nonrandomized trials have focused on children younger than 6 years.[19,20] In the Live, Eat, and Play (LEAP) randomized controlled trial of 2112 children aged 5 to 9 years in Australia,[23] consultations with general practitioners on obesity-related behaviors did not result in significant BMI reduction at 9 or 15 months postenrollment. In a nonrandomized study of 1128 children aged 3 to 6 years who attended primary care clinics in Singapore,

Ray et al[19] found that nurse-led counseling sessions were effective in reducing obesity prevalence. In another nonrandomized trial conducted within US-based primary care pediatric offices, motivational interviewing by pediatricians and dietitians was effective in reducing BMI percentile among 91 overweight children aged 3 to 7 years.[20] Although each of these studies showed the feasibility and, in some, the effectiveness of primary care–based interventions for obesity management, none of these trials involved the entire primary health care team; 2 were further limited by their nonrandomized design; and the 1 US-based study had a small sample size.

The purpose of this study was to assess the extent to which a primary care–based intervention, compared with the usual care control condition, resulted in a smaller increase in BMI and improvement in obesity-related behaviors among children aged 2 through 6 years at elevated risk of obesity.

METHODS

STUDY DESIGN, SETTING, AND RANDOMIZATION

High Five for Kids is a cluster randomized controlled trial in 10 primary care pediatric offices of Harvard Vanguard Medical Associates, a multisite group practice in Massachusetts. The intervention duration is 2 years and includes an intensive 1-year intervention period followed by a less intensive maintenance period. This article reports the results after the first year of intervention. To pair practices in preparation for blocked, or stratified, randomization, we first divided the practices into the biggest 4 and smallest 6, then matched within those groups as closely as possible on racial/ethnic composition. Within each of 5 pairs, a computerized routine randomly allocated one practice to the intervention group and one to the usual care control group.

PARTICIPANTS

Participants comprised children aged 2.0 to 6.9 years whose BMI (calculated as weight in kilograms divided by height in meters squared) was in the 95th percentile or higher or whose BMI was in the 85th to less than 95th percentile if at least 1 parent was overweight (BMI ≥ 25) and who received their pediatric care at Harvard Vanguard Medical Associates between August 2006 and October 2008. We excluded (1) children whose parent or guardian could not respond to interviews in English or Spanish, (2) children whose families were planning to leave Harvard Vanguard Medical Associates, (3) families for whom the primary care clinician thought the intervention was not appropriate, and (4) children with chronic medical conditions.

Using the electronic medical records, we identified 3253 children who had a BMI in the 85th percentile or higher sometime within the year prior to their index well-child care visit. After each pediatric provider offered medical clearance, and approximately 1 month prior to the child's scheduled well-child care visit, we mailed a letter to each parent introducing the study. The letter included an opt-out telephone number to call if the family did not want to participate. We telephoned those individuals who did not opt out within 7 days after mailing the letter. During the telephone call, research staff conducted a baseline interview and mailed a written informed consent to parents. Research assistants assessed parental BMI by interview. Participants were enrolled once we confirmed their BMI at the scheduled well-child care visit and we received written informed consent.

At 1 year, participants completed a telephone interview with research staff and had their heights and weights measured as part of their annual well-child care visit. We offered all participants $20 for completing each telephone interview. We also reimbursed intervention participants for the co-pay incurred at each visit with the nurse practitioners. All study procedures were approved by the human subjects committee of Harvard Pilgrim Health Care.

TREATMENT GROUPS

Usual Care

Participants randomized to usual care received the current standard of care offered by their pediatric practice. This included well-child care visits and follow-up appointments for weight checks with their pediatrician or a subspecialist (eg, nutritionist). Visits for families in the usual care group included the baseline and annual well-child care visits.

Intervention

The overarching model for this intervention was the Chronic Care Model,[24] which posits that changes in primary care to produce functional patient outcomes require changes for all members of the practice team (**Figure 1**). Major components of the intervention involved changes to the health care system. We trained all members of the practice team to play an active role in the intervention. We enhanced the electronic medical record system to assist clinicians with decision support, patient tracking, follow-up, scheduling, and billing (Figure 1). After reorganization of the delivery of primary and acute care, the pediatric nurse practitioners conducted chronic disease management visits with intervention participants. Prior to the start of the intervention, we negotiated with the regional insurance companies to pay for up to 4 visits for both overweight and obese patients in the first year of the study.

We trained the pediatric nurse practitioners to be the key intervening clinicians and to use motivational interviewing during four 25-minute, in-person chronic disease management visits and three 15-minute telephone calls in the first year of the intervention. Motivational interviewing is a communication technique that enhances self-efficacy, increases recognition of inconsistencies between actual and desired behaviors, teaches skills for reduction of this dissonance, and enhances motivation for change.[25-28] Components include de-emphasizing labeling, giving the parent responsibility for identifying which behaviors are problematic, encouraging parents to clarify and resolve ambivalence about behavior change, and setting goals to initiate the change process.[25,27,28] We trained the primary care pediatricians in the intervention practices to use brief, focused negotiation skills[29] at all routine well-child care visits to endorse family behavior change. Brief, focused negotiation is based on the concepts of motivational interviewing but tailored for brief sessions such as the clinical encounter. To ensure accurate measurements of heights and weights, we trained all medical assistants in intervention and usual care practices on conducting research-standard anthropometric measurements. We also trained the medical receptionists to schedule initial and follow-up visits with the nurse practitioners based on the study protocol.

We developed several resources to assist the physicians and nurse practitioners in supporting participants and their family in behavior change. For the patient waiting rooms, we created posters highlighting our targeted behaviors to encourage dia-

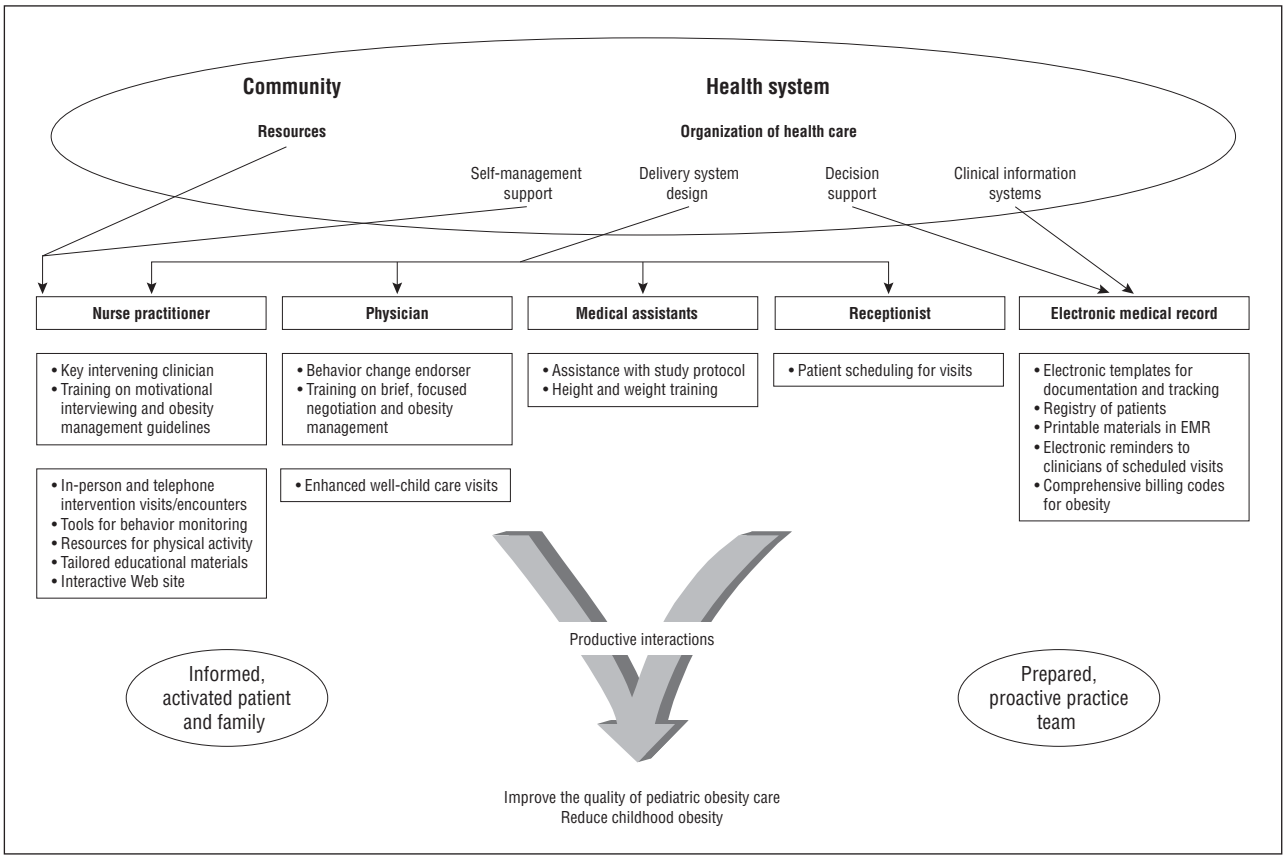

Figure 1. Conceptual framework, based on the Chronic Care Model, of the High Five for Kids study. EMR indicates electronic medical record.

logue during well-child care visits (**Figure 2**). For the chronic disease management visits with the nurse practitioners, we developed educational modules targeting television viewing and fast food and sugar-sweetened beverage intake that were matched to a family's stage of readiness to change[27]; printed and electronic tools for self-management support; lists of local resources for physical activity; and an interactive Web site with educational materials, recipes, and other features. To further support behavior change, the nurse practitioners provided small incentives such as water bottles, books, and snack containers. In addition, the nurse practitioners offered interested families an electronic television monitoring device to assist with the goal of reducing television viewing.

OUTCOME MEASURES

Our primary outcome was change in BMI from baseline to 1 year. Medical assistants measured children's weight, without shoes, using an electronic, calibrated scale (Seca, Birmingham, United Kingdom) and height using a stadiometer. We calculated BMI and age- and sex-specific BMI *z* scores and percentiles.[30]

The behavioral goals for children in the intervention were less than 1 h/d of television and video viewing, removing the television from or avoiding putting a television in the room where the child sleeps, 1 serving/wk or less of fast food, and 1 serving/d or less of sugar-sweetened beverages. To assess average daily television and video viewing, we used previously validated questions.[31] We also asked if the child had a television in the room where he or she sleeps. We measured daily sugar-sweetened beverage intake using questions from a validated semiquantitative child food frequency questionnaire[32] and we measured fast food intake using a single question shown to be associated with BMI in an adolescent cohort.[33] We also measured the child's daily fruit and vegetable intake[34] and outdoor physical activity time.[35] During interviews with research staff, the parent who brought the child to his or her well-child care visit reported his or her height and weight range, from which we estimated his or her BMI. Research assistants asked the parent to report the height and weight of the child's other parent. Parents also reported their educational attainment, marital status, annual household income, and their child's race/ethnicity.

We culled data from the electronic medical record on completed visits and telephone calls. To assess parents' acceptance of and satisfaction with the intervention components, we asked parents in the intervention group during the 1-year interview to rate how satisfied they were with the program. We also asked parents if they would recommend the program to their family or friends and whether they had chosen to work on specific behaviors.

DATA ANALYSIS

We first examined baseline distributions of child and parent characteristics by intervention status. In intent-to-treat analyses, we used crude and adjusted multivariate regression models, corrected for clustering by practice, to examine differences from baseline to 1 year between the intervention and usual care groups. For continuous outcomes, we used linear regression models, and for dichotomous outcomes, we used logistic regression models. For all models, to account for intraclass correlation, we performed generalized linear mixed models that accounted for clustering by practices (PROC GLIMMIX in SAS version 9.2; SAS Institute Inc, Cary, North Carolina).

Figure 2. High Five for Kids poster for pediatric primary care waiting rooms.

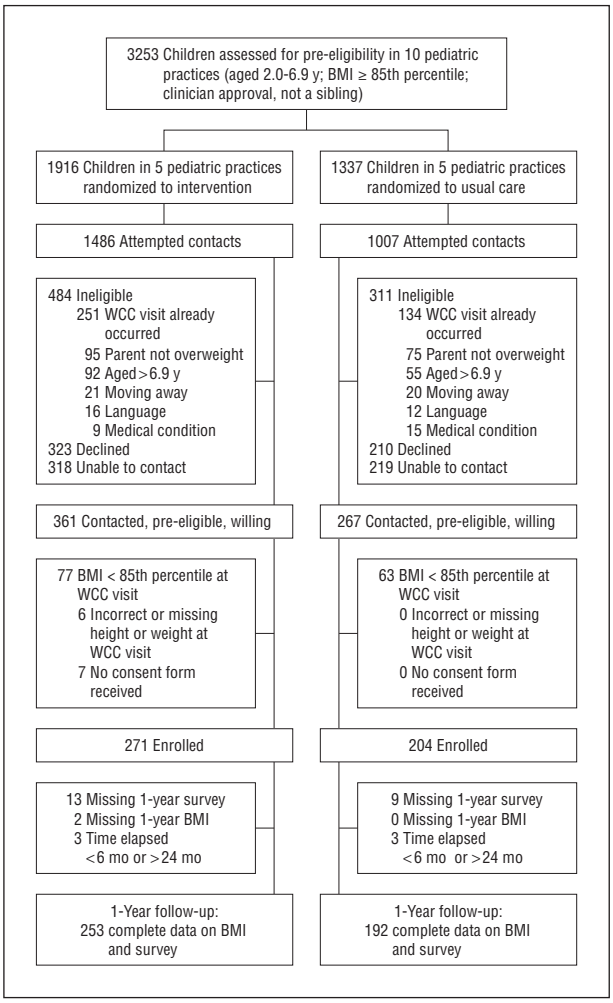

Figure 3. Participant flow for the High Five for Kids study. BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); WCC, well-child care.

RESULTS

Figure 3 shows the participant flow in the High Five for Kids study. We enrolled 271 children in the intervention group and 204 in usual care. Two hundred fifty-three participants in the intervention group (93% of those enrolled) and 192 participants in usual care (94% of those enrolled) completed a 1-year telephone interview and well-child care visit for BMI measurement. **Table 1** shows characteristics of our study sample overall and by intervention assignment. At baseline, mean (SD) BMI was 19.2 (2.6) among intervention children and 19.1 (2.0) among usual care children and BMI *z* scores were 1.88 (0.69) and 1.82 (0.56), respectively. Fifty-three percent of intervention children had a BMI in the 95th percentile or higher vs 60% of usual care children. Children randomized to the intervention group were more likely to be racial/ethnic minorities, have an obese parent, and live in lower-income households (Table 1). There were no group differences at baseline in health behaviors (Table 1).

Table 2 shows participants' BMI at baseline and at 1 year by intervention assignment. At 1 year, BMI had increased by a mean of 0.31 in the intervention group and 0.49 in the usual care group, yielding a crude difference of –0.19. After multivariable adjustment, compared with usual care, intervention participants had a smaller, nonsignificant change in mean BMI from baseline to 1 year than usual care participants (–0.21; 95% confidence interval [CI], –0.50 to 0.07; $P=.15$). We observed similar results using change in age- and sex-specific BMI *z* score as the outcome (–0.05 unit; 95% CI, –0.14 to 0.04; $P=.28$). In post hoc stratified analyses, we observed statistically significant intervention effects on BMI among girls (–0.38; 95% CI, –0.73 to –0.03; $P=.03$) but not boys (0.04; 95% CI, –0.55 to 0.63; $P=.89$) and among participants in households with annual incomes of $50 000 or less (–0.93; 95% CI, –1.60 to –0.25; $P=.01$) but not in higher-income households (0.02; 95% CI, –0.30 to 0.33; $P=.92$).

Table 3 shows baseline and 1-year levels of our behavioral outcomes. In adjusted models, intervention participants decreased their television and video viewing more than usual care participants (–0.36 h/d; 95% CI, –0.64 to –0.09; $P=.01$). We also observed greater decreases in fast food intake (–0.16 serving/wk; 95% CI, –0.33 to 0.01; $P=.07$) and sugar-sweetened beverage intake (–0.22 serving/d; 95% CI, –0.52 to 0.08; $P=.15$), though the confidence intervals for these effects did not exclude a null effect. For the dichotomous outcome of television in the room where the child sleeps, we did not observe an intervention effect (Table 3).

Over their multiple visits and telephone calls, participating families could choose to work on 1 or more behavioral targets. Of the 253 participants in the intervention group, 68% chose to work on decreasing their child's sugar-sweetened beverage intake, 62% chose to work on

Table 1. Baseline Characteristics and Behaviors of Participants in the High Five for Kids Study Overall and by Intervention Assignment

	No. (%)		
	Overall (n=445)	Intervention (n=253)	Usual Care (n=192)
Child characteristics			
Age, mean (SD), y	4.9 (1.2)	4.8 (1.2)	5.2 (1.1)
Sex			
F	215 (48)	121 (48)	94 (49)
M	230 (52)	132 (52)	98 (51)
Race/ethnicity			
White	252 (57)	118 (47)	134 (70)
Black	84 (19)	70 (28)	14 (7)
Latino	74 (17)	48 (19)	26 (14)
Other	35 (8)	17 (7)	18 (9)
BMI, mean (SD)	19.2 (2.4)	19.2 (2.6)	19.1 (2.0)
BMI, *z* score, mean (SD)	1.85 (0.63)	1.88 (0.69)	1.82 (0.56)
BMI category			
85th-94th percentile	195 (44)	118 (47)	77 (40)
≥95th percentile	250 (56)	135 (53)	115 (60)
Time elapsed from baseline to follow-up visit, mo, mean (SD)	12.8 (2.2)	12.9 (2.3)	12.7 (2.0)
Child health behaviors			
Sugar-sweetened beverage intake, servings/d	2.1 (1.7)	2.3 (1.8)	2.0 (1.5)
Fast food consumption, servings/wk	1.1 (0.9)	1.2 (0.9)	1.1 (0.9)
Total television and video viewing, h/d	2.6 (1.5)	2.7 (1.6)	2.4 (1.3)
Television in room where child sleeps	158 (36)	100 (40)	58 (30)
Other health behaviors			
Fruit and vegetable intake, servings/d	2.4 (1.5)	2.4 (1.5)	2.4 (1.5)
Outdoor active playtime, h/d	2.0 (1.4)	1.9 (1.5)	2.1 (1.4)
Parent and household characteristics			
Parent overweight/obesity status			
Normal weight (BMI<25)	17 (4)	8 (3)	9 (5)
Overweight (BMI 25 to <30)	189 (43)	90 (36)	99 (52)
Obese (BMI≥30)	238 (54)	154 (61)	84 (44)
Parent educational attainment			
Some college or below	171 (38)	106 (42)	65 (34)
College graduate	274 (62)	147 (58)	127 (66)
Annual household income, $			
≤50 000	126 (29)	88 (36)	38 (20)
≥50 001	313 (71)	160 (64)	153 (80)
Marital status			
Married	338 (76)	187 (75)	151 (79)
Not married	107 (24)	66 (26)	41 (21)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

decreasing their child's fast food intake, 63% chose to work on decreasing their child's television and video viewing, but only 9% chose to work on removing the television from or avoiding putting a television in the room where their child sleeps. We stratified models by whether the family chose to work on the behavior and used usual care as the comparison for each model. In these stratified analyses, we observed greater intervention effects among participants who chose to work on specified behaviors (**Figure 4**).

We aimed for intervention participants to complete 6 intervention activities with the nurse practitioner by 1 year. Among the 253 intervention participants, 141 (56%) had completed at least 2 of 6 activities. Compared with usual care, intervention participants who completed 2 or more activities by 1 year had greater decreases in television and video viewing (–0.58 h/d; 95% CI, –0.92 to –0.24; $P=.001$) and sugar-sweetened beverage intake (–0.31 serving/d; 95% CI, –0.74 to 0.12; $P=.15$). Intervention participants with fewer than 2 activities by 1 year had only minimal decreases in their television and video viewing (–0.04 h/d) and sugar-sweetened beverage intake (–0.02 serving/d). There was no difference in BMI or fast food intake change based on adherence to the intervention protocol.

Based on follow-up questions of the 253 intervention participants, 97% reported being "somewhat" or "very satisfied" with the High Five for Kids program and 91% reported they would recommend the program to their family and friends.

COMMENT

In this 1-year follow-up of a primary care–based, cluster randomized controlled trial we found that a multicomponent obesity intervention based on the Chronic Care Model improved television and video viewing particu-

Table 2. Change in BMI From Baseline to 1 Year by Intervention Assignment and Within Subgroup

Outcome	No. (%)			β (95% CI)		*P* Value
	Baseline	1 Year	Change	Crude Difference[a]	Adjusted Difference[b]	
BMI, mean (SE)						
Intervention	19.2 (0.2)	19.5 (0.2)	0.31 (0.09)	−0.19 (−0.50 to 0.12)	−0.21 (−0.50 to 0.07)	.15
Usual care	19.1 (0.1)	19.6 (0.2)	0.49 (0.10)			
BMI Outcome by Subgroup						
Child age at baseline						
<60 mo						
Intervention	19.0 (0.2)	19.0 (0.3)	0.01 (0.13)	−0.20 (−0.64 to 0.24)	−0.29 (−0.75 to 0.17)	.22
Usual care	18.9 (0.2)	19.1 (0.3)	0.22 (0.18)			
≥60 mo						
Intervention	19.4 (0.2)	20.0 (0.3)	0.58 (0.12)	−0.05 (−0.38 to 0.28)	−0.13 (−0.48 to 0.22)	.46
Usual care	19.3 (0.2)	19.9 (0.2)	0.63 (0.12)			
Child sex						
F						
Intervention	19.2 (0.2)	19.5 (0.3)	0.30 (0.12)	−0.33 (−0.69 to 0.03)	−0.38 (−0.73 to −0.03)	.03
Usual care	19.3 (0.2)	19.9 (0.3)	0.63 (0.14)			
M						
Intervention	19.2 (0.2)	19.5 (0.3)	0.33 (0.14)	−0.03 (−0.61 to 0.55)	0.04 (−0.55 to 0.63)	.89
Usual care	19.0 (0.2)	19.4 (0.3)	0.36 (0.14)			
Child race/ethnicity						
White						
Intervention	19.0 (0.2)	19.2 (0.3)	0.18 (0.12)	−0.24 (−0.59 to 0.10)	−0.19 (−0.54 to 0.16)	.30
Usual care	18.9 (0.2)	19.3 (0.2)	0.42 (0.11)			
Black						
Intervention	19.6 (0.3)	20.1 (0.4)	0.50 (0.19)	−0.60 (−1.60 to 0.40)	−0.64 (−1.61 to 0.32)	.20
Usual care	19.5 (0.5)	20.6 (0.7)	1.08 (0.43)			
Latino						
Intervention	19.3 (0.4)	19.8 (0.5)	0.46 (0.21)	0.01 (−0.71 to 0.73)	0.09 (−0.72 to 0.90)	.82
Usual care	19.8 (0.5)	20.2 (0.7)	0.45 (0.31)			
Other						
Intervention	18.6 (0.3)	18.6 (0.3)	0.03 (0.36)	−0.61 (−1.53 to 0.32)	−0.48 (−1.58 to 0.63)	.41
Usual care	19.5 (0.5)	20.1 (0.6)	0.64 (0.30)			
Parent education						
≤Some college						
Intervention	19.6 (0.3)	20.1 (0.4)	0.49 (0.16)	−0.42 (−0.93 to 0.09)	−0.36 (−0.92 to 0.19)	.20
Usual care	19.1 (0.2)	20.0 (0.3)	0.91 (0.20)			
≥College graduate						
Intervention	18.9 (0.2)	19.1 (0.2)	0.18 (0.11)	−0.09 (−0.38 to 0.20)	−0.14 (−0.44 to 0.16)	.37
Usual care	19.1 (0.2)	19.4 (0.2)	0.27 (0.10)			
Household income, $						
≤50 000						
Intervention	19.6 (0.3)	20.0 (0.4)	0.40 (0.17)	−1.02 (−1.65 to −0.38)	−0.93 (−1.60 to −0.25)	.01
Usual care	19.9 (0.4)	21.3 (0.5)	1.42 (0.29)			
≥50 001						
Intervention	19.0 (0.2)	19.3 (0.2)	0.27 (0.11)	−0.01 (−0.35 to 0.33)	0.02 (−0.30 to 0.33)	.92
Usual care	19.0 (0.2)	19.2 (0.2)	0.26 (0.09)			
Parental overweight/obesity status at baseline						
BMI 25 to <30						
Intervention	18.9 (0.2)	19.5 (0.4)	0.58 (0.19)	0.10 (−0.45 to 0.65)	−0.04 (−0.66 to 0.58)	.89
Usual care	18.8 (0.2)	19.3 (0.3)	0.48 (0.18)			
BMI≥30						
Intervention	19.9 (0.3)	20.2 (0.4)	0.27 (0.17)	−0.57 (−1.13 to 0.00)	−0.29 (−0.90 to 0.31)	.34
Usual care	19.9 (0.4)	20.1 (0.5)	0.84 (0.19)			

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval.
[a] Corrected for clustering within practice.
[b] Adjusted for child age, sex, and race/ethnicity; parent education and overweight/obesity status at baseline; household income; and time elapsed from baseline to follow-up visit.

larly among families who chose to work on reducing television time and removing or avoiding putting a television in the room where the child sleeps. Children in the High Five for Kids intervention group had a smaller, but nonsignificant, increase in BMI overall. In addition, in post hoc analyses, the intervention significantly improved BMI among girls and those living in lower-income households.

To our knowledge, the High Five for Kids study is the first randomized controlled trial in a primary care setting

Table 3. Change in Health Behaviors From Baseline to 1 Year by Intervention Assignment

	Mean (SE)			β (95% CI)		
	Baseline	1 Year	Change	Crude Difference[a]	Adjusted Difference[b]	*P* Value
Behavioral outcomes						
Sugar-sweetened beverages, servings/d						
Intervention	2.25 (0.11)	1.66 (0.08)	−0.59 (0.10)	−0.26 (−0.54 to 0.01)	−0.22 (−0.52 to 0.08)	.15
Usual care	1.95 (0.11)	1.63 (0.09)	−0.33 (0.06)			
Fast food consumption, servings/wk						
Intervention	1.16 (0.06)	0.94 (0.05)	−0.22 (0.05)	−0.20 (−0.37 to −0.02)	−0.16 (−0.33 to 0.01)	.07
Usual care	1.13 (0.06)	1.11 (0.06)	−0.02 (0.06)			
Total television and video viewing, h/d						
Intervention	2.67 (0.10)	2.13 (0.07)	−0.53 (0.09)	−0.45 (−0.71 to −0.20)	−0.36 (−0.64 to −0.09)	.01
Usual care	2.44 (0.10)	2.36 (0.09)	−0.07 (0.09)			
				OR (95% CI)		
Television in bedroom, No. (%)[c]						
Intervention	100 (40)	75 (30)	−25 (10)	0.71 (0.37 to 1.33)	0.65 (0.32 to 1.32)	.23
Usual care	58 (30)	49 (26)	−9 (5)			
				β (95% CI)		
Other behavioral outcomes						
Fruit and vegetable intake, servings/d						
Intervention	2.43 (0.09)	2.65 (0.10)	0.22 (0.09)	0.06 (−0.21 to 0.33)	0.12 (−0.17 to 0.42)	.41
Usual care	2.39 (0.11)	2.55 (0.11)	0.16 (0.11)			
Outdoor active playtime, h/d						
Intervention	1.88 (0.09)	1.94 (0.09)	0.06 (0.10)	−0.13 (−0.44 to 0.18)	−0.24 (−0.57 to 0.09)	.16
Usual care	2.08 (0.10)	2.28 (0.12)	0.20 (0.13)			

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Corrected for clustering within practice.
[b] Adjusted for child age, sex, and race/ethnicity; parent education and overweight/obesity status at baseline; household income; and exact time elapsed from baseline to follow-up visit.
[c] Additionally adjusted for having a television in the bedroom at baseline.

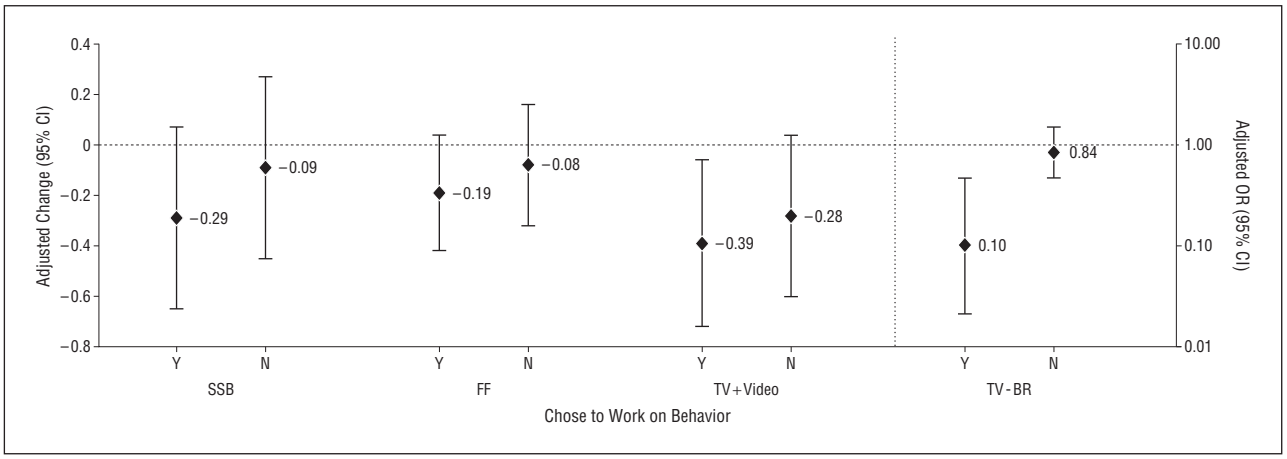

Figure 4. Change in health behaviors from baseline to 1 year according to whether the family chose to work on the behavior. CI indicates confidence interval; FF, fast food intake; OR, odds ratio; SSB, sugar-sweetened beverage intake; TV-BR, television in the child's bedroom; TV+Video, television and video viewing.

aimed at reducing obesity among preschool-aged children. A recent review of primary care–based interventions for treating overweight and obese children and adolescents[22] identified no moderate- to high-intensity interventions for children younger than 6 years and only the LEAP trial,[23] a low-intensity intervention that involved consultations with general practitioners on nutrition, physical activity, and sedentary behavior, included children 5 years and older. Our intervention was also innovative in that we attempted to effect sustainable changes in the health care system to prevent and manage childhood obesity. We recognized that the complexity of childhood obesity as a chronic medical problem required a new paradigm to improve obesity-related outcomes. Thus, based on the Chronic Care Model, the High Five for Kids intervention involved changes in the roles and responsibilities for the entire practice team and retraining of clinicians to support family behavior change, as well as updating clinical information systems and providing families links to their community for physical activity. We designed intervention components to be sustainable in a "real-world" primary care setting by training existing clinical staff to de-

liver the intervention. The intervention was also designed to be of moderate to high intensity requiring 6 intervention activities over a 1-year period.

In our intervention, the overall adjusted mean difference (intervention vs usual care) in BMI was –0.21 at 1 year. This magnitude of effect is very similar to that of the LEAP study[23] in which the adjusted mean difference in BMI was –0.20 (95% CI, –0.6 to 0.1) at 9 months. Several factors could have contributed to the lack of a statistically significant intervention effect on BMI. First, our intervention involved only the primary care setting and not children's communities or environment. It is possible that primary care–based interventions alone will not effect change in BMI but could complement and potentially enhance more comprehensive efforts in multiple settings. Second, adherence to intervention activities was relatively low; a little more than half of the participants completed at least 2 of the 6 visits/telephone calls. It is possible that the intervention "dose" delivered was not sufficient in effecting changes in BMI. Third, we taught the nurse practitioners to use motivational interviewing to structure their visits and telephone calls. Parents were provided a choice of behaviors to work on in a nonprescriptive style and this could have led to parents choosing behaviors that could have had a lower impact on BMI, eg, fruit and vegetable intake. Fourth, it is possible that BMI changes might lag behind the behavioral changes we observed in our intervention. Thus, we will evaluate the effect of the intervention after the planned 2-year intervention period.

Cross-sectional,[36-38] longitudinal,[39,40] and experimental[41-43] evidence suggest that television viewing and televisions in bedrooms are associated with obesity risk in children. Although several interventions have attempted to reduce television viewing, only 3 published studies have included children younger than 6 years,[41,42,44] only 2 of which successfully decreased television viewing.[41,42] Using intervention strategies similar to Dennison et al[41] and Epstein et al,[42] we found that children in the intervention group decreased their television and video viewing by 0.36 h/d. The magnitude of effect was higher (–0.58 h/d) if parents chose to work on reducing their child's television and video viewing. This magnitude of effect was similar to the 2 published interventions that included preschool-aged children. Our results lend support to multimodal interventions to reduce television viewing among young children.

We observed greater intervention effects among female participants and among those living in lower-income households. It is possible that the sex differences we observed could be due to parents of girls being more attuned to issues of weight, diet, and activity and could have been more responsive to the intervention. A similar sex difference in intervention effect has been shown in other childhood obesity intervention studies.[45] Participating children living in lower-income households had higher BMIs at baseline. It is possible the intervention was more effective among these children because they had more "room to move." These findings deserve further investigation.

This intervention had several limitations. First, although we attempted to match the pediatric sites to obtain similar participant characteristics in intervention and usual care, unbalanced participant characteristics at baseline occurred. This imbalance may have also affected differences in parent obesity and household income. However, adjusted and unadjusted results were similar, suggesting that any imbalance in observed (or unobserved) characteristics did not affect inferences. Second, electronic medical records, which we used for decision support and recruiting and tracking of intervention participants, are not available in all pediatric practices. Thus, our intervention may not generalize to all pediatric settings. Third, although we used validated measures to assess our behavioral outcomes, we used parental report of behaviors rather than objective measures. Thus, it is possible that parents could exaggerate self-reported improvements in behaviors. For this reason, our primary outcome was BMI, a more objective measure. Fourth, because our intervention was not a factorial design, we are not able to specifically say which components were more effective. However, our results indicate that participants with more fidelity to protocol had greater improvement in their behaviors, possibly indicating that with greater fidelity to protocol, we could have had greater magnitudes of effects.

In summary, after 1 year, we found that the High Five for Kids study improved television-viewing behaviors among preschool-aged children but did not have significant effects on BMI or diet-related behaviors. We plan further follow-up to evaluate the intervention effects over a longer period and examine the components of such an intervention that are maximally effective, scalable, and cost-effective.

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Rationale and design of the STAR randomized controlled trial to accelerate adoption of childhood obesity comparative effectiveness research☆,☆☆,★,★★

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ABSTRACT

Background: Comparative effectiveness research (CER) evidence on childhood obesity provides the basis for effective screening and management strategies in pediatric primary care. The uses of health information technology including decision support tools in the electronic health records (EHRs), as well as remote and mobile support to families, offer the potential to accelerate the adoption of childhood obesity CER evidence.

Methods/design: The Study of Technology to Accelerate Research (STAR) is a three-arm, cluster-randomized controlled trial being conducted in 14 pediatric offices in Massachusetts designed to enroll 800, 6 to 12 year old children with a body mass index (BMI) ≥ 95th percentile seen in primary care at those practices. We will examine the extent to which computerized decision support tools in the EHR delivered to primary care providers at the point of care, with or without direct-to-parent support and coaching, will increase adoption of CER evidence for management of obese children. Direct-to-parent intervention components include telephone coaching and twice-weekly text messages. Point-of-care outcomes include obesity diagnosis, nutrition and physical activity counseling, and referral to weight management. One-year child-level outcomes include changes in BMI and improvements in diet, physical activity, screen time, and sleep behaviors, as well as cost and cost-effectiveness.

Conclusions: STAR will determine the extent to which decision support tools in EHRs with or without direct-to-parent support will increase adoption of evidence-based obesity management strategies in pediatric practice and improve childhood obesity-related outcomes.

Abbreviations: BMI, body mass index; EHR, electronic health record; HVMA, Harvard Vanguard Medical Associates; CER, Comparative effectiveness research; HIT, Health information technology

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1. Introduction

In 2012, the Institute of Medicine report on Accelerating Progress in Obesity Prevention [1] called on health care professionals to increase their support structure for achieving better population health and obesity prevention. For children, the primary care setting provides the structure and opportunities to alter the subsequent course of health and disease for children at risk for obesity and its complications. Regular primary care visits during childhood allow detection of elevated body mass index (BMI) levels and offer opportunities for prevention, screening, and treatment of obesity. The continuity of the pediatrician/family relationship, as well as new models of care that promote family-centered care for children with chronic illnesses [2,3], are further examples of how primary care-based interventions to manage childhood obesity are particularly likely to be of benefit.

Despite their advantages, primary care settings have not realized their full potential in obesity management. Since 1998, when the first Expert Recommendations on the evaluation and treatment of childhood obesity were released, pediatric providers have often failed to diagnose childhood obesity and only inconsistently use BMI [4] and/or provide nutrition and physical activity counseling [5–9]. Although more parents of overweight and obese children reported that their doctors told them of this condition in 2007 through 2008 versus in 1999 through 2000, the proportion still amounts to fewer than one-quarter [10]. As screening for and recognition of obesity is the first step towards appropriate management, system-wide changes to encourage adoption of standardized practice approaches to obesity management in primary care can address these gaps [11,12].

We designed the Study of Technology to Accelerate Research (STAR) randomized controlled trial to test strategies for accelerating the adoption of childhood obesity comparative effectiveness research (CER) evidence by pediatric clinicians and families. This study is funded by the Office of the Secretary for Planning and Evaluation in the Department of Health and Human Services in response to a call for proposals to accelerate adoption of comparative effectiveness research results by providers and patients (RFA-AE-10-001). In this article we describe the rationale and design of the STAR study, which is due to complete data collection in September, 2013.

2. Study rationale

2.1. Childhood obesity comparative effectiveness research

The Federal Coordinating Council for Comparative Effectiveness Research and the Institute of Medicine have highlighted accelerating the adoption of CER evidence as a national research priority [13,14]. Childhood obesity is a high priority CER topic, in part because of the high prevalence, its associated co-morbidities, and the need for testing of available prevention and treatment strategies. Recent CER evidence on childhood obesity provides the basis for effective screening and management strategies [15,16].

Included in the available CER evidence is the United States Preventive Services Task Force (USPSTF) report released in February 2010 which provided evidence-based recommendations on screening and management of obesity in children [17]. The USPSTF recommendations, based on over 15 good-quality weight management interventions among children 4 to 18 years of age [16], determined there was sufficient evidence to recommend that clinicians screen children ≥6 years of age for obesity using BMI and offer them comprehensive, intensive behavioral interventions to promote improvement in weight status [17]. The USPSTF review offers strong CER evidence that 1) screening and evaluation of children for obesity is an important prelude to effective treatment, 2) comprehensive treatment including counseling for weight loss, and healthful nutrition and physical activity is effective, and 3) behavioral management techniques to make and sustain lifestyle changes are important intervention components [18].

2.2. Strategies to accelerate the adoption of CER evidence among pediatric clinicians and families

2.2.1. Decision support delivered using health information technology

The use of health information technology, such as electronic health records (EHRs), offers potential to accelerate the adoption of childhood obesity CER evidence [19,20]. EHRs enable delivery of decision support tools for clinicians at the point-of-care that can be linked to CER-based management algorithms and that meet national benchmarks of pediatric obesity quality of care. In pediatric outpatient settings, electronic decision support has already been shown to improve prescribing patterns [21], increase immunization rates [22], and improve delivery of preventive asthma care [23]. We have previously shown that commonly used functions in the EHR that could facilitate pediatric obesity management include viewing growth charts and trajectories, accessing previous laboratory test results, using structured templates to facilitate documentation and referrals, and the ability to print tailored after-visit summaries with parent educational materials [24]. In in-depth interviews we conducted with pediatric clinicians as part of the formative work for the STAR study, clinicians also suggested combining structured templates already commonly used for well child care visits with content that would meet obesity-related quality benchmarks and that would assist clinicians in incorporating behavioral modification tools in their visits [25].

2.2.2. Direct-to-parent support using remote and mobile technologies

Health information technology strategies may be especially effective if augmented by outreach and support directly to patients and families. In a school-based setting, direct outreach to parents about children's BMI screening was an informative, motivational tool for parents and resulted in improvement in family diet and activity [26,27]. Additionally, telephone support has been employed to deliver motivational interviewing and brief focused negotiation to effect behavior change. Recently, mobile technology strategies such as text messaging have been used to provide outreach and support for behavior change to patients. One study showed parents preferred text messages to phone calls when used for immunization reminders [28]. Few studies, however, have assessed text messages as a self monitoring tool and to communicate educational messages for management of childhood obesity [29].

3. Conceptual framework

Studies based on a sound conceptual framework, with adequate attention to the various levels within health care systems that need to be targeted for effective implementation of any intervention can substantially increase the likelihood that an intervention will be effective. The overarching model for the STAR intervention is the Chronic Care Model developed by Wagner et al. [30]. The Chronic Care Model identifies the essential elements of a health care system that encourage high-quality care of chronic conditions. Evidence-based change concepts under each element including changes to clinical information systems, decision support tools, self-management support, and delivery system design, foster productive interactions between informed, "activated" parents who collaborate with providers who have resources and expertise. While the model's originators have applied it to the care of adult chronic disease, we and others recently adapted it to primary care management of obesity in children [31].

4. Methods

4.1. Overview of study design

STAR is a cluster-randomized controlled trial being conducted within 14 pediatric offices of Harvard Vanguard Medical Associates (HVMA), a multi-specialty group practice in eastern Massachusetts. We randomly assigned each practice to one of 3 intervention arms (Fig. 1): 1) computerized point-of-care decision support (alerts) to pediatric primary care providers; 2) computerized alerts *plus* direct-to-parent outreach and support relating to their child's BMI, recommended screening, and management; and 3) usual care (control). The target population is children ages 6 to12 years with a BMI ≥ 95th percentile. The primary, intention-to-treat, analysis will examine whether there is a difference between the extent to which each intervention arm improves adoption of CER evidence on point-of-care obesity screening and management, and improves children's BMI and obesity-related behaviors over a 1-year intervention period. We will also assess the cost and cost-effectiveness of the intervention. All study activities were approved by the Institutional Review Board at Harvard Pilgrim Health Care.

4.2. Randomization

We used a stratified block randomization scheme to assign practices to one of the 3 study arms. Strata were based on the volume of children aged 6.0 to 12.9 with a BMI ≥ 95th percentile seen for well-child visits at each site from April 2010 through March 2011. A biostatistician (KPK) blinded to the names of the practices ordered them on this characteristic, then introduced a false practice at a random spot within the order to make the number of "practices" evenly divisible by 3. Strata consisted of consecutive groups of three practices from this ordered list. He then used a pseudo-random number generator in SAS 9.2 (SAS Institute, Cary NC) to assign one practice from each strata to each of the arms, with the exception that the false practice was deterministically assigned to the usual care arm. This resulted in 5 practices in each of the intervention arms and 4 in the usual care arm.

4.3. Blinding

Research staff performing all assessments is blinded to specific study hypotheses and to intervention assignment. Study participants and the pediatricians in each practice are blinded to specific study hypotheses but not to intervention assignment.

4.4. Eligibility and recruitment

Eligibility for STAR includes: 1) child is 6.0–12.9 years old at baseline, 2) child's BMI ≥ 90th percentile for age and sex at the baseline well child visit, 3) child has received well child care at HVMA within the past 15 months, and 4) at least one parent can communicate in English. Children were excluded if: 1) their sibling had already been enrolled in the study, 2) their family was planning to leave HVMA within the study

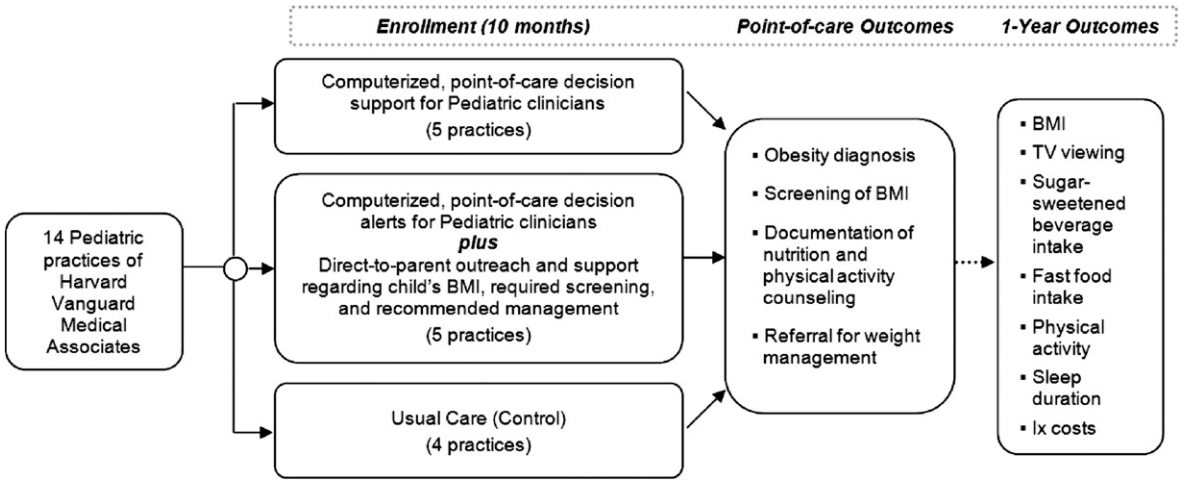

Fig. 1. Study design, randomization, and outcomes of the *Study of Technology to Accelerate Research (STAR)* Intervention, a cluster randomized controlled trial in pediatric practices in eastern Massachusetts, 2011–2013.

time frame, 3) their clinician did not feel the study was appropriate for them or their families, or 4) they had a chronic medical condition that impacted their diet or physical activity.

Recruitment began in October, 2011 and will end in August 2012. After receiving permission from primary care providers to contact eligible patients, study staff sends each family a letter approximately one month prior to the child's scheduled well child visit introducing the study and inviting the family to participate. The letter includes an opt-out phone number to call if parents do not want to be contacted. Parents are also encouraged to call this number if they are interested in participating. We call parents who do not refuse additional contact beginning 7 days after mailing the letter. Research assistants who were blinded to intervention groups establish eligibility, explain the study, answer questions, obtain verbal consent, and complete the baseline survey over the phone. Research assistants verify contact information and mail parents a $20 gift card for completing the baseline survey. They also mailed a written informed consent form required for participation in the remainder of the study's activities. After receiving their signed consent form, we inform participants of their assigned intervention group. The participant flow to date for STAR is shown in Fig. 2.

4.5. Sample size estimations

STAR is recruiting a total of 800 children and their parents across the 14 practices of HVMA within a 10-month period. Based on previous studies within these practices, we anticipate 680 (~85%) children will complete the study. Data collected as part of High Five for Kids, a moderate intensity obesity intervention in HVMA, revealed standard deviations of approximately 1.35 kg/m^2 for the difference between BMI measurements 1 year apart [31]. Based on these estimates, with 80% power and a sample size of 680, we will be able to detect differences of about 1.1 kg/m^2. The USPSTF found the amount of absolute or relative weight change associated with moderate intensity obesity interventions, such as the STAR study, was 0.85–3.3 kg/m^2 difference in mean BMI 6–12 months after starting treatment, compared with controls [16]. Thus, our sample size will allow for ample power to examine 1-year change in BMI.

4.6. Intervention arms

4.6.1. Usual care

Participants randomized to the control group receive the current standard of care offered by their pediatric office. This includes well child visits and follow-up appointments for weight checks with their primary care provider, subspecialist, or a nutritionist. They also receive generic health-related materials in the mail from STAR. Clinicians in the usual care arm do not have access to the computerized point-of-care alerts for the duration of the intervention.

4.6.2. Intervention

4.6.2.1. Computerized point-of-care alerts. In the 10 practices randomized to the intervention, we modified the existing EPIC EHR to deploy a BestPractice® alert to pediatricians at the time of a well child care visit with a child between the ages of 6–12 years with a BMI≥95th percentile (Fig. 3 and Appendix). Medical assistants measure height and weight and enter the values into the EHR which automatically calculates BMI. The alert was designed to trigger as a new window "in front of" the screen on which the clinician was working to identify children with a BMI≥95th percentile. The alert contains links to the CDC growth charts, links to existing childhood obesity CER evidence, and a link to a pre-populated, SmartSet® standardized well child visit template specific for obesity that includes: 1) place and instructions for documentation and coding of BMI percentile and diagnosis of obesity (ICD-9 Diagnosis Code V85.54), 2) documentation of nutrition (ICD-9 V65.3) and physical activity (ICD-9 V65.41) counseling, 3) placing referrals for internal to HVMA or outside weight management programs, 4) placing orders for obesity-related laboratory studies if appropriate (e.g. fasting lipid profile and glucose), and 5) links to printable patient education information and to a study website with additional obesity-related educational materials only for intervention participants.

We provided clinicians with a list of local weight management programs that deliver moderate (26–75 h) or high (>75 h) intensity behavioral treatment based on the recommendations by the USPSTF. We made this list available to clinicians via a study-specific website which serves as a repository of materials for obesity management. The study website also features resources to aid clinicians during follow up obesity visits, including an outline of how to structure the visits, printable patient handouts on each of the STAR target behaviors, a searchable database of local physical activity programs, and tools for improving obesity-related communication with parents through a motivational interviewing style of counseling. Additionally, the website has many links to outside resources for clinicians to access more information on obesity, parenting, media and child health, sleep, and sugary drinks. We also gave each intervention site posters to hang in the waiting and exam rooms (Fig. 4). The poster outlines each of the study behavioral goals and is intended to help cue parents to talk about these goals with their children and their clinician.

We conducted on-site visits at each of the 10 intervention sites, as well as a webinar to introduce the study and explain the EHR components. After the alert was launched, we conducted a second round of on-site visits to provide technical assistance to clinicians using these new EHR tools at the intervention practices. We also offered clinicians 1-on-1 support and training by a study staff member. In addition, all health professionals in the Harvard Vanguard Medical Associates health care system have access to cultural competency trainings as part of their continuing education credits. During the on-site visits, we provided clinicians suggestions on appropriate language for discussing body mass index with parents and children.

4.6.2.2. Direct to parent outreach and support. In one of the intervention arms (5 practices), we provided direct to parent outreach and support to their enrolled families in addition to the computerized decision support tools available for their clinicians. Prior to the well child visit, study staff mail a letter to parents in this arm that provides an explanation of their child's most recent BMI from their previous well child care visit and shows their child's BMI and weight category on the CDC BMI charts. The letter encourages parents to discuss BMI

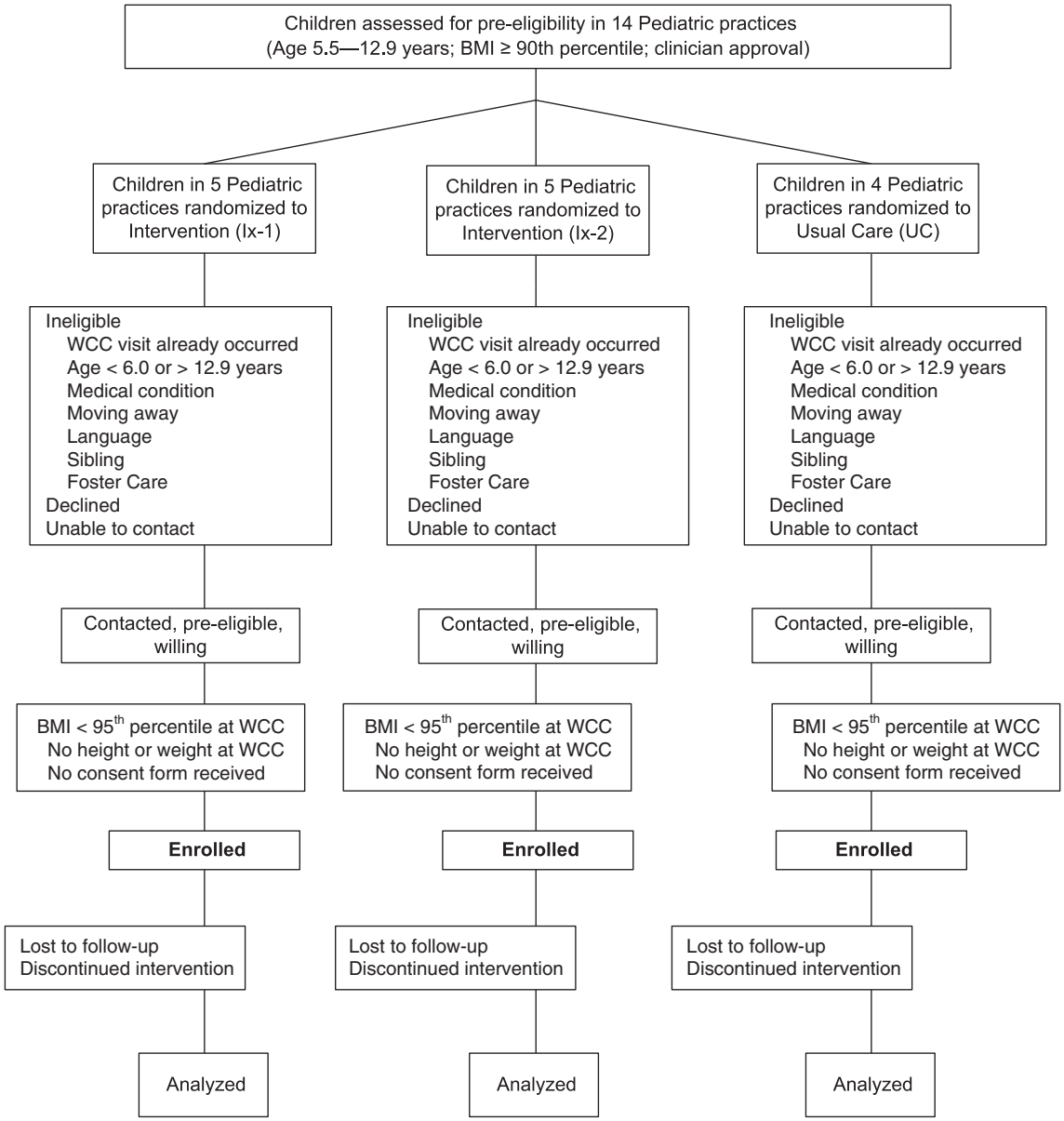

Fig. 2. Flow of clusters and individuals, based on CONSORT guidelines, for the *Study of Technology to Accelerate Research (STAR)* Intervention, a cluster randomized controlled trial in pediatric practices in eastern Massachusetts, 2011–2013.

with their doctor at their child's upcoming visit. Following the well child care visit, parents receive a mailed letter from their clinician endorsing obesity-related behavior change and offering support for the child's involvement in the study. The letter also includes a welcome message from the participant's assigned STAR study health coach. The clinician endorsement mailing is followed by a mailed brochure that outlines the STAR behavior goals and the schedule of study contacts with their assigned health coach. The schedule includes a phone call from a study health coach at 1, 3, 6 and 9 months after the well child visit. Study health coaches use a motivational counseling style to identify what health behavior goal(s) parents are interested in working on with their children, how they think they can make that change, and what might get in the way of meeting that goal. Between the telephone calls, health coaches mail educational handouts to participants that address the targeted health behaviors. An incentive for the child is included in two of these mailings. The children are also sent 4 issues of a healthy cooking magazine for kids during the intervention year.

Study health coaches also use text messages to provide behavior change support. In most weeks parents receive 2 text messages. The first is an educational message about one of the recommended behaviors, and the second is a self-monitoring message that asks how the child did with a certain target behavior the day before. The outgoing text asks

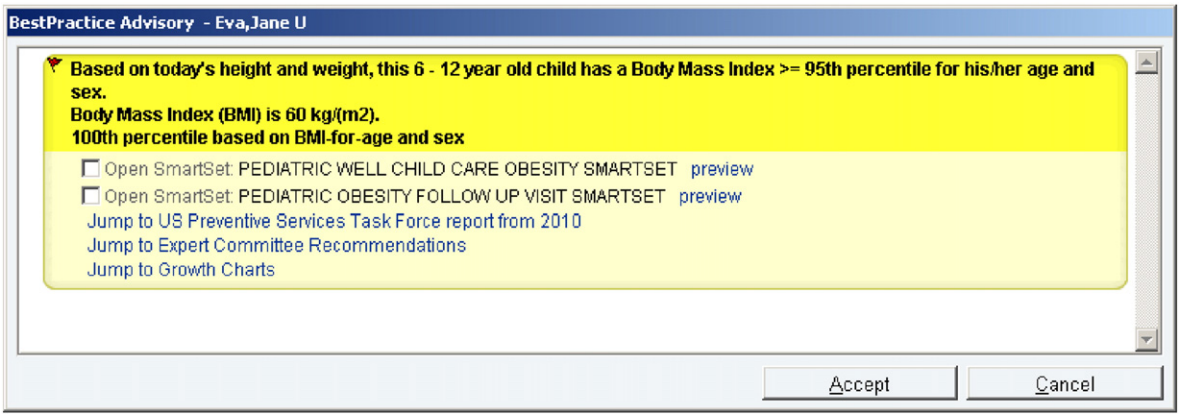

Fig. 3. Screen shot of electronic health record BestPractice® alert developed for the *Study of Technology to Accelerate Research (STAR)* Intervention, to alert pediatric clinicians at the time of a well child care visit of a child between the ages of 6–12 years with a BMI ≥ 95th percentile.

parents to reply to these messages, and in turn they receive an automated feedback response message tailored to how they indicated they are doing meeting that behavior goal. For example, it might say "Great job!" "That's close to the goal. Keep at it!" or "Change is hard. Keep trying! See the STAR tip sheet for ways to tackle the challenge." For parents who

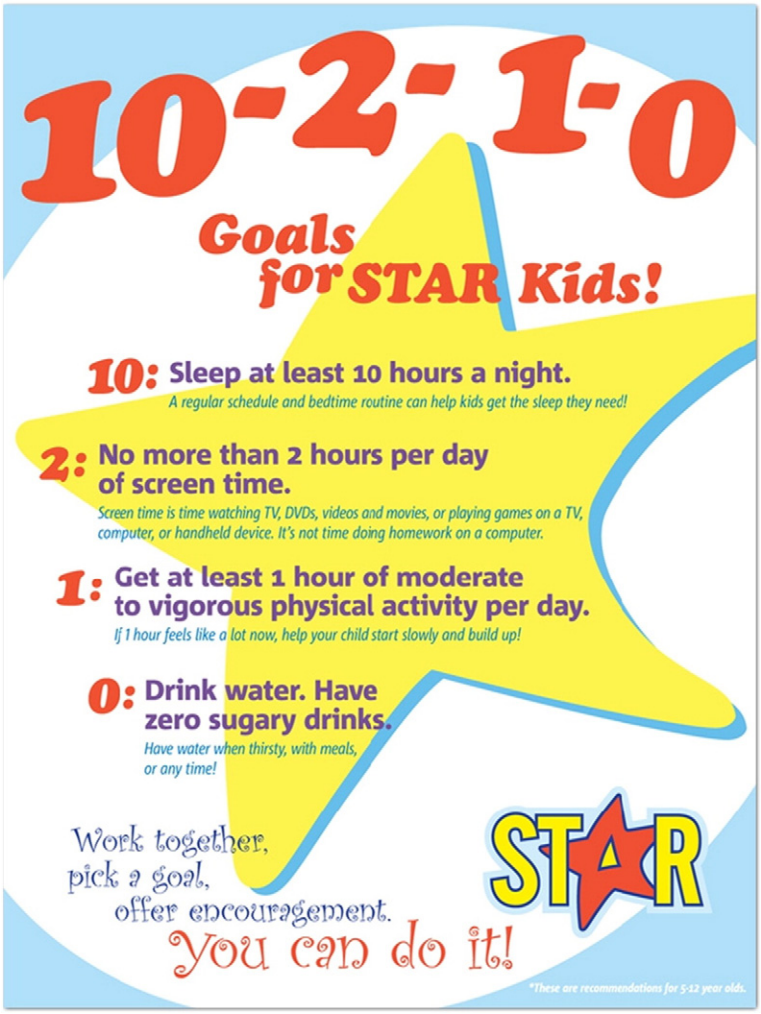

Fig. 4. Waiting room poster developed for the *Study of Technology to Accelerate Research (STAR)* Intervention, highlighting several behavioral outcomes of the study.

Table 1
Behavioral targets and measures used in the *Study of Technology to Accelerate Research (STAR)* Intervention, a cluster randomized controlled trial in pediatric practices in eastern Massachusetts, 2011–2013.

Behavior	Intervention goals	Measures and validity relationships
Diet and diet quality		
Sugar-sweetened beverages	• Lower daily intake of beverages with sugar added	Parent report using questions from a validated semi-quantitative child food frequency questionnaire.[35] Associated with BMI.[36]
Family meals	• Increase frequency of meals eaten together as a family	Parent report of times/week child ate dinner or supper together with at least some of the family;[37] associated with dietary intake and with child BMI.[38,39]
Fast food	• Lower weekly intake of fast food meals	Modified question adapted from the Growing Up Today Study [40]; associated with BMI.
Television and screen time		
Screen time exposure viewing	• Limiting screen-viewing time to<2 h/day	Parent report of average daily hours spent watching TV or videos; playing video games; and using the computer;[41] associated with child BMI.[42]
TV in room where child sleeps	• No TV in room where child sleeps	Presence of TV in bedroom; related to BMI [43,44] in children.
Sleep duration and routines		
Sleep duration	• Increase sleep duration to 10 h/day	Parent report of average amount of daily sleep their children obtained; associated with childhood BMI. [45–47]
Regular bedtime	• Regular bedtime on most days	Parent report of typical bedtime on weekday and weekend days. [48]
Physical activity	• At least 1 h of moderate to vigorous physical activity/day.	Parent report of child's average weekly hours spent in three classes of recreational activity: walking, light-to-moderate activities, and vigorous physical activities.[49]

decline the text messaging component, an email option is available that mimics the text messaging system.

4.6.2.3. Outcome measures. Our main outcomes are at both the system and the individual level. System level outcomes include point-of-care and 1-year measures of obesity-related quality of care; child-level outcomes include 1-year changes in child BMI and obesity-related behaviors. We are also measuring the cost of the intervention. We collect outcomes measures using the child's electronic health record from the baseline and 1-year well child care visit and using researcher-administered surveys of parents. To measure obesity-related quality of care at each well child care visit, we conduct a data pull of the EHR to look for pediatric obesity Healthcare Effectiveness Data and Information Set (HEDIS) measures which include 1) documentation and diagnostic coding of a BMI percentile and 2) documentation of counseling or referral for nutrition and physical activity counseling [32]. An additional quality of care outcome we measure is the number of obese children who left their well child care visits with a referral or follow-up plan for weight management.

One year child outcomes include changes from baseline in BMI, obtained from the EHR from each well child care visit, as well as changes in behaviors. HVMA medical assistants measure height and weight according to the written standardized protocol of the health centers and all undergo bi-annual trainings and quality assurance of their height and weight measurements using standard training materials [33]. Research assistants administer a telephone survey to parents at baseline and at one year to assess behavioral outcomes. These are summarized in Table 1.

We will assess the cost of the intervention with two goals: (a) to inform clinicians and health care systems about what investment would be required to adopt this intervention in other settings, and (b) to generate key assumptions for analysis of the cost-effectiveness of the intervention. To assess fixed direct costs e.g. those required to develop and implement the intervention, we collect information on the cost of developing all aspects of the intervention (e.g., the EHR decision support tools, the telephone and text messaging capabilities) as well as the up-front cost of all training required for the clinicians on the use of the decision support tools and the health coaches for delivering the direct-to-parent outreach and support. To measure marginal direct costs, e.g. those associated with all types of intervention contacts between the health coach and parents such as telephone calls and text messages, we use health coach process logs to calculate these costs and vendor contracts supporting our intervention's technology (e.g., text messaging service).

4.6.2.4. Data analysis. We will examine baseline distributions of participant characteristics by intervention status. In intent-to-treat analyses, we will correct for clustering by practice, and examine differences from baseline to 1 year between the 2 intervention and usual care groups.

5. Discussion

STAR will determine whether there are differences in the extent to which decision support tools in EHRs along with direct-to-parent support via text and telephone will increase adoption of comparative effectiveness research evidence on childhood obesity among primary care clinicians and parents and ultimately improve childhood obesity-related outcomes.

As in any study, this one is subject to several potential limitations. One is generalizability. Much pediatric primary care is currently provided in settings unlike HVMA, i.e. small practices without electronic health records. However, as a relatively large medical group, HVMA is a typical health care setting for many children and their families, and EHRs are increasingly penetrating even small practices. Thus the intervention we propose is likely to generalize to more and more pediatric settings in the future. Furthermore, with so few effective strategies to accelerate adoption of childhood obesity CER evidence, it is important to show effectiveness in some model settings that can later be adapted to the range of

settings in which children receive care. Second, parents could exaggerate improvements in behaviors (social desirability bias). This is a limitation of all behavioral interventions, and is another reason to have child BMI as one of the outcomes. Third, the 3-year timeline of this study does not allow measurement of outcomes beyond 1 year.

If successful, this project will provide new and sustainable approaches for accelerating adoption of comparative effectiveness research evidence for childhood obesity, for improving quality of care for childhood obesity in pediatric primary care, and for effectively supporting patients and families in improving obesity-related behaviors outside of the clinical setting.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.cct.2012.10.005.

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EFFECTS OF AN ANGIOTENSIN-CONVERTING–ENZYME INHIBITOR, RAMIPRIL, ON CARDIOVASCULAR EVENTS IN HIGH-RISK PATIENTS

THE HEART OUTCOMES PREVENTION EVALUATION STUDY INVESTIGATORS*

ABSTRACT

Background Angiotensin-converting–enzyme inhibitors improve the outcome among patients with left ventricular dysfunction, whether or not they have heart failure. We assessed the role of an angiotensin-converting–enzyme inhibitor, ramipril, in patients who were at high risk for cardiovascular events but who did not have left ventricular dysfunction or heart failure.

Methods A total of 9297 high-risk patients (55 years of age or older) who had evidence of vascular disease or diabetes plus one other cardiovascular risk factor and who were not known to have a low ejection fraction or heart failure were randomly assigned to receive ramipril (10 mg once per day orally) or matching placebo for a mean of five years. The primary outcome was a composite of myocardial infarction, stroke, or death from cardiovascular causes.

The trial was a two-by-two factorial study evaluating both ramipril and vitamin E. The effects of vitamin E are reported in a companion paper.

Results A total of 651 patients who were assigned to receive ramipril (14.0 percent) reached the primary end point, as compared with 826 patients who were assigned to receive placebo (17.8 percent) (relative risk, 0.78; 95 percent confidence interval, 0.70 to 0.86; $P<0.001$). Treatment with ramipril reduced the rates of death from cardiovascular causes (6.1 percent, as compared with 8.1 percent in the placebo group; relative risk, 0.74; $P<0.001$), myocardial infarction (9.9 percent vs. 12.3 percent; relative risk, 0.80; $P<0.001$), stroke (3.4 percent vs. 4.9 percent; relative risk, 0.68; $P<0.001$), death from any cause (10.4 percent vs. 12.2 percent; relative risk, 0.84; $P=0.005$), revascularization procedures (16.0 percent vs. 18.3 percent; relative risk, 0.85; $P=0.002$), cardiac arrest (0.8 percent vs. 1.3 percent; relative risk, 0.63; $P=0.03$), heart failure (9.0 percent vs. 11.5 percent; relative risk, 0.77; $P<0.001$), and complications related to diabetes (6.4 percent vs. 7.6 percent; relative risk, 0.84; $P=0.03$).

Conclusions Ramipril significantly reduces the rates of death, myocardial infarction, and stroke in a broad range of high-risk patients who are not known to have a low ejection fraction or heart failure. (N Engl J Med 2000;342:145-53.)

ALTHOUGH dyslipidemia, diabetes, smoking, and hypertension are major risk factors for cardiovascular disease, they do not fully account for the risk. Therefore, other risk factors must be identified in order to reduce mortality and morbidity even further. Epidemiologic and experimental data suggest that activation of the renin–angiotensin–aldosterone system has an important role in increasing the risk of cardiovascular events.[1] Angiotensin-converting–enzyme inhibitors block the activation of the renin–angiotensin system and could retard the progression of both heart failure and atherosclerosis. In a meta-analysis of three studies[1-3] that included more than 9000 patients with low ejection fractions, treatment with angiotensin-converting–enzyme inhibitors reduced the risk of myocardial infarction by 23 percent. This finding, which has not been widely accepted, was independent of the ejection fraction, the cause of heart disease, concomitant use of medications, diabetes status, and blood pressure, suggesting that angiotensin-converting–enzyme inhibitors may have a role in preventing myocardial infarction in a broad range of patients, not just those with low ejection fractions. Angiotensin-converting–enzyme inhibitors may also reduce the risk of stroke, by lowering blood pressure, and may prevent complications related to diabetes.[4] These hypotheses require direct confirmation in prospective, randomized clinical trials.

Therefore, in a high-risk population, we evaluated the effects of an angiotensin-converting–enzyme inhibitor, ramipril, in preventing the primary out-

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come, which was a composite of death from cardiovascular causes, myocardial infarction, or stroke, as well as each outcome separately. Secondary outcomes included death from any cause, the need for revascularization, hospitalization for unstable angina or heart failure, and complications related to diabetes. Other outcomes included worsening angina, heart failure, and the development of diabetes.

METHODS

Study Design

The double-blind, two-by-two factorial, randomized Heart Outcomes Prevention Evaluation study evaluated ramipril and vitamin E in 9541 patients. A substudy compared a low dose of ramipril (2.5 mg per day) with a full dose (10 mg per day) or placebo; there were 244 patients in each group. The results of the placebo-controlled study of full-dose ramipril are given here. The effects of vitamin E are reported in a companion paper.[5] The design of the study has been reported previously[6]; a brief summary follows.

Patients

Men and women who were at least 55 years old were eligible for the study if they had a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes plus at least one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low high-density lipoprotein cholesterol levels, cigarette smoking, or documented microalbuminuria).[6] Patients were excluded if they had heart failure, were known to have a low ejection fraction (<0.40), were taking an angiotensin-converting–enzyme inhibitor or vitamin E, had uncontrolled hypertension or overt nephropathy, or had had a myocardial infarction or stroke within four weeks before the study began. All patients provided written informed consent.

In this large study it was impractical to measure left ventricular function in all patients. Instead, echocardiograms were obtained at three centers in 496 patients who were enrolled in a substudy. Of these patients, 2.6 percent had an ejection fraction of less than 0.40. A subsequent review of the charts of randomized patients showed that ventricular function had been evaluated before randomization in 5193. Only 421 of these patients (8.1 percent) had a low ejection fraction, and none had heart failure before randomization. We performed a separate analysis of the 4772 patients who were documented to have a normal ejection fraction.

All 10,576 eligible patients participated in a run-in phase in which they received 2.5 mg of ramipril orally once daily for 7 to 10 days followed by matching placebo for 10 to 14 days. A total of 1035 patients were subsequently excluded from randomization because of noncompliance (<80 percent of pills taken), side effects, abnormal serum creatinine or potassium levels, or withdrawal of consent. Of the 9541 remaining patients, 4645 were randomly assigned to receive 10 mg of ramipril once per day, 4652 were randomly assigned to receive matching placebo, and 244 were randomly assigned to receive a low dose (2.5 mg per day) of ramipril. Treatment was scheduled to last five years.

At randomization, patients were assigned to receive ramipril (or matching placebo) at a dose of 2.5 mg once a day for one week, 5 mg for the next three weeks, and then 10 mg. In addition, all patients were randomly assigned to receive 400 IU of vitamin E per day or matching placebo. Follow-up visits occurred at one month and six months and every six months thereafter. At each visit, data were collected on the outcome events, compliance, and side effects leading to a discontinuation of study medications. All primary and secondary events were documented and were centrally adjudicated with the use of standardized definitions.[5]

Organization of the Study

Patients were recruited from December 1993 to June 1995 at 129 centers in Canada, 27 centers in the United States, 76 centers in 14 western European countries, 30 centers in Argentina and Brazil, and 5 centers in Mexico. The review board at each institution approved the protocol. The study was organized and coordinated by the Canadian Cardiovascular Collaboration Project Office at McMaster University in Hamilton, Ontario. Adjunct offices were located in London, United Kingdom; São Paulo, Brazil; and Rosario, Argentina. An independent steering committee oversaw the study.

Outcomes

The primary study outcome was a composite of myocardial infarction, stroke, or death from cardiovascular causes. Each of these outcomes was also analyzed separately. Secondary outcomes were death from any cause, the need for revascularization, hospitalization for unstable angina or heart failure, and complications related to diabetes (whether or not hospitalization was required). Other outcomes were worsening angina, cardiac arrest, heart failure (whether or not hospitalization was required), unstable angina with electrocardiographic changes, and the development of diabetes. These outcomes are defined in a companion paper.[5]

Statistical Analysis

The study was originally designed to follow participants for a mean of 3.5 years. However, before the end of this period, the steering committee (whose members were unaware of any of the results) recommended increasing the duration of follow-up to five years to account for the impact of a possible lag before treatment had its full effect. Assuming an event rate of 4 percent per year for five years, we calculated that 9000 patients would be required for the study to have 90 percent power to detect a 13.5 percent reduction in the relative risk with a two-sided alpha level of 0.05 and with data analyzed on an intention-to-treat basis. Survival curves were estimated according to the Kaplan–Meier procedure, and treatments were compared with use of the log-rank test. Because of the factorial design, all analyses were stratified for the randomization to vitamin E or placebo. Subgroup analyses were conducted with the use of tests for interactions in the Cox regression model. This model was used to estimate the effects of treatment after stratification for randomization to vitamin E or its placebo.

An independent data and safety monitoring board monitored the progress of all aspects of the study. Four formal interim analyses were planned. The statistical monitoring boundary indicating that ramipril had a beneficial effect was a difference in the primary outcome of 4 SD between groups during the first half of the study and of 3 SD during the second half. The respective boundaries indicating that ramipril had a harmful effect were 3 SD and 2 SD. On March 22, 1999, the monitoring board recommended termination of the study because of the clear evidence of a beneficial effect of ramipril (consistent crossing of the monitoring boundaries in two consecutive reviews). At that time, the data showed a 20 percent reduction in the relative risk of the primary outcome (95 percent confidence interval, 12 percent to 28 percent; z statistic, −4.5; $P<0.001$). The results of the study were disclosed to the investigators at two meetings held on April 17 and April 24, 1999. The cutoff date for all events included in the main analysis was set for April 15, 1999, and final visits were scheduled to be completed by June 30, 1999. Vital status was ascertained for 9535 of the 9541 randomized patients (99.9 percent) at the end of the study.

RESULTS

Characteristics of the Patients

The base-line characteristics of the 9297 patients who underwent randomization are shown in Table 1. There were 2480 women, 5128 patients who were at least 65 years old, 8162 who had cardiovascular disease, 4355 who had hypertension, and 3577 who had diabetes.

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	RAMIPRIL GROUP (N=4645)	PLACEBO GROUP (N=4652)
Age — yr	66±7	66±7
Blood pressure — mm Hg	139±20/79±11	139±20/79±11
Heart rate — beats/min	69±11	69±11
Body-mass index	28±4	28±4
Female sex — no. (%)	1279 (27.5)	1201 (25.8)
History of coronary artery disease — no. (%)	3691 (79.5)	3786 (81.4)
Myocardial infarction	2410 (51.9)	2482 (53.4)
Within ≤1 year	452 (9.7)	446 (9.6)
Within >1 year	1958 (42.2)	2036 (43.8)
Stable angina pectoris	2544 (54.8)	2618 (56.3)
Unstable angina pectoris	1179 (25.4)	1188 (25.5)
CABG	1192 (25.7)	1207 (25.9)
PTCA	853 (18.4)	806 (17.3)
Stroke or transient ischemic attacks — no. (%)	500 (10.8)	513 (11.0)
Peripheral vascular disease — no. (%)†	1966 (42.3)	2085 (44.8)
Hypertension — no. (%)	2212 (47.6)	2143 (46.1)
Diabetes — no. (%)	1808 (38.9)	1769 (38.0)
Documented elevated total cholesterol level — no. (%)	3036 (65.4)	3089 (66.4)
Documented low HDL cholesterol level — no. (%)	842 (18.1)	881 (18.9)
Current cigarette smoking — no. (%)	645 (13.9)	674 (14.5)
Medications — no. (%)		
Beta-blockers	1820 (39.2)	1853 (39.8)
Aspirin or other antiplatelet agents	3497 (75.3)	3577 (76.9)
Lipid-lowering agents	1318 (28.4)	1340 (28.8)
Diuretics	713 (15.3)	706 (15.2)
Calcium-channel blockers	2152 (46.3)	2228 (47.9)
Left ventricular hypertrophy on electrocardiography — no. (%)	379 (8.2)	406 (8.7)
Microalbuminuria — no. (%)	952 (20.5)	1004 (21.6)

*Plus–minus values are means ±SD. The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters. CABG denotes coronary-artery bypass grafting, PTCA percutaneous transluminal coronary angioplasty, and HDL high-density lipoprotein.

†Peripheral vascular disease included claudication, a history of peripheral arterial disease, or a ratio of blood pressure in the ankle to blood pressure in the arm of less than 0.90.

TABLE 2. REASONS FOR DISCONTINUATION OF TREATMENT.

VARIABLE	RAMIPRIL GROUP (N=4645)	PLACEBO GROUP (N=4652)
	no. of patients (%)	
Discontinuation at any time	1511 (32.5)	1430 (30.7)
Permanent discontinuation	1343 (28.9)	1268 (27.3)
Reasons for stopping*		
Cough	340 (7.3)	85 (1.8)
Hypotension or dizziness	88 (1.9)	70 (1.5)
Angioedema	17 (0.4)	7 (0.2)
Uncontrolled hypertension	109 (2.3)	183 (3.9)
Clinical events	309 (6.7)	418 (9.0)
Other	1101 (23.7)	1074 (23.1)
Use of nonstudy angiotensin-converting–enzyme inhibitor at any time*†	648 (14.0)	839 (18.0)
Reasons for use		
Heart failure	249 (5.4)	335 (7.2)
Proteinuria	59 (1.3)	60 (1.3)
Hypertension	222 (4.8)	300 (6.4)
Other	294 (6.3)	335 (7.2)

*The categories are not mutually exclusive.

†Clinical progression of disease may have resulted in the need for open-label angiotensin-converting–enzyme inhibitors.

Compliance

Among the patients who were randomly assigned to the ramipril group, 87.4 percent were taking ramipril or an open-label angiotensin-converting–enzyme inhibitor at one year, 85.0 percent were doing so at two years, 82.2 percent were doing so at three years, 75.1 percent were doing so at four years, and 78.8 percent were doing so at the final follow-up visit. The percentage of patients who were receiving 10 mg of ramipril per day was 82.9 percent at one year, 74.6 percent at two years, 70.9 percent at three years, 62.4 percent at four years, and 65.0 percent at the last visit. Among the patients who were randomly assigned to receive placebo, 3.4 percent were receiving an angiotensin-converting–enzyme inhibitor at one year, 6.0 percent were doing so at two years, 8.1 percent were doing so at three years, 10.8 percent were doing so at four years, and 12.3 percent were doing so at five years. The most common reasons for discontinuing treatment are outlined in Table 2. More patients in the ramipril group than in the placebo group stopped treatment because of cough (7.3 percent vs. 1.8 percent) or hypotension or dizziness (1.9 percent vs. 1.5 percent). By contrast, more patients in the placebo group than in the ramipril group stopped treatment because of uncontrolled hypertension (3.9 percent vs. 2.3 percent) or because of a clinical event — a primary or secondary outcome (8.9 percent vs. 6.6 percent). The percentage of patients who were receiving nonstudy angiotensin-converting–enzyme inhibitors for heart failure was 5.4 percent in the ramipril group and 7.2 percent in the placebo group; 1.3 percent and 1.3 percent, respectively, were receiving such drugs because of proteinuria, and 4.8 percent and 6.4 percent for control of hypertension. The use of open-label angiotensin II–receptor antagonists in both groups was low (1.6 percent in the ramipril group and 1.8 percent in the placebo group), but the reasons for such use were similar to those for angiotensin-converting–enzyme inhibitors.

Blood Pressure

The mean blood pressure at entry was 139/79 mm Hg in both groups. The mean blood pressure was 133/76 mm Hg in the ramipril group and 137/78 mm Hg in the placebo group at one month, 135/76 mm Hg and 138/78 mm Hg, respectively, at two years, and 136/76 mm Hg and 139/77 mm Hg, respectively, at the end of the study.

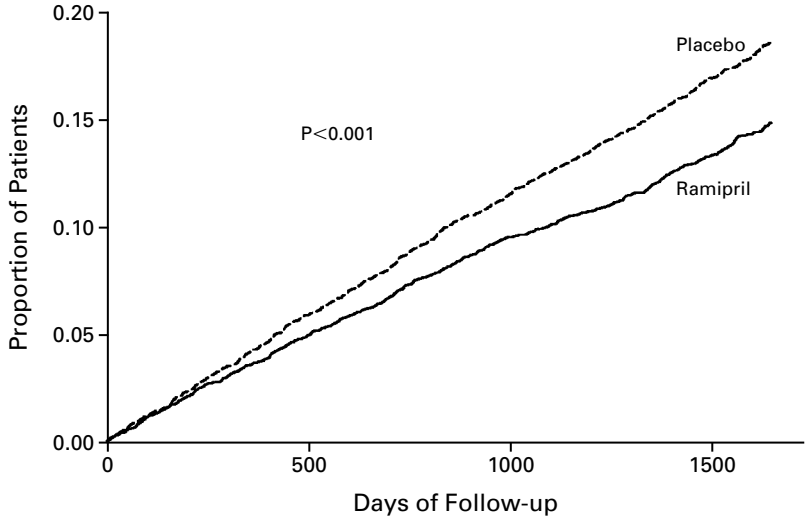

Figure 1. Kaplan–Meier Estimates of the Composite Outcome of Myocardial Infarction, Stroke, or Death from Cardiovascular Causes in the Ramipril Group and the Placebo Group.

The relative risk of the composite outcome in the ramipril group as compared with the placebo group was 0.78 (95 percent confidence interval, 0.70 to 0.86).

TABLE 3. INCIDENCE OF THE PRIMARY OUTCOME AND OF DEATHS FROM ANY CAUSE.

OUTCOME	RAMIPRIL GROUP (N=4645)	PLACEBO GROUP (N=4652)	RELATIVE RISK (95% CI)*	z STATISTIC	P VALUE†
	no. (%)				
Myocardial infarction, stroke, or death from cardiovascular causes‡	651 (14.0)	826 (17.8)	0.78 (0.70–0.86)	−4.87	<0.001
Death from cardiovascular causes§	282 (6.1)	377 (8.1)	0.74 (0.64–0.87)	−3.78	<0.001
Myocardial infarction§	459 (9.9)	570 (12.3)	0.80 (0.70–0.90)	−3.63	<0.001
Stroke§	156 (3.4)	226 (4.9)	0.68 (0.56–0.84)	−3.69	<0.001
Death from noncardiovascular causes	200 (4.3)	192 (4.1)	1.03 (0.85–1.26)	0.33	0.74
Death from any cause	482 (10.4)	569 (12.2)	0.84 (0.75–0.95)	−2.79	0.005

*CI denotes confidence interval.

†P values were calculated with use of the log-rank test.

‡In the substudy, 34 of 244 patients (13.9 percent) assigned to take a low dose of ramipril (2.5 mg per day) reached the composite end point, as compared with 31 of 244 assigned to take 10 mg of ramipril per day (12.7 percent) and 41 of 244 assigned to placebo (16.8 percent). The inclusion of the data from the low-dose group did not change the overall results (relative risk of the primary outcome, 0.78; 95 percent confidence interval, 0.70 to 0.86).

§All patients with this outcome are included.

Primary Outcomes and Deaths from Any Cause

A total of 651 patients in the ramipril group (14.0 percent) died of cardiovascular causes or had a myocardial infarction or stroke, as compared with 826 patients in the placebo group (17.8 percent; relative risk, 0.78; 95 percent confidence interval, 0.70 to 0.86; P<0.001) (Fig. 1 and Table 3). Treatment with ramipril also reduced the risk of the primary outcome among patients who were receiving vitamin E (338 patients who received both agents reached the end point, as compared with 421 patients who received only vitamin E; relative risk, 0.79; P=0.001) or its placebo (313 patients who received ramipril and the vitamin E placebo reached the end point, as compared with 405 patients who received the vitamin E placebo alone; relative risk, 0.76; P<0.001; P=0.79 for the comparison of the two relative risks). In addition, there were significant reductions in risk when each of these end points was analyzed separately: 282 patients in the ramipril group died of cardiovascular causes, as compared with 377 patients in the placebo group (relative risk, 0.74; 95 percent confidence interval, 0.64 to 0.87; P<0.001); 459 patients in the ramipril group had a myocardial infarction, as compared with

TABLE 4. INCIDENCE OF SECONDARY AND OTHER OUTCOMES.

OUTCOME	RAMIPRIL GROUP (N=4645)	PLACEBO GROUP (N=4652)	RELATIVE RISK (95% CI)*	z STATISTIC	P VALUE†
	no. (%)				
Secondary outcomes‡					
Revascularization	742 (16.0)	852 (18.3)	0.85 (0.77–0.94)	−3.17	0.002
Hospitalization for unstable angina	554 (11.9)	565 (12.1)	0.98 (0.87–1.10)	−0.41	0.68
Complications related to diabetes§¶	299 (6.4)	354 (7.6)	0.84 (0.72–0.98)	−2.16	0.03
Hospitalization for heart failure	141 (3.0)	160 (3.4)	0.88 (0.70–1.10)	−1.16	0.25
Other outcomes					
Heart failure§	417 (9.0)	535 (11.5)	0.77 (0.67–0.87)	−4.09	<0.001
Cardiac arrest	37 (0.8)	59 (1.3)	0.62 (0.41–0.94)	−2.28	0.02
Worsening angina§	1107 (23.8)	1220 (26.2)	0.89 (0.82–0.96)	−2.91	0.004
New diagnosis of diabetes‖	102 (3.6)	155 (5.4)	0.66 (0.51–0.85)	−3.31	<0.001
Unstable angina with electrocardiographic changes‡	175 (3.8)	180 (3.9)	0.97 (0.79–1.19)	−0.30	0.76

*CI denotes confidence interval.

†P values were calculated with use of the log-rank test.

‡These events were centrally adjudicated.

§All cases are included, whether or not hospitalization was required.

¶Complications related to diabetes include diabetic nephropathy (defined as urinary albumin excretion of at least 300 mg per day or urinary protein excretion of 500 mg per day), the need for renal dialysis, and the need for laser therapy for diabetic retinopathy.

‖The denominator in the ramipril group is the 2837 patients who did not have diabetes at base line. The denominator in the placebo group is the 2883 patients who did not have diabetes at base line.

570 patients in the placebo group (relative risk, 0.80; 95 percent confidence interval, 0.70 to 0.90; P< 0.001); and 156 patients in the ramipril group had a stroke, as compared with 226 patients in the placebo group (relative risk, 0.68; 95 percent confidence interval, 0.56 to 0.84; P<0.001). The risk of death from any cause was also significantly reduced by treatment with ramipril (relative risk, 0.84; 95 percent confidence interval, 0.75 to 0.95; P=0.005).

Secondary and Other Outcomes

Significantly fewer patients in the ramipril group than in the placebo group underwent revascularization (742 vs. 852; relative risk, 0.85; P=0.002), and there was a trend toward fewer hospitalizations for heart failure in the ramipril group (141 vs. 160; relative risk, 0.88; P=0.25) (Table 4). However, treatment with ramipril had no effect on the likelihood of hospitalization for unstable angina. In addition, significantly fewer patients in the ramipril group than in the placebo group had a cardiac arrest (37 vs. 59; relative risk, 0.62; P=0.02), worsening angina (1107 vs. 1220; relative risk, 0.89; P=0.004), heart failure (417 vs. 535; relative risk, 0.77; P<0.001), a new diagnosis of diabetes (102 vs. 155; relative risk, 0.66; P<0.001), or complications related to diabetes (299 vs. 354; relative risk, 0.84; P=0.03).

Subgroup Analysis

The beneficial effect of treatment with ramipril on the composite outcome was consistently observed among the following predefined subgroups: patients with diabetes and those without diabetes, women and men, those with evidence of cardiovascular disease and those without such evidence, those younger than 65 years of age and those 65 years of age or older, those with hypertension at base line and those without it, and those with microalbuminuria and those without it (Fig. 2). In addition, there was a clear benefit of ramipril among patients with evidence of coronary artery disease at base line and those with no evidence of it, among those with a history of myocardial infarction and those with no such history, and among those with a documented ejection fraction of 0.40 or greater (332 of 2379 patients reached the end point in the ramipril group vs. 451 of 2393 patients in the placebo group; relative risk, 0.73; 95 percent confidence interval, 0.63 to 0.84; P<0.001). Benefits were also observed whether or not patients were also taking aspirin or other antiplatelet agents, beta-blockers, lipid-lowering agents, or antihypertensive drugs at randomization.

Temporal Trends

The reduction in the risk of the composite outcome with ramipril therapy was evident within one year after randomization (169 patients reached the end point in the ramipril group, as compared with 198 in the placebo group; relative risk, 0.85; 95 percent confidence interval, 0.70 to 1.05) and was significant at two years (326 vs. 398 patients; relative risk, 0.82; 95 percent confidence interval, 0.70 to 0.94).

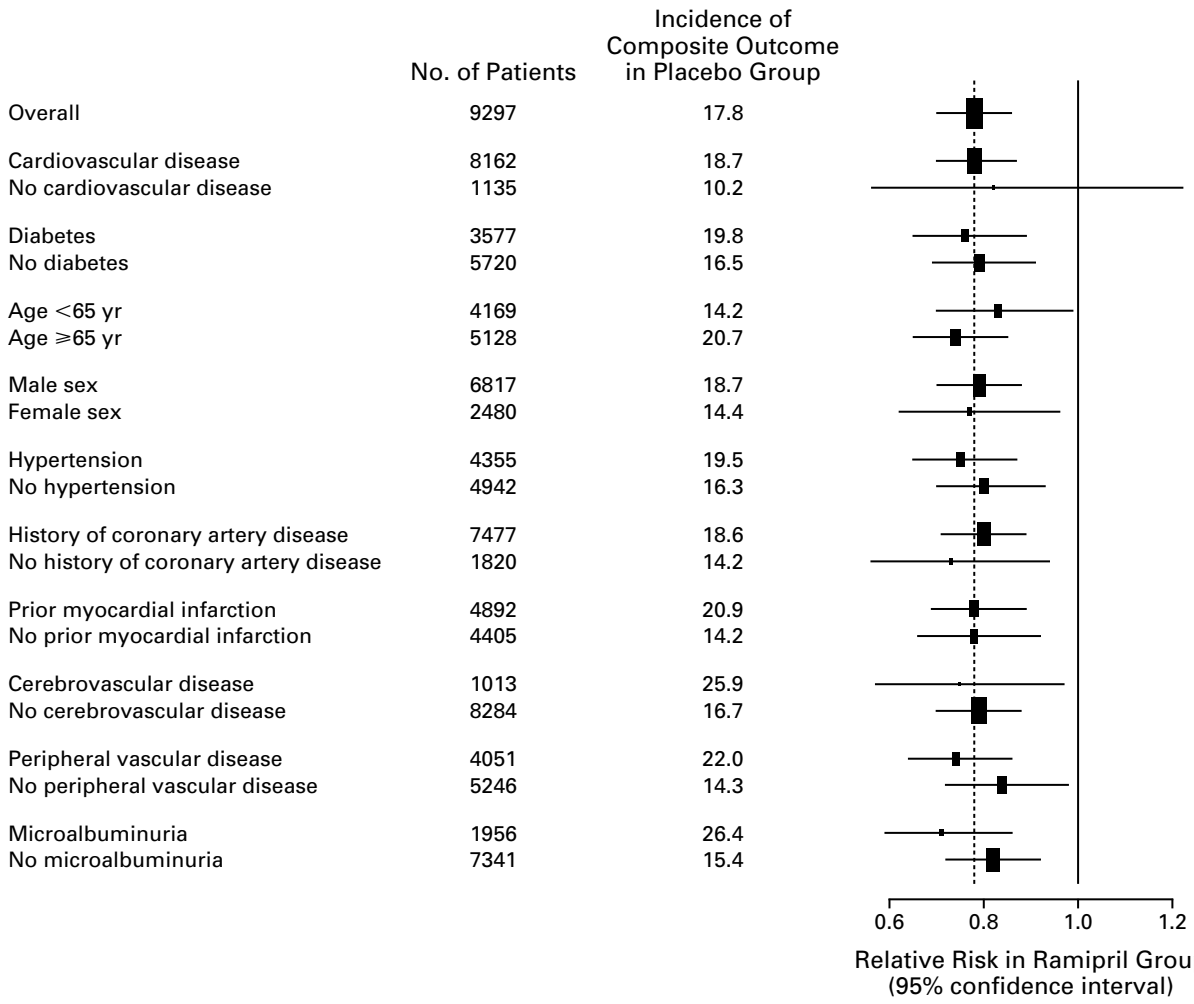

Figure 2. The Beneficial Effect of Treatment with Ramipril on the Composite Outcome of Myocardial Infarction, Stroke, or Death from Cardiovascular Causes Overall and in Various Predefined Subgroups.

Cerebrovascular disease was defined as stroke or transient ischemic attacks. The size of each symbol is proportional to the number of patients in each group. The dashed line indicates overall relative risk.

The relative risk was 0.78 in the second year, 0.73 in the third year, and 0.74 in the fourth year, when the data on patients who were still alive at the end of the preceding year were analyzed.

DISCUSSION

Our findings show that ramipril, an angiotensin-converting–enzyme inhibitor, is beneficial in a broad range of patients without evidence of left ventricular systolic dysfunction or heart failure who are at high risk for cardiovascular events. Treatment with ramipril reduced the rates of death, myocardial infarction, stroke, coronary revascularization, cardiac arrest, and heart failure as well as the risk of complications related to diabetes and of diabetes itself.

Our findings indicate that the spectrum of patients who would benefit from treatment with an angiotensin-converting–enzyme inhibitor is quite broad and complement those of previous studies of patients with low ejection fractions[3] or heart failure and acute myocardial infarction.[7] The underlying rationale for our study was that the inhibition of angiotensin-converting enzyme would prevent events related to ischemia and atherosclerosis, in addition to those related to heart failure and left ventricular dysfunction (although patients with these two conditions were excluded from the study). We therefore included a broad range of patients with any manifestation of coronary artery disease (e.g., a history of myocardial infarction or revascularization, unstable angina, or stable angina), a history of cerebrovascular disease or peripheral vascular disease, or diabetes and one cardiovascular risk factor, and ramipril was beneficial in all these subgroups.

A total of 3577 patients in our study had diabetes, 1135 of whom had no clinical manifestations of cardiovascular disease, and the event rate in this group was about half that in the other patients (10.2 percent vs. 18.7 percent). Nonetheless, overall, treatment with ramipril was beneficial in patients with diabetes.

The magnitude of the benefit of treatment with ramipril with respect to the primary outcome was at least as large as that observed with other proven secondary prevention measures, such as treatment with beta-blockers,[8] aspirin,[9] and lipid-lowering agents,[10] during four years of treatment. In addition, there were reductions in the rates of revascularization, heart failure, complications related to diabetes, and new cases of diabetes. The rapid and sustained response to ramipril and the continuing divergence in results between the ramipril group and the placebo group indicate that longer-term treatment may yield even better results. Ramipril was also well tolerated.

The benefits of ramipril were observed among patients who were already taking a number of effective treatments, such as aspirin, beta-blockers, and lipid-lowering agents, indicating that the inhibition of angiotensin-converting enzyme offers an additional approach to the prevention of atherothrombotic complications. Only a small part of the benefit could be attributed to a reduction in blood pressure, since the majority of patients did not have hypertension at base line (according to conventional definitions) and the mean reduction in blood pressure with treatment was extremely small (3/2 mm Hg). A reduction of 2 mm Hg in diastolic blood pressure might at best account for about 40 percent of the reduction in the rate of stroke and about one quarter of the reduction in the rate of myocardial infarction.[11] However, the results of recent studies, such as the Hypertension Optimal Treatment study,[12] suggest that for high-risk patients (e.g., those with diabetes), it may be beneficial to lower blood pressure even if it is already within the "normal" range. Moreover, a recent reanalysis of 20 years of blood-pressure data from the Framingham Heart Study[13] suggests that the degree of benefit expected from a decrease in blood pressure may have been underestimated. Despite these considerations, it is likely that angiotensin-converting–enzyme inhibitors exert additional direct mechanisms on the heart or the vasculature that are important. These may include antagonizing the direct effects of angiotensin II on vasoconstriction,[1] the proliferation of vascular smooth-muscle cells,[1] and rupture of plaques[14]; improving vascular endothelial function[1]; reducing left ventricular hypertrophy; and enhancing fibrinolysis.[1]

We also observed a reduction in the incidence of heart failure in patients with no evidence of impairment of left ventricular systolic dysfunction. These data complement those of a study of patients with a low ejection fraction[15] and studies of patients after myocardial infarction,[1-3,7,16,17] which demonstrated that treatment with angiotensin-converting–enzyme inhibitors prevents heart failure, and the studies of patients with documented low ejection fractions and heart failure, which indicated that angiotensin-converting–enzyme inhibitors reduced the rate of hospitalization for heart failure.[17] Both these results and our findings suggest that angiotensin-converting–enzyme inhibitors will be beneficial for patients who are at high risk for heart failure, irrespective of the degree of left ventricular systolic dysfunction.

We believe that the extent to which our results may have been affected by the inclusion of patients with undiagnosed low ejection fractions is very small, because a large substudy of 496 consecutive patients at three centers indicated that only 2.6 percent had an ejection fraction of less than 0.40, an extensive review of charts identified only 8.1 percent of patients with a low ejection fraction before randomization, and treatment was clearly beneficial in the subgroup of 4772 patients who were documented to have preserved ventricular function (relative risk, 0.73; 95 percent confidence interval, 0.63 to 0.84; $P<0.001$) and in those with no history of myocardial infarction (relative risk, 0.77; 95 percent confidence interval, 0.65 to 0.91; $P=0.002$).

We observed a marked reduction in the incidence of complications related to diabetes and new cases of diabetes. These effects may be mediated by improved insulin sensitivity, a decrease in hepatic clearance of insulin, an antiinflammatory effect, improved blood flow to the pancreas,[18] or an effect on abdominal fat.[19] The results are also consistent with the results of the recent Captopril Prevention Project study,[20] which indicated a lower rate of newly diagnosed diabetes in patients who were randomly assigned to receive captopril than in those who were assigned to receive a diuretic or beta-blocker, and with the results of other trials, which reported that treatment with an angiotensin-converting–enzyme inhibitor slowed the progression of nephropathy among patients with type 2 diabetes[21] as well as those without diabetes.[22]

Our findings clearly demonstrate that ramipril, a long-acting angiotensin-converting–enzyme inhibitor, reduces the rates of death, myocardial infarction, stroke, revascularization, cardiac arrest, heart failure, complications related to diabetes, and new cases of diabetes in a broad spectrum of high-risk patients. Treating 1000 patients with ramipril for four years prevents about 150 events in approximately 70 patients.

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APPENDIX

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Infrastructure Needs

Implementation of the Department of Veterans Affairs' first point-of-care clinical trial

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ABSTRACT

Objectives The Massachusetts Veterans Epidemiology Research and Information Center in collaboration with the Stanford Center for Innovative Study Design set out to test the feasibility of a new method of evidence generation. The first pilot of a point-of-care clinical trial (POCCT), adding randomization and other study processes to an electronic medical record (EMR) system, was launched to compare the effectiveness of two insulin regimens.

Materials and Methods Existing functionalities of the Veterans Affairs (VA) computerized patient record system (CPRS)/veterans health information systems and technology architecture (VISTA) were modified to support the activities of a randomized controlled trial including enrolment, randomization, and longitudinal data collection.

Results The VA's CPRS/VISTA was successfully adapted to support the processes of a clinical trial and longitudinal study data are being collected from the medical record automatically. As of 30 June 2011, 55 of the 67 eligible patients approached received a randomized intervention.

Discussion The design of CPRS/VISTA made integration of study workflows and data collection possible. Institutions and investigators considering similar designs must carefully map clinical workflows and clinical trial workflows to EMR capabilities. POCCT study teams are necessarily interdisciplinary and interdepartmental. As a result, executive sponsorship is critical.

Conclusion POCCT represent a promising new method for conducting clinical science. Much work is needed to understand better the optimal uses and designs for this new approach. Next steps include focus groups to measure patient and clinician perceptions, multisite deployment of the current pilot, and implementation of additional studies.

The Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC) and the Stanford Center for Innovative Study Design have developed a new method for the implementation of experimental clinical research. The point-of-care clinical trial (POCCT) is designed to be embedded directly into the clinical care setting thereby addressing the issues of cost and translation, and creating an integrated environment of research-based care. The POCCT capitalizes on the Veterans Affairs (VA) electronic medical record (EMR) system to perform study activities traditionally conducted by a study team such as enrolment, randomization, and longitudinal data collection. In addition, as evidence accumulates in favor of a specific intervention, it can be transitioned to decision support in the same EMR. As a result, POCCT integrate clinical research and clinical care providing a valuable tool for achieving the vision of a 'learning healthcare system'.

In this article, the implementation of the VA's first POCCT is described, citing experience to date with an ongoing comparative effectiveness study comparing two common regimens of administering insulin. The informatics-related challenges and strategies used to overcome them are the primary focus of this article, with additional consideration of the potential of POCCT to diffuse within and beyond the VA healthcare system.

BACKGROUND AND SIGNIFICANCE

Reports from the Institute of Medicine, the Federal Coordinating Council for Comparative Effectiveness Research, and the Congressional Budget Office[1–4] cite the lack of evidence that can be used to support a given course of treatment as a significant obstacle to improving the quality and lowering the cost of healthcare. Also recognized is the inability of current models to meet this need fully. Currently used methods of scientific evidence generation may not be enough to meet the growing demand for relevant evidence. Randomized controlled trials (RCT) are considered to be the gold standard in clinical research. However, the apparatus (ie, the infrastructure) needed to conduct these clinical studies is often cost prohibitive. A large proportion of the cost to conduct RCT derives from support of the personnel needed to conduct recruitment activities, to collect and analyze data, and to perform surveillance for safety events. Furthermore, the generalizability of the results generated by RCT to a broad patient population is often limited due to the narrowly defined inclusion criteria and the intensive study protocol. Observational studies exist as alternative study designs to the RCT and offer a more feasible and cost-effective method to provide clinical evidence. Study-defined procedures for observational studies are often less intensive than those found in RCT and the generalizability of the results is not as limited. Observational studies, though, may be inadequate to provide evidence in support of medical decision-making due to inherent issues of bias and confounding by indication.

It is in light of the widening evidence gap and need for alternative scientific models that MAVERIC and the Stanford Center for Innovative

Study Design sought to design and implement a methodology that combines the scientific rigor of randomization with treatment delivered at the clinical point of care. POCCT are designed to be an intermediate strategy for experimental comparative effectiveness research that retains the benefits of both types of study design. Randomization is maintained from RCT in order to overcome the issues of confounding that plague observational studies, and an observational style of follow-up is used to improve feasibility, cost, and generalizability. Moreover, the POCCT study is intended to be implemented at the bedside while the patient is receiving medical care from their provider, therefore eliminating the need for a large-scale infrastructure that is not re-usable. In essence, POCCT is a randomized observational study that can be easily conducted within the context of medical care and deployed for minimal cost.[5]

Aspects of POCCT have been proposed and in some cases implemented by others.[6–8] Vickers and Scardino[9] discussed the idea of implementing pragmatic clinical trials in some detail. This is, to the best of our knowledge, the first implementation of a clinical trial using the EMR to randomize interventions and then collect all study variables. Implementation of the mechanisms required to facilitate enrolment, randomization, and longitudinal collection of patient data is made possible by the flexible design of the VA's computerized patient record system (CPRS), the clinical care component of the veterans health information systems and technology architecture (VISTA). For convenience and due to the interrelated nature of the two products, they are referred to here as CPRS/VISTA. CPRS/VISTA is available as open source software and was developed in collaborative, open source fashion by clinicians and information technology professionals within and outside of the VA healthcare system over the course of more than three decades. As a result, it has several functionalities that have proved valuable in their ability to support patient care management.[10]

Rather than offer only applications designed to perform specific clinical tasks such as decision support or drug–drug interaction monitoring, CPRS/VISTA capitalizes on customizable data objects and workflows. Clinical application coordinators employed by each VA hospital use these functionalities to assemble customized clinical improvement programs in CPRS/VISTA such as quality measurement, decision support, and clinical reminders. A partial list of existing CPRS/VISTA functionalities and their common uses is provided in table 1.

MATERIALS AND METHODS

Description of the pilot study

The POCCT insulin regimen pilot is an open-label, randomized trial comparing sliding scale versus weight-based insulin therapies for all non-intensive care unit inpatients with diabetes. Consented patients are randomly assigned to treatment arms using a Bayesian adaptive randomization method. Adaptive randomization methods adapt over time to favor the 'winning' intervention. This approach is more pragmatic in nature, allowing evidence to be used more quickly to inform better care. The details of this randomization design are described elsewhere.[5] The primary endpoint in the pilot study is length of stay. Secondary endpoints include glycemic control and readmission for glycemic control. The VA Boston Healthcare System (VABHS) is the first hospital enrolling for this study with enrolment scheduled to extend to other New England VA hospitals within the year. The protocol was approved by the VABHS Institutional Review Board including a Health Insurance Portability and Accountability Act (HIPAA) authorization waiver for access to protected health information in CPRS/VISTA.

Adaptation of CPRS/VISTA to support POCCT

The first POCCT pilot was launched primarily to evaluate the feasibility of performing a POCCT in an inpatient setting that offered a controlled environment and easy identification of a specific patient population. We are interested in both the challenges to adapting the EMR to support POCCT as well as house staff physicians and patient willingness to participate.

The implementation of a POCCT is dependent on bringing three vectors into alignment: (1) the processes of an RCT; (2) the processes of clinical care; (3) and the functionality of the EMR. The closer these three vectors can be aligned, the less friction there is in combining clinical science and clinical care using a POCCT. In attempting to reach this alignment, we avoided the development of new functionality within CPRS/VISTA to increase the likelihood of wider deployment of POCCT. Table 2 shows the intersection of these three vectors as implemented for

Table 1 A partial list of existing functionalities in CPRS/VISTA

CPRS/VISTA functionality	Description
Consults	Used by a clinician to notify other clinicians or individuals that their services are needed
Orders	Any type of order can be entered from customizable order menus. Orders can also be placed via reminder dialogs, allowing orders to be automatically entered based on values specified as 'finding items'. Orders are released with electronic signatures
Order set	Order sets are a group of any type of orders setup to be entered by clicking on a single entry
Progress note template	Local clinical application coordinators create progress note templates with custom titles and form fields to document an event or service delivered
Reminder dialog template	A special type of template designed to allow a clinician to process a clinical reminder that is due (eg, a flu shot, beta-blocker after a heart attack, annual diabetic foot examination, etc). Reminders can be configured to enter orders and can also be associated with progress note titles, as is being done with this POCCT
Finding item	Structured data can be flagged as a finding item allowing workflows and logic to be keyed off of them (eg, enter a specific order when finding item value = x). Finding items are often nested within reminder dialogs, alerting clinicians of specific patient conditions and requisite actions
Health factor	Data object named locally and attached to elements of reminder dialogs as findings. Health factors can be tracked and associated with visits, making it possible to capture the arm each POCCT subject is randomly assigned to
Computed finding	Accessible through the reminder dialogs, computed findings are a way to invoke a MUMPS programme or routine. We use a computed finding to call the MUMPS randomization function
CPRS alert	Alerts generally relate to ordered items, like a consult, or to bring attention to an event (eg, consult has been answered). Recipients can be set at the system, division, team level or with user preference. An orderable item can be flagged to send an alert when ordered (as we do with orders of sliding scale and weight-based insulin). Local sites can create alerts or choose from any of any number of alerts available nationally

CPRS, computerized patient record system; POCCT, point-of-care clinical trial; VISTA, veterans health information systems and technology architecture.

Table 2 Intersection of study processes, clinical processes, and CPRS/VISTA functionality as implemented for this POCCT

RCT process	Clinical process	CPRS/VISTA functionality
Identify eligible subjects	Clinician begins to order insulin regimen for patients with diabetes	Customizable order menu displays randomization option (see figure 1)
Educating interested clinicians/ patients about study	Clinician reads CPRS/VISTA study option on order menu and discusses with patient and both agree to consider enrolment	Consult sent to study nurse. Health factor created to track clinician and patient consideration
Documentation of consent/ non-consent	Study nurse reviews informed consent using official, paper-based HIPAA authorization and informed consent forms	Health factors capture agreement to consent/non-consent or record review-only consent allowing electronic tracking. A progress note is added to the medical record for consented patients
Randomization	N/A	A computed finding calls the MUMPS randomization routine
Intervention	Clinician receives an alert to sign unsigned order	An order set is automatically created based on the results of the computed finding. A CPRS alert is created and sent to the clinician
Data collection	N/A	Periodic pulls from the CPRS/VISTA databases provide longitudinal data collection

CPRS, computerized patient record system; HIPAA, Health Insurance Portability and Accountability Act; POCCT, point-of-care clinical trial; VISTA, veterans health information systems and technology architecture.

this POCCT. The design is described in additional detail in the following sections.

Initial order process

The POCCT workflow begins when any clinical provider attempts to place an order for sliding scale or weight-based insulin regimens from the VABHS existing endocrine order menu. As shown in figure 1, the VABHS order entry screen was changed by a local clinical application coordinator to include a third option entitled, 'VA clinical trial. Randomize to sliding scale or weight based insulin study. Choose this option if there is no preference for insulin protocol.' Clinicians who choose this third option are shown an informational screen that describes the study and provides order options indicating whether they are interested in proceeding with enrolment. By selecting, 'No. The patient may not be approached. Proceed with usual care', clinicians are returned to the previous order screen. A health factor is automatically created to allow the study team to track the number of refusals generated at this stage in the process.

Alternatively, the clinician may select 'Yes. The research team may approach this patient for consideration of enrolment.' CPRS/VISTA features 'consults' that can be generated automatically from placed orders. Selecting that the patient may be approached at the order screen automatically pre-populates and sends a consult to the study nurse. The clinician is then directed back to the order entry menu to place an order for either weight based or sliding scale until the patient can be consented and randomly assigned. This 'holding order' also ensures that care is not disrupted in the event that the study nurse is unavailable (eg, after hours, on weekends, etc).

Response to consult

On receiving the 'POC research insulin dosing request' consult, the study nurse explains the study to the patient and obtains informed consent. If the patient is randomly assigned, the pre-randomization insulin order is discontinued by the study nurse. If the patient declines to participate in the study, a pre-populated progress note is automatically entered into the EMR, which is forwarded to the ordering clinician for review and signature. In this first pilot the study nurse also notifies the clinician directly to ensure proper communication. Refusal or acceptance of random assignment and/or chart review is tracked using health factors, making it possible to track patient decisions. Patients not interested in consenting for random assignment are invited to consent for chart review. The chart review option is incorporated in the study to enable comparisons of patients accepting versus refusing random assignment. If the research nurse is not available to consent the patient, an alternative member of the research team who is designated to receive POCCT consult notifications selects the option 'patient cannot be enrolled for other reasons' on the consult reminder dialog. The clinician is alerted through the automatic generation of a pre-populated progress note that is forwarded to the ordering clinician.

Randomization

An enrolment progress note is created if the clinician and patient agree to random assignment. The progress note capitalizes on a CPRS/VISTA feature called a computed finding. A computed finding allows structured data to be passed to underlying methods to derive weights, averages, comparisons, etc. For POCCT a computed finding is employed that calls a random number generator ($RANDOM) native to the MUMPS programming language that underpins VISTA. The maximum allowable number of 1000 is passed and $RANDOM returns a random number between 0 and 999. The return of a number between 0 and 999, as opposed to a binary result for intervention assignment (eg, 0 or 1), is necessary to support the study's Bayesian adaptive randomization design. As the trial 'learns' which intervention is more beneficial, the returned integer allows the team to set up a moving threshold for that assignment (eg, 60/40, 70/30, etc).

The returned value is used by the computed finding to create an insulin order, in effect assigning the subject to the appropriate intervention arm. Progress notes for both patients accepting and declining participation are automatically created for and forwarded to the ordering clinician. Medication orders are pre-populated according to treatment assignment and must be signed by clinicians. A CPRS/VISTA alert is therefore used to prompt the clinician to sign and complete the randomized order. The study nurse also contacts the clinician directly and later verifies that the order has been 'released' by the clinician. Finally, a health factor is created that documents which of the two arms the patient was randomly assigned to. This allows the study team to identify subjects and their interventions quickly in the CPRS/VISTA database. The 'response to consult' and 'randomization' processes and the CPRS/VISTA mechanisms used to facilitate them are shown in figure 2.

Data collection

Although this first pilot POCCT was launched in Boston, the POCCT programme is planned for national expansion. Towards the goal of national expansion, the pilot study was used to test the feasibility of collecting national clinical data from CPRS/

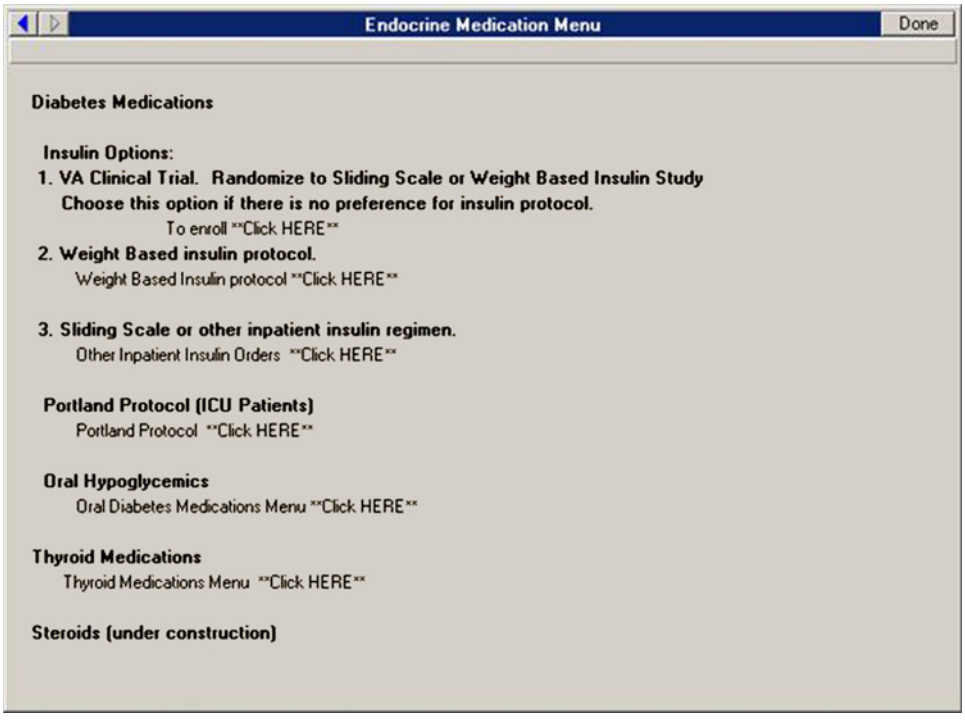

Figure 1 The endocrine medication menu currently in use in the Veterans Affairs Boston healthcare system with option 1 set to enrol and randomly assign patients into a point-of-care clinical trial.

VISTA. CPRS/VISTA is a distributed but integrated system with over 100 instances at VA medical centers, each containing its own database. It relies on calls from one system to another to create a complete picture of a given patient's history. At the time of the launch of our first POCCT, there was no single source of all national clinical data. The Veteran's Information and Computing Infrastructure (VINCI), a collaborative effort between the VA Office of Information Technology and the VA Office of Research and Development and the Office of Information Technology's corporate data warehouse are making progress towards providing such a resource. Both VINCI and the corporate data warehouse provided a foundation for much of the data needed for our study. Additional data elements not yet included in VINCI were obtained using the medical domain web services, which package CPRS/VISTA remote procedure calls as web services.

At present, all data extraction processes are launched manually on a weekly basis. Extract transfer load routines are in development that will automatically extract data from VINCI and a batch processes will call the appropriate web services, both on a nightly basis.

Outreach and education

At the start of the project a grand rounds presentation was given about the POCCT programme and more specifically about the VA Boston healthcare system's role as the first pilot site. Other study promotion activities have included informational sessions at weekly conferences, posting study flyers in house staff work stations and informal meetings with house staff physicians and nurse practitioners assigned to each of the ward teams. The chief resident has been enlisted as a clinical champion of the programme and has played an important role in supporting our efforts to inform new interns and residents about the study. The nurse coordinator approaches interns and residents with eligible patients for whom random assignment was not considered. Nurse coordinator follow-up is intended to increase awareness and guide house staff through the process as well as to understand reasons why providers may not elect to assign their patients randomly.

RESULTS

The first patient was enrolled into the insulin regimen POCCT on 12 October 2010. After several rounds of system testing and validation of both workflow and the accuracy of the data collected, all previously described CPRS/VISTA functionalities are working well and data are being collected periodically from the CPRS/VISTA databases. Based on user feedback, minor changes to verbiage on the insulin order menu screens have been made to make it easier for clinicians to recognize the randomization option. The total amount of time to set up all necessary customizations for a site, including validation/quality assurance, amounts to approximately 1 week of one full-time employee's time.

As of 30 June 2011, 105 patients were eligible for enrolment. There were 18 cases in which clinicians declined enrolment because of a preference for one of the insulin regimens. Another 17 eligible patients were not considered for the study because house staff did not initiate a consult (10 patients) or respond to the nurse coordinator's enquiries (seven patients). Of the 67

Table 3 Enrolment into the insulin regimen POCCT pilot as of 30 June 2011

Enrolment	
Eligible patients	105
Patients enrolled	64 (60.95%)
Of those enrolled	
Patients randomly assigned	55
Patients in chart review	8
Patient withdrawn	1
Clinician initiated point-of-care consults	19/67 (28.36%)
Of those declined	
Clinician refusal	18
Patients who declined participation	3
Not enrolled	
Patients not enrolled (no consult received or no response from physician)	17
Patients not enrolled for other reasons (administrative issues)	3

POCCT, point-of-care clinical trial.

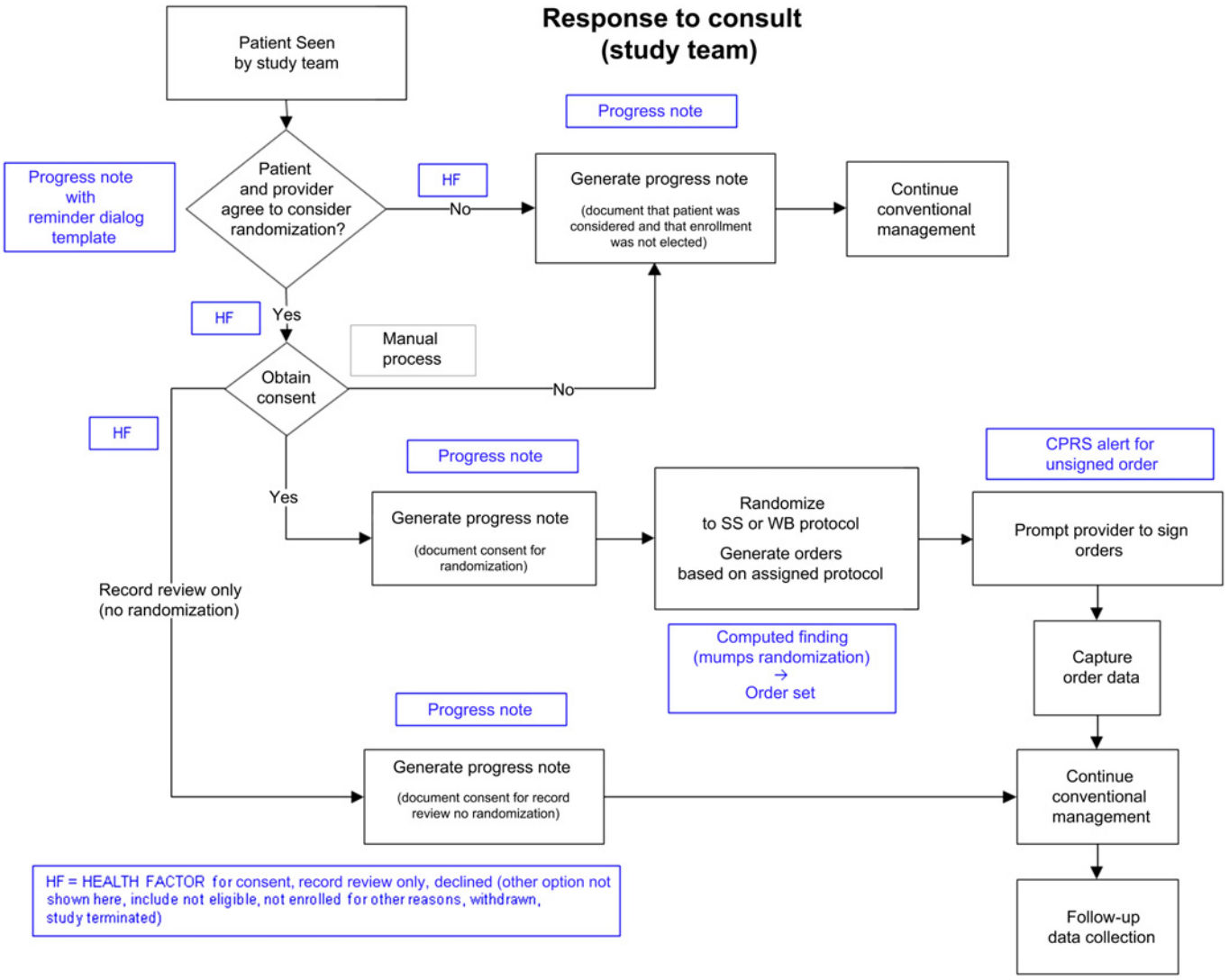

Figure 2 Point-of-care clinical trial insulin regimen pilot study workflow and computerized patient record system functionalities used to support it.

patients invited to participate, 55 were randomly assigned, three declined participation, and eight agreed to chart review only. Clinicians initiated the point-of-care consults unprovoked by the study coordinator in 27.14% of opportunities (table 3).

DISCUSSION

Although we are still at the early stages of understanding the implications of and optimal designs for POCCT, our experience in designing and deploying this first POCCT has led to several lessons learned from which others considering similar efforts may benefit.

Patient and clinician acceptance

We are encouraged by a positive enrolment rate of approximately 61% of all eligible patients. Our preliminary results indicate strong patient support for the idea of a POCCT, based on the assignment of randomized interventions of 82% of patients approached. Most patients were agreeable to random assignment, and anecdotal comments from them suggest that they were supportive of the study question and perceived their participation as minimal risk.

Our experience with engaging house staff physicians in recruiting patients at the point of care has not been as successful. House staff physicians initiated the randomization option at the time of ordering insulin in only 28.35% of eligible patients, although they did agree to random assignment and entered a point-of-care consult when approached by the study coordinator in 80% of requests. While in most academic medical centers residents actively manage the inpatient services, our institution may present specific challenges leading to low participation. The medical ward teams in the VA Boston healthcare system are composed of 16 interns and residents from three residency training programs with rotating schedules every 3 weeks. The high rate of turnover and relatively small population of eligible patients (four to five a week) lessens the opportunity for interns and residents to incorporate this novel mechanism into their practice.

To address the low rate of participation among residents and interns the initial order screen in CPRS/VISTA was recently revised to force an opt-in or opt-out of randomization before proceeding to the standard weight-based and sliding scale order menu. This requires a purposeful decision to accept or reject randomization and allows more granular tracking of reasons for refusal. A study is currently underway that will conduct patient and clinician focus groups to understand more fully these stakeholders' perspectives.

In retrospect, we believe the ideal setting for implementing the first use case might have been in a clinical area where a limited and more stable number of providers exists. Clinicians who completed the POCCT order set in response to the study nurse's request commented that the process was easy and quick to complete. Unfortunately, only a few have had the chance to repeat the process during their rotation. A more stable group of providers would provide a better opportunity to assess clinician behavior and evaluate how well POCCT might be adopted into practice.

Using the EMR to support POCCT

We have thus far been impressed with the ability of existing CPRS/VISTA capabilities to support the functionalities required to conduct a POCCT. Most beneficial from a software development standpoint is the modular and generalizable design of CPRS/VISTA. Underlying any custom quality measurement or specific clinical reminder application within CPRS/VISTA are objects and workflows that can be assembled and then customized to meet any number of clinical information initiatives. In addition, access to national longitudinal clinical data, although still from multiple sources, has proved feasible.

An important next step for the POCCT programme is deployment to additional sites. While some of the customizations we have made to CPRS/VISTA can be packaged and exported (eg, clinical reminders, alerts, health factors) the architecture of CPRS/VISTA prevents the export of order menus. As a result, any site wishing to implement this insulin-based POCCT must create custom order menus. Detailed step-by-step instructions were made to support clinical application coordinators responsible for installing POCCT-related deployable packages and menu customizations.

Our experiences in adapting CPRS/VISTA may hold lessons for those considering the design and adoption of other EMR systems. In table 2 we outline the necessary functionalities for conducting a POCCT. The two ways for EMR systems to achieve such functionalities are to create specific clinical trial modules or to design their systems to be modular and customizable such as the workflows and data objects of CPRS/VISTA. Current requirements for reimbursement under Health and Human Services' 'meaningful use' and EMR vendor certification policies are based more on the implementation of specific functionalities (eg, implement drug–drug interaction checks) and digitizing data rather than supporting customizable workflows, standard data formats, and unfettered access to well-defined and documented EMR databases. Policies that ensure the ability of owners of EMR systems to access all data and develop new workflows will be necessary to foster future innovations such as POCCT.[11]

Limitations

While integration with the EMR introduces a range of previously unavailable advantages, there are limitations introduced by the dependency of POCCT on the EMR that must be considered. The questions POCCT can be used to answer are limited by the data elements collected in the EMR. In addition, the quality of data elements available must be carefully considered during the design of a POCCT. Healthcare institutions interested in implementing POCCT must also assess the ability of their EMR systems to support the functionalities required to identify, enrol, randomly assign, and track the data elements of individual subjects.

The ability of EMR systems to support POCCT may also be dependent on the specifics of a proposed POCCT. For example, our ability to identify patients in the insulin pilot is based on the use of an endocrine order menu. Studies of a non-pharmaceutical intervention (eg, delivery of a mental health therapy) may require alternative mappings of existing clinical workflows. Finally, the ability of local clinical application coordinators to customize CPRS/VISTA that made our pilot possible may present challenges to national deployment efforts. In researching the next sites to deploy the insulin regimen POCCT we have encountered sites with endocrine ordering menus different from the one employed in Boston. These lessons learned have led the POCCT team and VA Office of Research and Development to create a new process for assessing the appropriateness of proposed studies for the POCCT mechanism. This new process will combine existing deliberations (eg, scientific validity, study design, etc) with POCCT-specific considerations.

Sociocultural considerations

The greatest obstacles to widespread adoption of POCCT are likely to be imposed by policy and cultural considerations. POCCT blurs the line between the two often distinct paradigms of clinical care and clinical research. Patients, clinicians, and hospital administrators must consider the effect on the clinician–patient relationship introduced by the admission of equipoise and the assignment of care by randomization. The introduction of POCCT also challenge institutional review boards to consider carefully the definitions of 'engaged in research' and the requirements related to informed consent. A system designed to gather evidence in support of one treatment versus another at the point of care that can be transitioned to clinical decision support may force reconsideration of what is research versus operational improvement.

Another important consideration is the interdisciplinary nature of the design and implementation of POCCT and the level of commitment required from several organizations within the healthcare system. The core team involved in the VA's first pilot study using a POCCT has required an expert in diabetes care, experts in clinical trial design and execution, biostatisticians, an epidemiologist, a project manager, an ethicist, informatics expertise in database design, CPRS/VISTA and medical domain web services, and a dedicated study nurse. The team's modest success is contingent on support received from our local institutional review board, hospital administrators, and house staff. In addition, modifications to CPRS/VISTA were approved and facilitated by leadership at the network level (the New England Veterans Integrated Service Network) and access to longitudinal clinical data was supported by several teams within the Office of Information Technology. As is always the case for interdepartmental system development, executive sponsorship at the highest levels of the organization has been critical for POCCT.

CONCLUSION

The first implementation of a POCCT in the VA has demonstrated the feasibility of this new method of evidence production. Existing functionalities within the VA's EMR system are currently employed to identify eligible patients, facilitate enrolment, perform randomization, and collect longitudinal data. Early results show both patient and clinician acceptance of the integration of a clinical trial into routine clinical care, although more work needs to be done to understand stakeholders' perspectives. Executive sponsorship and interdisciplinary collaboration have been critical to our success

to date, and a national programme for designing and deploying POCCT is underway within the VA's Office of Research and Development. As evidence accumulates in this first trial, we look forward to converting it to actionable decision support at the point of care using existing CPRS/VISTA decision support functionality. The next step in our assessment of the feasibility of POCCT is expansion of the current pilot study to VA sites throughout the New England region. In the meantime, new studies are in consideration and alternative models of obtaining informed consent are being explored as next steps in the development of the Office of Research and Development's point-of-care research programme.

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Contributors LDA: lead author and ultimately responsible for the manuscript's content; RF: authored portions of background, methods, and discussion sections; SG, JON, TS and CC: designed several aspects of the architecture described, contributed to the methods section, and edited the manuscript accordingly. PW, MB and JE: helped implement the first pilot and contributed to the discussion and methods sections. PL and LF: responsible for formulating the VA's Point of Care Research programme and launching this pilot. They also obtained the funding for this programme and edited the content of this manuscript.

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Competing interests None.

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CLINICAL TRIALS *DESIGN* *Clinical Trials* 2011; **8:** 183–195

A point-of-care clinical trial comparing insulin administered using a sliding scale *versus* a weight-based regimen

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Background Clinical trials are widely considered the gold standard in comparative effectiveness research (CER) but the high cost and complexity of traditional trials and concerns about generalizability to broad patient populations and general clinical practice limit their appeal. Unsuccessful implementation of CER results limits the value of even the highest quality trials. Planning for a trial comparing two standard strategies of insulin administration for hospitalized patients led us to develop a new method for a clinical trial designed to be embedded directly into the clinical care setting thereby lowering the cost, increasing the pragmatic nature of the overall trial, strengthening implementation, and creating an integrated environment of research-based care.

Purpose We describe a novel randomized clinical trial that uses the informatics and statistics infrastructure of the Veterans Affairs Healthcare System (VA) to illustrate one key component (called the point-of-care clinical trial – POC-CT) of a 'learning healthcare system,' and settles a clinical question of interest to the VA.

Methods This study is an open-label, randomized trial comparing sliding scale regular insulin to a weight-based regimen for control of hyperglycemia, using the primary outcome length of stay, in non-ICU inpatients within the northeast region of the VA. All non-ICU patients who require in-hospital insulin therapy are eligible for the trial, and the VA's automated systems will be used to assess eligibility and present the possibility of randomization to the clinician at the point of care. Clinicians will indicate their approval for informed consent to be obtained by study staff. Adaptive randomization will assign up to 3000 patients, preferentially to the currently 'winning' strategy, and all care will proceed according to usual practices. Based on a Bayesian stopping rule, the study has acceptable frequentist operating characteristics (Type I error 6%, power 86%) against a 12% reduction of median length of stay from 5 to 4.4 days. The adaptive stopping rule promotes implementation of a successful treatment strategy.

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Limitations Despite clinical equipoise, individual healthcare providers may have strong treatment preferences that jeopardize the success and implementation of the trial design, leading to low rates of randomization. Unblinded treatment assignment may bias results. In addition, generalization of clinical results to other healthcare systems may be limited by differences in patient population. Generalizability of the POC-CT method depends on the level of informatics and statistics infrastructure available to a healthcare system.

Conclusions The methods proposed will demonstrate outcome-based evaluation of control of hyperglycemia in hospitalized veterans. By institutionalizing a process of statistically sound and efficient learning, and by integrating that learning with automatic implementation of best practice, the participating VA Healthcare Systems will accelerate improvements in the effectiveness of care. *Clinical Trials* 2011; **8**: 183–195. http://ctj.sagepub.com

Introduction

Medical decision making is informed by clinical trials and observational studies. Randomization in clinical trials reduces or eliminates biases of observational studies, such as selection by indication and confounding from unmeasured prognostic factors that affect treatment decisions and outcomes. By their purpose, randomized clinical trials (RCTs) can be designed on a spectrum ranging from *pragmatic* (comparing effectiveness of interventions in the most realistic of situations and with diverse subjects) to *explanatory* (comparing efficacy in precisely described clinical situations and selected patients) [1,2]. The goal of explanatory trials is to better understand how and why an intervention works while pragmatic clinical trials are designed to provide information needed to assist healthcare providers make informed clinical decisions [3].

The *Pragmatic–Explanatory Continuum Indicator Summary (PRECIS)* is a measure of where on this continuum an individual trial is situated [4]. It takes under consideration the attributes of an RCT such as flexibility of the interventions, practitioner expertise required, eligibility criteria, intensity of follow-up and adherence monitoring, and the nature and scope of the primary outcome. RCTs are considered on the pragmatic end of the spectrum when these attributes are chosen to allow the trial to more closely mimic conditions encountered in the clinical care arena. Examples include eligibility criteria that reflect the patient population likely to receive the intervention, study investigators with expertise and experiences similar to the healthcare providers who will ultimately administer the treatments, treatment protocols that allow the flexibility required in routine clinical care, and outcome measures, and follow-up procedures that would be part of routine clinical care. Despite their reflection of routine clinical care, pragmatic trials are currently still complicated and expensive to implement, because of the use of dedicated study personnel to recruit participants, administer the intervention and monitor the participants for study outcomes and adverse events.

We are testing a real implementation of a new methodology for clinical trials, that we have called point-of-care clinical trials (POC-CTs), with features designed to maximize the pragmatic nature of studies. Aspects of the approach we describe here have been proposed or implemented by others [5–8] and discussed in detail under the name of the 'clinically integrated randomized trial' by Vickers and Scardino [9]. The defining characteristic here is that to the maximum extent possible the clinical trial apparatus is embedded in routine clinical care. Optimally, this would include recruitment and randomization of study subjects at their POC by their usual healthcare provider. Once randomized to a treatment arm subjects would continue to be treated by their healthcare provider with minimal or no deviation from usual care. Follow-up of participants would thus reflect current clinical practice. Assessment of subject compliance and practitioner adherence to protocol, and ascertainment of clinically relevant endpoints would be performed through medical record review, with minimal contamination of the clinical care 'ecosystem' by intrusive study dependencies. The intrusiveness of study operations, from randomization through endpoint ascertainment, would be greatly reduced if performed using tools familiar to healthcare providers and data already present in an electronic medical record (EMR).

A POC-CT shifts away from the asynchronous, distinct, and separate environments of research and clinical care, toward a real-time integrated system of research-based care. The goal of POC-CTs is to deliver the best care to patients while

learning from each experience and redefining that care. Under this new paradigm, ongoing results would be more rapidly and more likely adopted by providers who participated in the studies. By synthesizing research with practice and tools to learn from that process, participating facilities can move to the goal of becoming 'learning healthcare systems.'

In this article, we describe a specific POC-CT designed to test the feasibility and usefulness of the method, in answering a question of relevance to the Veterans Affairs (VA) Healthcare System. The clinical context and issues are described and ethical issues discussed. The use of outcome adaptive randomization to enhance implementation also addresses the frequentist operating characteristics of the design. The kinds of comparativeness questions best suited to POC-CT are argued.

Illustrative example: sliding scale insulin regimen *versus* weight-based insulin protocol

We describe a POC-CT which compares two common regimens of administering insulin therapy to hospitalized patients requiring insulin; the sliding scale and weight-based approach. The VA has an EMR that includes electronic ordering of medications and protocols for both of these insulin regimens. Review of EMR data at the VA Boston Healthcare System demonstrated that each of these two approaches is used with approximately equal frequency and discussions with treating clinicians indicated that choice of method administration is based on personal preference and not on patient specific determinants.

There are no published data comparing the effectiveness or the adverse effects of the sliding scale or a weight-based insulin protocol in treating inpatients with hyperglycemia. For the sliding scale, short acting insulin is administered three to four times daily according to the degree of hyperglycemia, and no basal insulin is administered. This regimen, therefore, responds to hyperglycemia after it occurs, and does not prevent it. The weight-based insulin protocol is a twice daily regimen of basal intermediate-acting insulin (NPH) plus a pre-meal twice a day regimen of short acting regular insulin, plus a correction dose of regular insulin depending on the degree of hyperglycemia. In addition, depending on the amount of the correction dose, the basal doses are adjusted upward for the next day's NPH insulin dose to manage the hyperglycemia.

Study design

Overall, the study is an open-label, randomized trial comparing sliding scale to a weight-based regimen in non-intensive care units (ICU) inpatients in a single large VA healthcare facility. There will be no modification to the treatment protocols already in use which will be accessed through the existing order entry menu. Consented patients will be randomized to treatment arms using an adaptive randomization method. Subjects are otherwise treated as usual. That is to say, there is no treatment protocol imposed other than insulin regimen beyond randomization. *There are no required diagnostic procedures and no study-specific follow-up events required*. Outcomes and covariates data will be collected directly from the computerized patient record system (CPRS). The primary endpoint is hospital length of stay (LOS); secondary endpoints include glycemic control and readmissions for glycemic control within 30 days of hospital discharge. Analysis will be based on intention to treat.

We considered using a cluster-randomized design, but the number of natural clusters (treatment units) within a hospital is small and having enough clusters to achieve adequate power would require opening the study at many hospitals, posing too many complex issues for a first use of POC-CT. Furthermore, we are interested in testing the feasibility of individual patient-level randomization, and the use of adaptive randomization to 'close the implementation gap.' While it is possible to imagine an adaptive cluster-randomized design, we have little information on the parameters necessary for design of such a study.

Eligibility

All non-ICU patients who require sliding scale or weight-based insulin therapy are eligible. The decision to obtain consent from a given individual will be made by the ordering clinician at the time of an insulin order (see section 'Methods'). There are no exclusions.

Treatment regimens

The treatment regimens are sliding scale and weight-based insulin as currently operationalized at the VA Boston Healthcare System. The ordering clinician finds these protocols under the electronic endocrine order menu and is led through order entry screens that insure standardization of the treatment protocol. The sliding scale and weight-based insulin regimens order menus in place at the

medical center were not modified other than to add a third choice allowing for randomization through the POC-CT mechanism.

Follow-up

Consenting subjects will be followed until 30 days of post-randomization. Following informed consent subjects will not be contacted by the study team either during their hospitalization or after discharge. All follow-up data will be collected *via* the EMR.

Data collection

Variables collected include demographics (age and gender); admission date, discharge date, and bed location (acute *vs*. non-acute); bed service (medical, surgical, and other); admission and other medical diagnoses (ICD-9 classification); glucose, blood counts, creatinine, and estimated glomerular filtration rate (GFR) values; and body temperature, medications, administered blood transfusion products, readmission date, and readmission diagnosis (ICD-9) if within 30 days of discharge. Non-VA hospitalization data for all subjects enrolled in Medicare will be available through a data-sharing agreement between VA and the Centers for Medicare & Medicaid Services.

Outcomes

The clinical outcomes of potential relevance that were considered included episodes of suspected hypoglycemia and measures previously used in studies examining potential benefit of improved glycemic control such as: (1) shortened length of hospital stay; (2) fewer infections; (3) fewer episodes of acute kidney injury; (4) less need for renal dialysis; (5) lower blood transfusion requirements; and (6) less neuropathy.

LOS is selected as the primary outcome, because LOS has important cost implications, lowers the risk of hospital-acquired complications including falls and infections, and might be expected to be shortened if diabetic control can be made more efficient. It is also readily ascertainable from the EMR. Secondary outcome measures include degree of glycemic control and readmission within 30 days of discharge with the primary readmission diagnosis of control of glycemia. Tertiary outcomes include infections, acute kidney injury, and anemia, all of which have been previously used as outcome measures in studies of insulin regimens. Infection will be defined as new antibiotic administration associated with either fever or leukocytosis. Acute kidney injury is defined as a decrease in estimated GFR of greater than 50% and anemia as a drop in the hemoglobin level of at least 2 g/dL.

Recruitment and enrollment

The POC-CT process is implemented using software tools available in CPRS. CPRS is the clinical care component of the Veterans Health Information Systems and Technology Architecture (VISTA), which supports clinical as well as administrative applications. Software tools available in CPRS include order sets (predefined customizable sets of orders), templates for clinical notes, decision logic (reminder dialog templates), and defined data objects that extract data from the medical record for display purposes (patient data objects). CPRS also has the ability to store flags (indicators in the data base) known as 'health factors' related to clinical parameters and flags derived from the ordering process. These tools make it possible to identify certain data elements in real time (e.g., an insulin order) and to incorporate programmatic logic into the medical record's workflow based on the value of data elements. The order sets and templates utilized for this project were designed to be consistent in format and process with the existing system.

The following describes the workflow of the study and demonstrates how CPRS processes already familiar to clinicians were adopted for POC-CT (Figures 1 and 2):

1) The VISTA order entry screen for insulin has been modified to include a third option in addition to the current options to order sliding scale or the weight-based regimen. The third option is labeled 'No preference for insulin regimen, consider enrollment in an inpatient study of Weight Based vs. Sliding Scale protocols' (Figure 3).
2) Clinicians who choose this third option will be presented with a brief description of the study and given the option to either proceed or not with consideration of their patient for study enrollment.
3) Clinicians who choose not to continue will click on the button labeled 'No. The patient may not be approached. Proceed with usual care.' and will be returned to the previous order entry screen to continue without further consideration of this trial.

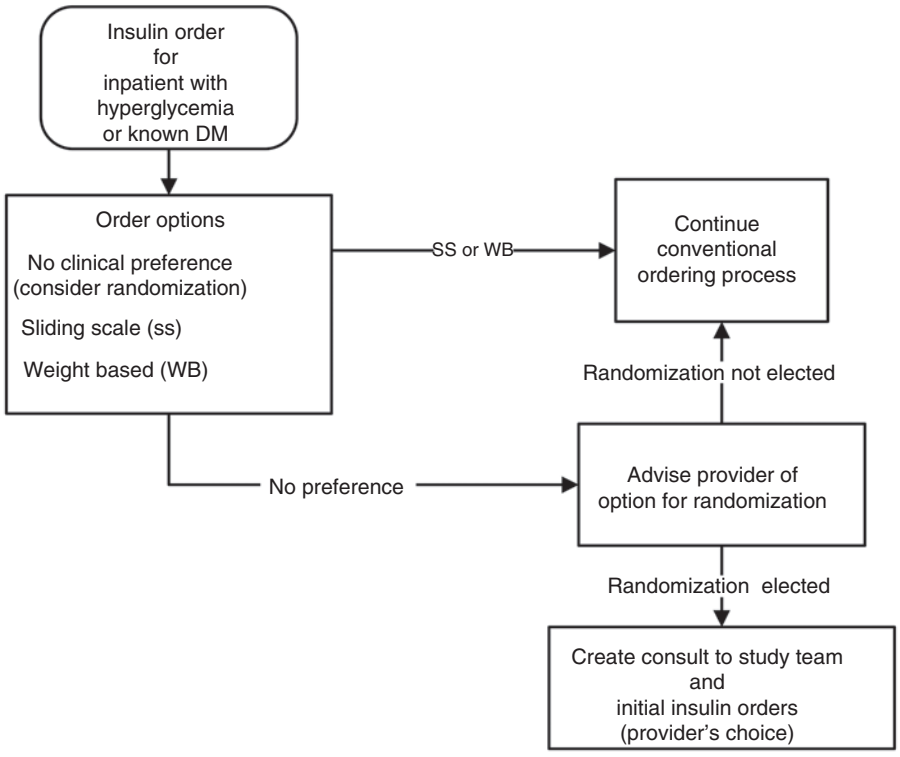

Figure 1 Initial order process performed by clinician

4) Clinicians who choose to proceed will click on the button labeled 'Yes. The research team may approach this patient for consideration of enrollment.' and will be brought to a consult entry screen. The consult entry screen will be pre-populated requesting a 'Research insulin dosing consent request.' After submitting this consult, the clinician will then be directed to the order entry menu and will order either sliding scale or weight-based insulin as per their choice. This order will serve as a holding order to provide insulin treatment until the patient can be consented and randomized.
5) Upon receiving the 'Research insulin dosing consent request,' the study nurse will discuss the study with the patient and obtain informed consent. If the patient declines enrollment, a template progress note completing the consult will be automatically entered. Patients who refuse randomization will be asked for consent to allow access to their VISTA data for comparison to the subset of patients who accepted randomization.
6) Patients who provide consent will be randomized through the VISTA system to one of the two insulin regimens. A template progress note activated by the study nurse will document randomization. This template progress note will generate 'health factors' that will serve to identify patients as subjects in the trial for tracking purposes in VISTA. It will also generate the order for whichever insulin regimen the subject was randomized to receive.
7) Progress notes (for both patients accepting and declining participation) and orders (for those accepting randomization) will be automatically forwarded to the original ordering clinician.
8) By signing these documents, the clinician completes the study enrollment process.

The protocol was approved by the VA Boston Institutional Review Board (IRB) who waived Health Insurance Portability and Accountability Act (HIPAA) authorization to allow the study team, once contacted and prior to seeing the patient, to have access to protected health information in the medical record. Importantly, clinicians, in simply referring patients to the study coordinator for recruitment and signing the insulin orders generated by the randomization procedures were not considered by the IRB to be 'engaged in clinical research' and thus were not required to be research credentialed.

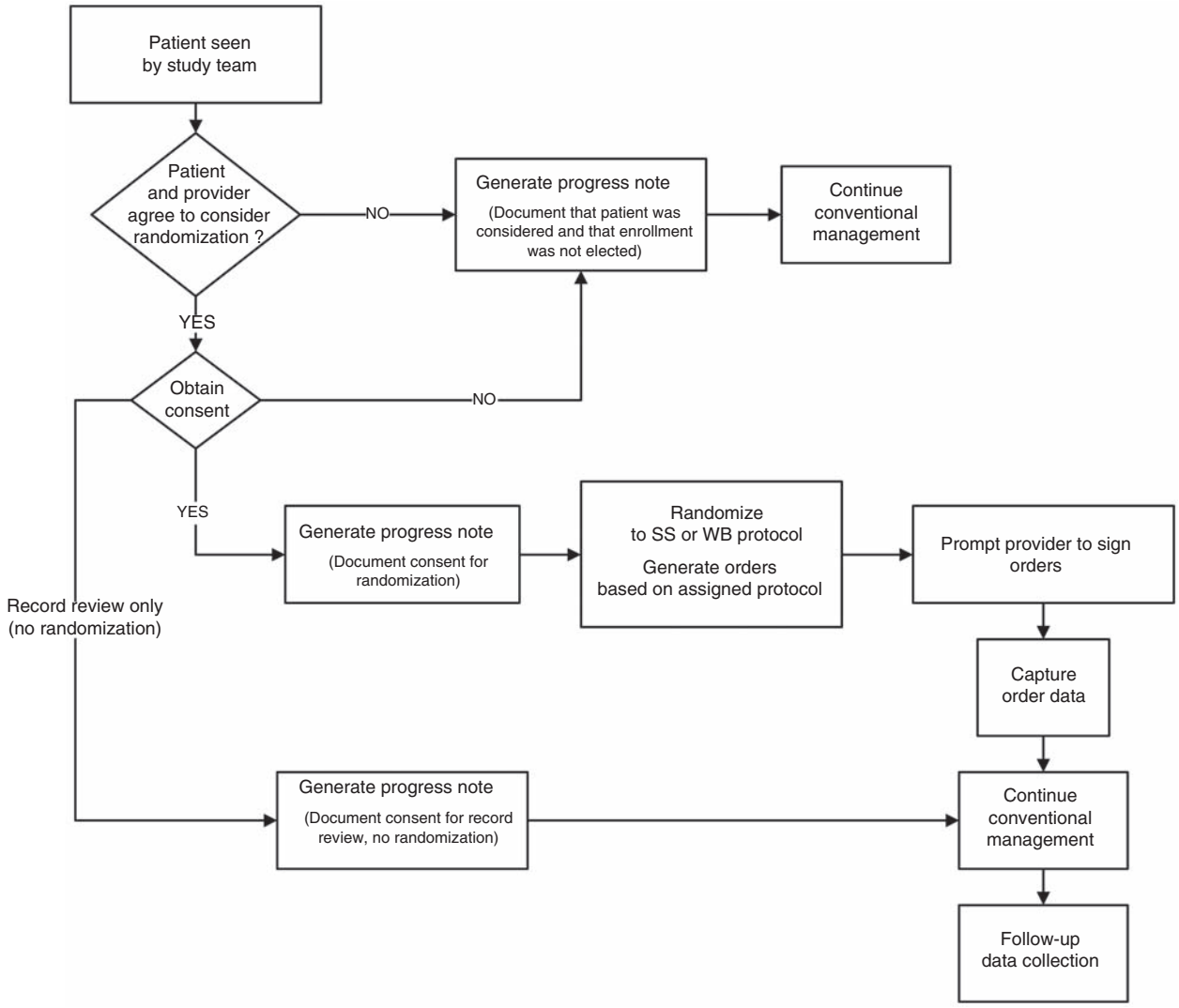

Figure 2 Workflow beginning when clinician has agreed to consider randomizing patient into one of two interventions

Statistical issues

We define three main aims: (1) to determine the physician and patient acceptance of POC randomization, (2) to test the null hypothesis of no difference against reasonable alternatives (two-sided), and (3) to demonstrate successful implementation of the superior strategy. The first aim requires descriptive statistical approaches, including estimating proportions and defining patient- and physician-level predictors of acceptance. The second aim requires tuning the design parameters to achieve acceptable operating characteristics. The third aim motivates an adaptive randomization, adjusting the assignment probabilities to increase the chances that patients are assigned to the better treatment.

Adaptive design

In the proposed study, the response or outcome is hospital LOS and the parameters of interest are the median LOS with each of the two protocols: (1) weight-based (Protocol A) and (2) sliding scale (Protocol B). We predict that the patients using the weight-based protocol will have a smaller median LOS than patients using the sliding scale protocol. To test this hypothesis, we propose using a Bayesian adaptive design.

The rules of adaptation considered herein modify the assignment probability each time the study accrues a new fixed number or 'batch' of patients, with practical batch sizes of at least 100 patients to allow more time for review and cleaning of data as is implicit in group sequential designs.

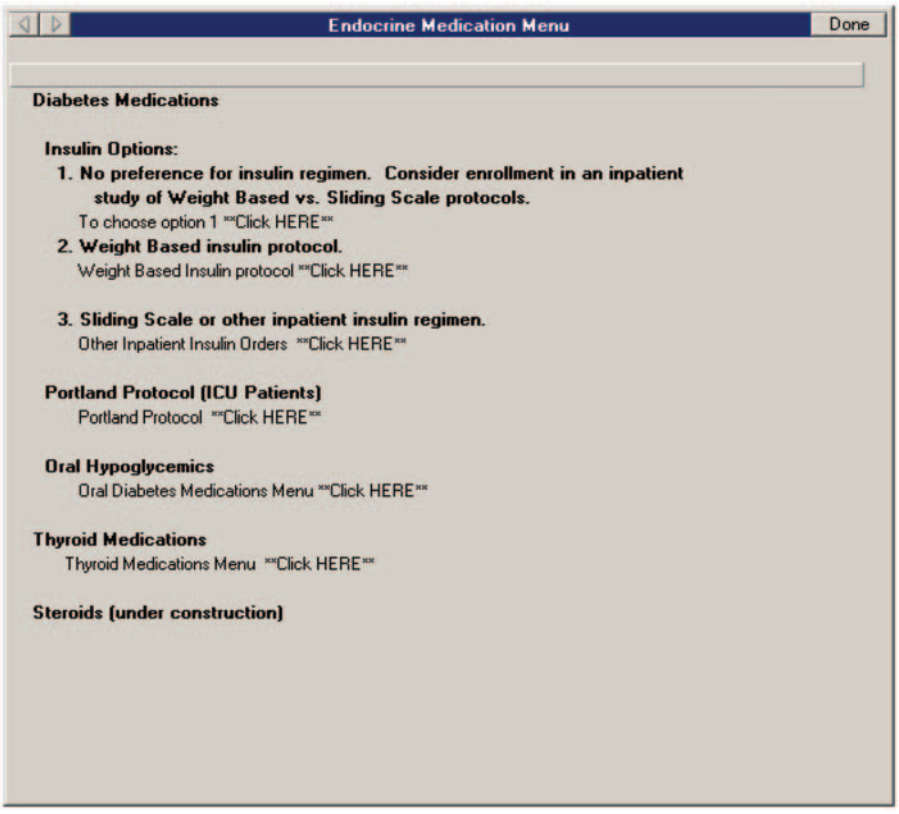

Figure 3 Screen shot of CPRS showing introduction of POC-CT option into the insulin options menu

According to this scheme (Figure 4)

1) First, subjects will be assigned to either weight-based protocol (Group A) with probability $\pi = 0.5$ or to sliding scale protocol (Group B) with probability $1 - \pi = 0.5$. This assignment probability is utilized for the first batch of patients.
2) Then, the data collected on the first group of subjects are used to calculate the probability that Protocol A is superior to Protocol B given the accumulated data, that is

$$\begin{aligned} p_A &= P(\text{Protocol A is superior to Protocol B}) \\ &= P(\theta_A < \theta_B | DATA) \end{aligned}$$

The '*DATA*' here refers to the data collected on the first batch of patients, with allowance for a period (UPDATE strip in Figure 4) in which the investigators clean the data and do the update and θ_A and θ_B are the median LOS in Groups A and B, respectively. The 'posterior' probability p_A ('*probability of Protocol A being superior to Protocol B given the data*') is calculated using Bayesian methods. Bayesian methods use prior information or beliefs, along with the current data, to guide the search for parameter estimates. Prior information/beliefs are input as a distribution, and the data then help refine that distribution and construct the posterior distribution. Our statistical model is based on an exponential data model for the LOS with conjugate Inverse Gamma prior for the median LOS [10]. Prior distributions in each group were chosen to be centered on the null median value and have a shape parameter α.

1) The posterior probability p_A is then used to evaluate whether the accumulated information overwhelmingly supports one protocol over the other so that the termination of the trial is warranted. In particular, we would stop the trial if

$$p_A > \kappa \text{ or } p_A < 1 - \kappa$$

where κ is the *cutpoint* reflecting the level of evidence demanded by the investigators to terminate the trial. If $p_A > \kappa$, then the study is terminated and Protocol A is chosen as being superior while if $p_A < 1 - \kappa$, the study is terminated and Protocol B is chosen to be superior. The value for κ is at the

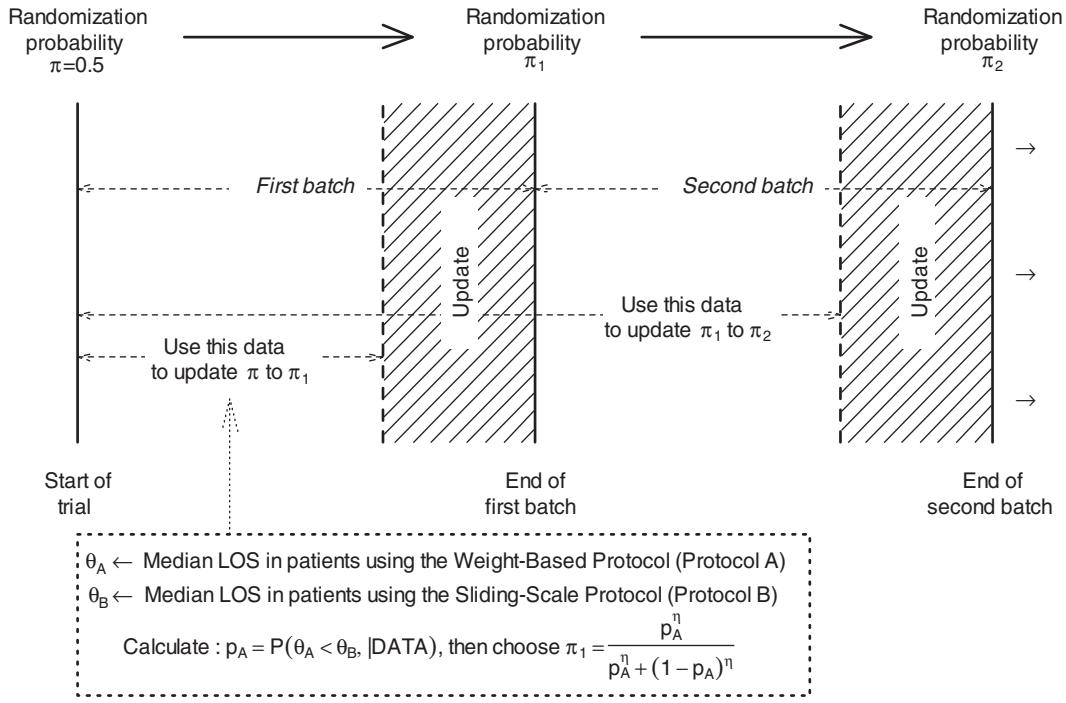

Figure 4 Diagram representing the flow of the design In the figure above, π represents the probability of assigning the weight-based protocol to a patient

investigators' disposal and it is usually a value that is close to 1 (for example 0.9, 0.95, or 0.99).

1) If the decision to terminate is not made, the posterior probability p_A is used to update the assignment probability to π_1 using the transformation [11]

$$\pi_1 = \frac{(p_A)^\eta}{(p_A)^\eta + (1-p_A)^\eta}$$

where $\eta > 0$ is a *calibration parameter*. If η is set to 1, the updated assignment probability is $\pi_1 = p_A$, while a value of $\eta = 0$ leads to a balanced randomization design. Values greater than 1 (less than 1) lead to more aggressive (less aggressive) adaptation.

1) The second batch of patients will then be assigned to Protocol A with probability π_1 and to Protocol B with probability $1 - \pi_1$. After the data on the second batch of patients are collected, the assignment probability π_1 is updated to π_2 using the above algorithm and the termination criterion is checked. If the termination criterion is met, the study is terminated. If not, the assignment probability π_1 is updated to π_2 using the above algorithm and the third batch is then enrolled.
2) This process is continued until either the termination criterion is met or the number of subjects enrolled reaches a pre-specified maximum number of subjects $N_{\max}$.

Proposed design

Extensive computer simulations were done to select a design for the study based on their operating characteristics. The following operating characteristics were considered in selecting the final design:

1) *Overall Type I error* – the chance of declaring one of the two protocols better at any time during the trial when in fact there is no difference between the two protocols.
2) *Overall power* – the chance of declaring a protocol better at any time during the trial when in fact that protocol is better.
3) *The number of patients assigned to each protocol.* The number of patients enrolled will depend on the data collected and hence is a random variable.
4) *Time until a decision is made.* The duration of the study will depend on the data collected and hence is a random variable.

We chose a design with the following parameters: prior shape parameter $\alpha = 100$, batch size = 200, cutpoint $\kappa = 0.99$, calibration parameter $\eta = 0.5$, and maximum number of patients to be randomized $N_{max} = 3000$. In addition, the updation occurs after 150 patients of each batch have entered the study, we do not update or allow stopping after the first batch, and we censor the LOS at 30 days.

We studied the above design under various scenarios. Our null hypothesis is that the median LOS with both protocols is 5 days. As alternative, we posit a minimal clinically important reduction of at least 12% in median LOS.

The operating characteristics of the design are represented in Table 1.

Type I error: Under the assumption of no difference (first row in Table 1 – median LOS is 5 days with both protocols) the probability of (incorrectly) selecting either protocol as superior was 0.06.

Power: Under the alternatives (median LOS with Protocol A < median LOS under Protocol B) presented in the remaining rows of the table, the probability of correctly selecting Protocol A represents the power. For a difference of 12% in median LOS, across the interim looks, the design will correctly select Protocol A as superior with 86% probability (power), while the probability of wrongly selecting Protocol B as superior decreases fast to levels close to 0%. The decision to stop increases with time (Figure 5); thus, the probability or terminating the trial by the 6th interim look (after 1400 subjects have been enrolled) is 50% and it increases to 86% by the 14th look (after all 3000 subjects have been enrolled).

From among the many alternatives designs we evaluated, we briefly discuss here the *balanced* design that has the same parameters as the design presented above. Additional information on the simulation study including the R [12] script used in running the simulations can be obtained from the authors.

With a balanced design, the Type I error is the same, the power is slightly higher (for example, 77% *vs*. 71% to detect a difference with Protocol A of 10% in median LOS), the median number of patients enrolled is about the same (~2000),

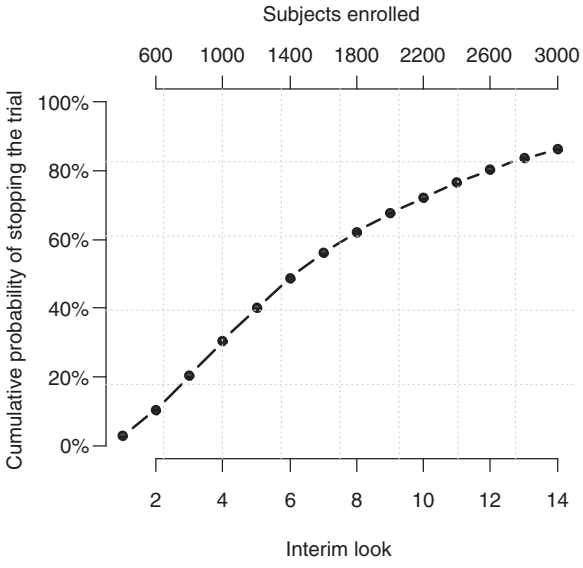

Figure 5 Cumulative probability of stopping the trial across interim looks; assumed median LOS with Protocols B and A are 5 and 4.4 days, respectively

Table 1 Operating characteristics of the proposed design

Difference in median LOS (B–A) in days [median under Protocol B = 5 days]	Probability of selecting Protocol A as superior (%)	Probability of selecting Protocol B as superior (%)	Median number of patients on Protocol A	Median number of patients on Protocol B	Median duration (days)[a]
0	3	3	1495	1461	599
0.1	8	1	1634	1292	598
0.2	17	0	1738	1125	597
0.3	30	0	1791	969	595
0.4	51	0	1719	778	581
0.5	71	0	1434	598	408
0.6	86	0	1075	465	316
0.7	95	0	825	380	240
0.8	99	0	673	332	201
0.9	100	0	540	289	164
1	100	0	506	268	157

[a]In calculating the duration of the study, we assumed an accrual rate of 5 patients per day.

Table 2 Operating characteristics under lognormal data model

Difference in median LOS (B–A) in days [median under Protocol B = 5 days]	Probability of selecting Protocol A as superior (%)	Probability of selecting Protocol B as superior (%)	Median number of patients on Protocol A	Median number of patients on Protocol B	Median duration (days)[a]
0	4	3	1469	1473	599
0.1	8	2	1594	1317	599
0.2	16	1	1711	1163	597
0.3	28	0	1759	998	595
0.4	46	0	1724	832	587
0.5	62	0	1600	696	485
0.6	78	0	1244	535	360
0.7	90	0	924	414	275
0.8	96	0	715	352	210
0.9	99	0	626	309	193
1	100	0	522	278	160

[a]In calculating the duration of the study, we assumed an accrual rate of 5 patients per day.

however, while with the balanced design the enrollment is balanced, with our proposed design the number of patients assigned to the superior treatment is higher.

The operating characteristic simulation is dependent on the accuracy of the data model used to generate the LOS. In Table 1, we use the exponential model to generate the data, as well as to do the updating. Thus, it makes the assumption that the Bayesian model is correctly specified, as is done in most published work, when estimating (frequentist) operating characteristics. But the LOS data from a historical sample of patients approximating the proposed study intake criteria indicates a heavier tail, such as log-normal. Therefore, we assessed the sensitivity of the assumptions by using the log-normal model to generate the data (but still using the exponential model for the updates; Table 2).

The difference between these two simulations illustrates the modest sensitivity of the operating characteristics to misspecification of the data model. For example, the Type I error estimate rises from 6% to 7%, and the power at a difference of 0.5 days drops from 71% to 62%. However, we consider the Type I error less relevant in this context, comparing the effectiveness of two widely used procedures for setting dose. In a different context, the Type I error might be more important. The probability of making the right choice when it matters (a full day difference) is high (100%) in the log-normal scenario, too. These results illustrate the value of a hybrid approach, where the Bayes method is confined to updating the randomization probability (thus closing the implementation gap and maximizing the number of patients receiving the right treatment) and inference is based on operating characteristics from a range of more realistic models.

Discussion

POC-CT methodology is well suited for studies with the following features:

- Interventions already approved by the FDA.
- A clinical question where there is equipoise regarding clinically relevant alternative interventions.
- Interventions that are part of routine practice, well tolerated, and have well-recognized toxicities which mitigates the need for adverse event monitoring beyond that in routine clinical care.
- Subject identification, inclusion and exclusion criteria, and endpoints that are accurately obtained from the EMR.
- Outcomes are objective and require little or no adjudication.
- Study protocol requiring minimal deviations from usual care.
- No systematic laboratory or clinical follow-up required for either safety or comparative effectiveness.

This trial is designed to be on the pragmatic extreme of the clinical trial spectrum with the subject consent process being the sole perturbation of the clinical care 'ecosystem.' The absence of study specific interventions, procedures, and monitoring together with passive data capture attempts to maximize the relevance of the findings to

current practice at the VA Boston Healthcare System. Adaptive randomization is designed to assign subjects preferentially to the treatment arm that, in real time, appears superior, with an 'efficacy' stopping rule that has acceptable Type I error. If the study terminates without reaching its 'efficacy' boundary, it will reliably rule out a substantial difference, in which case cost, convenience, and other factors will dictate which treatment arms continue to be supported. Such direct translation of study results into clinical practice defines a 'learning healthcare system.'

The clinical question posed in this protocol, comparison of insulin administration methods, was chosen because it is amenable to a maximally pragmatic study as defined by the PRECIS criteria and because:

- Broad participation by healthcare providers is expected. The clinical question is compelling and in practice there is apparent equipoise between the two regimens in that roughly half of patients are currently treated by each technique.
- The inclusion/exclusion criteria will allow enrollment of nearly all the VA Boston patients who require the intervention.
- The study interventions are currently utilized at VA Boston, have known toxicities that are monitored as part of usual care, and thus require no specific study related monitoring.
- All study data elements are objective, resident in the EMR and do not require study specific interactions or visits for capture.
- Adaptive randomization methodology leads to real-time incorporation of study results into practice, if one treatment proves superior.

The ability to implement this study is made possible by the VA's EMR environment. CPRS is in use at all the VA's 1500-plus points of care and was designed to incorporate clinical data as part of efforts to improve clinical care. As a result, it features several packages that allow end users to automatically generate reports, 'listen' for certain values associated with patient data objects, consider these values with programmatic logic, and introduce information and workflows directly into the EMR. To capitalize on this level of flexibility, most VA healthcare systems employ Clinical Application Coordinators, who use these tools to create and report measures of the quality of care, to implement guidelines, and to create clinical reminders based on the priorities of each hospital. This infrastructure will allow for the relatively easy roll-out of this and other POC-CT studies system-wide as well as systematic implementation of findings.

The ability to use existing functionalities, as opposed to developing custom software is important for a number of reasons. First, development of new software functionality is constrained by time for development, testing, and approval, and development resources. Second, by capitalizing on existing system functionality, we increase the likelihood of a successful deployment to other VA hospitals or clinics, each one of which employs CPRS. Finally, although this particular use of CPRS may be novel, the POC-CT processes are presented through familiar interfaces and into a culture of robust CPRS use, which we hope will facilitate adoption of this approach.

The ability of institutions to implement POC-CTs is dependent on the ability to use the EMR to: (1) identify events as they present in real time; (2) intervene in the clinical care workflow; and (3) track longitudinal data. It is worth noting that these functionalities are critical to the creation and implementation of many novel approaches to learn from and improve healthcare based on real data and that few systems offer such capabilities to end users. The need for such functionalities is of particular relevance in light of the US Federal Government's upcoming investment of $19 billion to support the adoption of EMRs [13]. Much of this funding is contingent on the adoption of 'certified' EMR systems and the 'meaningful use' of such systems. Definitions that require flexible integration with EMR data and workflows are essential to meeting the goals of such enormous investments [14].

The ethical and practical considerations of informed consent have been extensively discussed and debated [15–19] as have methods such as cluster randomization which might obviate or preclude individual informed consent [20,21]. Detailed analyses of these considerations are outside the scope of this article. However, as POC-CTs or similarly designed trials become an important component of clinical research, it will be incumbent on investigators, ethicists, and IRBs to fully consider the potential benefits and apparently minimal incremental risks of a POC-CT, and to take responsibility for helping their healthcare systems to lower the barriers to successful study design and implementation of improvements in care.

A study coordinator will obtain written informed consent for all subjects entered into this trial. This requirement accounts for a significant proportion of the study cost and introduces the single most tangible perturbation to the usual care workflow. We recognize that replacement of such full written informed consent by an alternative (such as simple 'notification' by the healthcare provider and verbal consent by the subject with subsequent

randomization through a fully automated computerized process) would result in an even more efficient design, with a closer match to clinical care. The IRB could consider such a variation on the usual research informed consent, on a study-by-study basis, especially when the POC-CT results in care materially identical to usual clinical practice. Parallel requirements would be a waiver of HIPAA authorization to obtain study data from the EMR and acknowledgement that treating clinicians who authorize automated randomization are not 'engaged' in research.

A POC-CT will likely require significantly less study-specific infrastructure and cost than traditional RCTs (after the up-front investment in coordinating center and informatics, already made by the VA). These advantages together with an economy of scale once an investment in the methodology has been made could lead to low incremental cost per study as well as allowing study designs of sufficient duration to capture clinically relevant (as opposed to surrogate) endpoints.

Limitations

Several issues may impede adoption of POC-CTs. Some patients may find it surprising and troubling that healthcare providers do not know what is the best treatment for them. This disclosure could make the consent process lengthy and difficult. Although the medical community might be at equipoise regarding treatment options, individual healthcare providers may have strong treatment preferences, either in general or for particular individual patients. Both of these issues could have ramifications for recruitment rates and the success of a POC-CT. We note that 'reluctance to randomize' is an issue for all RCT designs, not just POC-CT.

Most (if not all) uses of POC-CT we envision would have an open (unblinded) design, which raises the possibility of cross-contamination of treatments, or differential clinical interventions due to physicians' perceptions of patients' needs, or other failures of the exclusion principle, such as observational bias in the outcome. Therefore, the use of POC-CT may be restricted to clinical situations where the effects are likely to be minimal. We think that the EMR-based protocols we compare here, as well as the outcome of LOS, sharply reduce physician unblinding as a threat. We emphasize that POC-CT is not a universal alternative to the classical double-blind RCT with its many controls for bias; rather, it can be seen as a competitor to observational studies, by removing the particular bias from selection by indication that plagues such non-experimental studies.

Our pragmatic intent requires us to rely on individual clinician judgment of eligibility, which is another mark of distinction between POC-CT and conventional trials, which often have elaborate procedures for defining 'inclusion and exclusion.' This certainly restricts the use of POC-CT to contexts where such precision is unnecessary. However, it also contributes to the 'ecological validity' of treatment effects.

Highly pragmatic POC-CTs such as this study may yield results that are locally convincing but are not easily generalized to other healthcare systems. A healthcare system such as the VA, motivated to conduct POC-CTs and with the organization and infrastructure capable of supporting it, could generate 'locally selfish' evidence-based medicine to gain evidence of comparative effectiveness most relevant to its population and systems. In general, comparative effectiveness findings are most applicable to the systems and individuals who participated in its creation rather than to the 'free riders' – those who may desire evidence-based medicine but who are unwilling to be a part of that evidence.

The above may suggest that the POC-CT approach is limited to a narrow range of clinical questions and contexts. We are just now beginning to expand our list of possible use cases, and we do not want to speculate in advance of the facts. We agree with Vickers and Scardino [9] that features of POC-CT might be implemented in practice in four distinct areas: surgery, 'me too' drugs, rare diseases, and lifestyle interventions. In addition to questions of optimizing care (such as the insulin example described here) use cases currently under consideration include technology introduction (imaging, robotics, and biomarker-guided therapy), pre-hydration with bicarbonate *versus* saline with or without n-acetylcysteine in contrast-induced nephropathy, and comparing prolonged exposure and cognitive processing therapies as alternative treatment strategies for post-traumatic stress disorder.

Finally, the proposed study design using outcome adaptive randomization leads to real-time implementation into practice, and stimulates reconsideration of the role of the traditional peer review process that subjects study results to expert outside review before planning their implementation in practice.

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Policy Needs – Ethics and Trial Processes

Learning Health Care Systems and Justice

By RUTH R. FADEN, TOM L. BEAUCHAMP, AND NANCY E. KASS

Emily Largent, Steven Joffe, and Franklin Miller offer a stimulating contribution to the literature on integrating medical research and practice. We agree on both the need to move toward what the Institute of Medicine has called a learning health care system and the need for new conceptions for integrating research and practice within it. We also agree with the authors' view, first advanced by Robert Truog and colleagues in 1999, that it can be ethically acceptable to randomize patients without express consent in trials comparing widely used, approved interventions that pose no additional risk. With appropriate oversight, learning health care systems ought to conduct such trials on a regular basis.

Our approach to the ethical integration of research and practice differs from that of Largent, Joffe, and Miller in several respects, three of which we address here. First, we do not concentrate on *research* per se, but instead on what we take to be the broader category of *learning*. Learning includes what is now conventionally classified as research (with or without human subjects) and various other activities that often are not formally classified as research, such as quality improvement efforts and various segments of public health practice. These activities share the goal of obtaining information that can help improve health care services and systems.

Second, we focus on providing a justification for learning in health care as a morally essential, not morally optional, feature of a health care system. The justification is grounded in the critical role that learning plays in achieving and sustaining a *just* health care system, by which we mean a system in which present and future generations have guaranteed access to adequate and high-quality health care services without generating undue financial burdens on patients and families.

The required justification rests on two empirical assumptions: 1) a just health care system cannot be secured without continuous commitment to improving the quality and efficiency of health services, and 2) honoring this commitment depends on efficiently integrating into clinical service delivery a wide range of learning activities, including those conventionally classified as research. Nations cannot afford to provide everyone with every available medical intervention without regard to the magnitude of benefits and costs. In the face of this ineliminable constraint on resources, continuously gathering information about what works best for whom—and what does not—is vital.

If, as we think, all should contribute toward the goal of securing and maintaining a just health care system, then all of us who participate in the health care system, including patients, have an obligation to support and participate in the real-time integration of research and practice (as long as participants' quality of care or well-being is not significantly compromised). Often the integration does not require express, activity-specific consent, even when the activities would be classified as research involving human subjects.

Framing the ethics of learning health care in this way brings to the forefront the principal moral challenge confronting the integration of research and practice in the fractured health care systems typical in the United States. Duties to contribute to a just health care system provide a basic moral justification for integrating learning into practice. At the same time, we need to facilitate research-practice integration in less than just contexts in order to provide the knowledge base necessary for the system to become more just.

This observation takes us to a third point. Our overall objective is to provide a moral framework for integrating research and practice in today's health care settings. We approach this challenge through the broad category of learning activities, including clinical trials, quality improvement practices, and comparative effectiveness research. Classification schemes that bifurcate learning activities into the two crude categories of research and practice are increasingly outmoded. We should investigate models of integration and moral frameworks that reconceive the rights and duties operative in learning health care systems. In upcoming years, making this advance will be among the foremost tasks facing bioethics and health policy.

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Addressing Low-Risk Comparative Effectiveness Research in Proposed Changes to US Federal Regulations Governing Research

Nancy Kass, ScD
Ruth Faden, PhD, MPH
Sean Tunis, MD, MSc

On July 25, 2011, the Department of Health and Human Services published an advance notice of proposed rule making, outlining potential changes to the federal regulations overseeing human subjects research.[1] These regulations, known since 1991 as "the Common Rule," have been effective in ensuring that most human research in this country is reviewed prospectively by an institutional review board (IRB) charged with determining that risks of proposed research are minimized and acceptable and also ensuring that individual participants provide informed consent for most types of research before participation.

Some of the proposed changes suggested in the Advance Notice of Proposed Rulemaking (ANPRM) are designed to expand or deepen federal protections, whereas others are intended to reduce the oversight burden on investigators and IRBs for lower-risk research.[2] These proposed changes, however, do not suggest any specific regulatory changes that would affect comparative effectiveness research—specifically, the increasing body of work in comparative clinical effectiveness research (CCER) that, as described by the Patient Centered Outcomes Research Institute, compares the relative effectiveness and safety of alternative preventive, diagnostic, or treatment options.[3]

Such CCER studies often involve comparing widely used, US Food and Drug Administration (FDA)–approved therapies or diagnostic tools, with the goal of assisting patients and clinicians in making health care decisions.[4] Other high-priority CCER studies assess the health effects of clinical practices that have been widely adopted by clinicians, despite limited evidence about the risks and benefits. As highlighted in a federal call for grant applications, significant advances in CCER will depend on reducing the intensity and burden of oversight for human research participants in prospective clinical studies that compare the benefits and risks of interventions in common clinical use.[5]

The majority of the proposed changes in the ANPRM are sensitive to this concern that regulatory protections should not be overly burdensome. These changes seek to identify categories of research requiring less oversight, thereby "reducing burden, delay, and ambiguity" while allowing IRBs to focus on studies that "could seriously harm subjects." A significant proposed change is to "excuse" from IRB review altogether all survey, interview, and focus group research as well as, potentially, what the ANPRM describes as "social and behavioral research . . . involv[ing] . . . benign interventions . . . for which prior review does little to increase protections to subjects"—eg, some low-risk behavioral and social science interventional research.[1] The ANPRM notes that IRBs "have a tendency to overestimate the magnitude and probability of reasonably foreseeable risks"; thus, eliminating these studies, which typically pose minimal risk, from IRB review allows committees to concentrate on categories of research posing greater ethical concern. As noted in the ANPRM, this is consistent with recommendations from the Institute of Medicine that "The degree of scrutiny, the extent of continuing oversight, and the safety monitoring procedures for research proposals should be calibrated to a study's degree of risk. Minimal risk studies should be handled diligently, but expeditiously, while studies involving high risk should receive the extra time and attention they require."[6]

The failure of the ANPRM to address CCER specifically in its discussion of expedited or what the notice proposes calling "excused" research serves to perpetuate the view that all clinical research, of which clinical comparative effectiveness studies are a variant, involves more than minimal risk. In so many types of CCER, however, studies generally pose no or only minimal additional risks or burdens to patients over what patients would experience in clinical care. Although comparative effectiveness or patient-centered outcome studies using retrospective data analysis already are subject to minimal oversight, it seems that many prospec-

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tive studies of comparative effectiveness are of a low risk equivalent to that posed by many behavioral and social science research studies. Consider, for example, a prospective observational study comparing clinical outcomes among patients beginning treatment for hypertension with the choice of drug therapy determined by the clinical judgment of their physicians. Data available from patients' electronic health records are to be augmented by prospectively requesting patients to respond at regularly scheduled clinical appointments to a more detailed set of questions about lifestyle than would generally be expected under usual clinical practices. The ANPRM is silent as to whether an IRB may treat such a CCER study as it would a social science survey or would otherwise consider the study eligible for streamlined or minimal oversight. The ANPRM proposes creating a list of "categories of research" that should be eligible for "expedited review," thus "providing for streamlined document submission requirements for review." From the standpoint of risk or burden to patients, it is difficult to distinguish how such a project is fundamentally different from the kinds of research the ANPRM is proposing to "excuse" from IRB review and approval.

More complicated are whether some real-world, pragmatic clinical trials—also a prominent method for CCER—might be appropriate for streamlined IRB oversight, including, in some circumstances, waivers of written consent requirements.[7-9] Consider, for example, a pragmatic trial comparing 2 FDA-approved and widely used drugs, each of which has a significant evidence base of both clinical safety and effectiveness and each of which is well tolerated by most patients. It is not clear that patients participating in this trial would incur any additional clinical risk beyond what they would experience outside the trial. Indeed, the recent trend toward promoting the conduct of such CCER studies in practice settings, where patients are treated by their regular physicians,[10] who are free during the trial to change doses or drugs based on their clinical judgment, underscores that research of this type may pose minimal additional burden and risk to patients. In failing to address this type of low-risk research, the ANPRM may unintentionally reinforce the tendency of IRBs to consider all prospective clinical research—and certainly all prospective randomized research—as being of inherently higher risk, even with these low-risk designs.

A key unresolved question is whether random assignment is of sufficient distinctiveness to always be classified as "greater than minimal risk research" and thereby warrant full committee (rather than expedited or excused) review. For example, should the "greater than minimal risk" standard (and full committee review that follows) always be required for trials evaluating widely used and well-tolerated interventions and during which physicians can switch a patient's therapy at any time? There is no additional risk or burden to patients, and the quality and experience of patient care are minimally affected. It is perhaps too early in the collective experience of CCER to warrant a change to the Common Rule that would exempt trials that involve (only) initial random assignment from full IRB review or to allow waivers or modifications from requirements for full, prospective, signed informed consent.

It is not too soon, however, for changes to the Common Rule to include appropriate allowances for the increasing number of prospective observational clinical comparative effectiveness studies that can be anticipated. The ANPRM is the first significant proposed change to the Common Rule in 20 years; another such opportunity is not likely to emerge anytime soon. The timing of the reconsideration of the Common Rule with the rapid increase in investments in comparative effectiveness research highlights the importance of seizing this opportunity to advance the shared interests in ensuring that CCER evolves rapidly and ethically. Crafting a framework that promotes an appropriate level of oversight for CCER studies that closely simulate routine clinical practice will be essential for the efficient generation of the real-world evidence that patients and clinicians require.

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Keynote – REACT Trials

bmj.com
- Research: Implementation and adoption of nationwide electronic health records in secondary care in England (*BMJ* 2011;343:d6054)
- Editorial: Implementation of an electronic health record (*BMJ* 2011;343:d5887)

Pragmatic randomised trials using routine electronic health records

What to prescribe for a patient in general practice when the choice of treatments has a limited evidence base? **Tjeerd-Pieter van Staa and colleagues** argue that using electronic health records to enter patients into randomised trials of treatments in real time could provide the answer

Ten years ago, in a paper called *Britain's Gift*, the then editor of the *BMJ* and the director of the UK Cochrane Centre outlined a vision of medicine for the 21st century: easy access to good quality reviews of clinical evidence, and the streamlined recruitment of patients into randomised trials as a matter of routine whenever there is uncertainty about choice of treatment.

"For example," they explained: "we still do not know which treatments are useful for acute stroke, but if every patient in the world experiencing a stroke were admitted to trials we would have enough patients within 24 hours to answer many of these questions."[1]

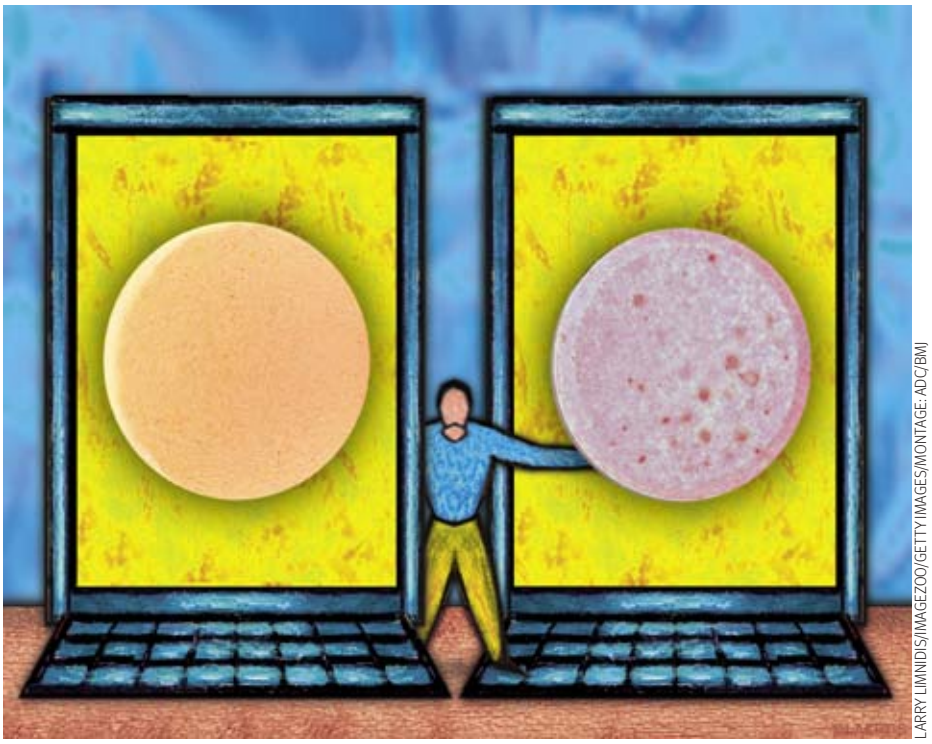
The first goal of easy access to good quality reviews of evidence is on its way to being realised. Trials, however, remain exceptional in everyday clinical care, and sometimes address comparisons that are irrelevant to doctors and patients because they compare new treatments with placebo rather than with the best treatments currently available. Furthermore, trials are often conducted in idealised or unrepresentative patient groups.[2] Because of these problems, randomised trials commonly fail to inform decisions in everyday clinical care: they address the abstract question of an intervention's efficacy under ideal conditions, rather than its effectiveness when used in usual clinical practice, on outcomes that are important to patients.[3 4]

Here we describe a UK project to implement randomised trials as unobtrusively as possible in the everyday clinical work of general practitioners (GPs), comparing treatments that are already in common use, and using routinely collected electronic healthcare records (EHR) both to identify participants and to gather results. We discuss the rationale for this approach, the potential for improving clinical evidence at low cost, and the barriers encountered.

Opportunities for using EHR data for randomised trials

Reports from both the Council for Science and Technology[5] and from the Academy of Medical Sciences[6] in 2005 and 2006 highlight the potential of EHR data for translational health research, and research with EHR data has been recognised as a key activity in the Department of Health's national health research strategy.[7] Healthcare records are routinely stored on computers in UK general practice (most people in the UK are registered with a general practitioner). Some GP databases can now be linked anonymously to other healthcare datasets, including hospital admissions records, death certificates, and disease registries. This record linkage system has been implemented within the general practice research database (GPRD) used in the trials presented here, and could be implemented more widely. It allows long term, anonymous, unobtrusive follow-up for major clinical outcomes, at low cost, and with no extra time burden for the clinician, health service, or patient.

Conventional trial recruitment is often problematic, with many trials failing to meet their recruitment targets.[8] The EHR database may also be used to recruit patients into trials: it is searched to compile a list of potentially eligible



LARRY LIMNIDIS/IMAGEZOO/GETTY IMAGES/MONTAGE: ADC/BMJ

Table 1 | Research questions, interventions, and measurements in two feasibility REACT trials initiated within the GPRD

RETRO-PRO: the effectiveness of simvastatin compared to atorvastatin—a feasibility study (ISRCTN33113202)	
Research questions	Feasibility of REACT trials; pilot for comparative effectiveness of simvastatin and atorvastatin in patients with primary hypercholesterolaemia and high cardiovascular disease risk
Intervention	Randomisation between simvastatin and atorvastatin in 300 patients; non-blinded
Outcome measures	Recruitment rates and technical challenges; changes in lipid levels at three months; duration of statin treatment over time; long term incidence of myocardial infarction, stroke, and death (as measured in the GPRD, linked hospital data, disease registry data, or death certificates)
eLUNG: the effectiveness of antibiotics compared to no antibiotics for exacerbations of chronic obstructive pulmonary disease: a feasibility study (ISRCTN72035428)	
Research questions	Feasibility of REACT trials; pilot for comparative effectiveness of antibiotics in patients with an exacerbation of chronic obstructive pulmonary disease and non-purulent sputum
Intervention	Randomisation between antibiotic (whichever the general practitioner uses as first line) or usual care in 150 patients; non-blinded
Outcome measures	Recruitment rates and technical challenges; patient diary over four weeks of the exacerbations of chronic pulmonary disease tool (EXACT-PRO) as completed on an electronic device; hospital admission over three months (as measured in GPRD and linked hospital data); long term incidence of mortality (as measured in GPRD or linked death certificates)

patients, which is sent securely to the clinician's desktop computer. When a patient on the eligibility list attends the practice for events related to the trial, a flag appears on screen to notify the clinician that the patient may be eligible for recruitment, with a link to the study website. If patient and clinician agree to participate and the GP confirms eligibility, the patient is randomised.

Table 1 outlines the research questions, interventions, and measurements in the first two feasibility trials for the randomised evaluations of accepted choices in treatment (REACT) trials that we are initiating. For these projects, there are daily downloads of GP EHR into the GPRD. The trial database can be compared periodically to the full research database for fraud detection and generalisability of the randomised population.

A key requirement for the REACT trials is that so called usual conditions apply as far as possible. Application of usual conditions is important to ensure external validity, and also to promote recruitment and retention: incompatibilities between the protocols for randomised trials and usual clinical practice can act as a barrier to recruitment.[8] The studies we have outlined are open label and non-blinded, with patients' progress monitored as usual in clinical practice, and these follow-up data extracted from the EHR. The only added feature in pragmatic randomised evaluations is that, among currently accepted treatments where there is no evidence on comparative effectiveness, treatment choices are based on random allocation rather than on arbitrary decisions by clinicians.

Such uncertainty in choice of treatments remains common. For many treatments in common use there is no evidence to inform choice between available options, and, for most new medicines, evidence based assessment of any added therapeutic value is not published at the time of market authorisation.[9] The UK database of uncertainties about the effects of treatments (DUETs) was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable, up to date, systematic reviews of existing research evidence.[10] Where there is no evidence comparing two commonly used treatments for the same condition, clinicians and patients have no way of knowing which is the more effective. In these circumstances, treatments are chosen arbitrarily, through a non-scientific, haphazard process. Treating patients in this arbitrary manner generates no new evidence to improve clinical practice.

It is unclear how a trial presents extra risk, where the randomisation is between two routine treatments already in widespread use, and with no evidence presently available to inform a choice between them

Where there is no evidence to guide the decisions of doctors and patients, it is ethically acceptable and actively desirable to offer willing patients the option of randomisation to assess which treatment is preferable. General Medical Council guidance requires doctors to resolve uncertainties about the effects of treatments,[11] and good medical practice requires that doctors communicate evidence clearly to patients. Randomisation with systematic data collection is the most rational and ethical way to resolve uncertainties.[12 13] Embedding randomised evaluations within usual clinical practice can achieve this goal, and increase the likelihood that clinicians will declare honestly to their patients when there is uncertainty about the relative merits of alternative treatment options.

In principle, as an ultimate goal, in every situation where there is genuine uncertainty about which of two or more widely accepted treatments is best, all willing patients could be offered randomisation as part of routine clinical care, and their progress followed up through EHR. If comparisons of accepted treatments could be conducted within the routine clinical practice setting in this fashion, the benefits would be considerable in terms of new evidence, and cost effectiveness in research.[14]

Challenges with using EHR data for randomised trials

The REACT approach does, however, face substantial challenges (table 2 lists opportunities and challenges, with strategies to address them, for REACT trials conducted within EHR databases). Firstly, and most importantly, are current norms in research governance. The requirements for informed consent and regulatory oversight in all trials are time consuming and expensive, even for trials comparing two interventions that have already been shown to be safe and are in widespread and routine use. This is a problem that has raised concerns over almost two decades.[15] Clinicians who admit there is uncertainty in a choice between two interventions, and wish to address the uncertainty by offering treatment in the context of a randomised evaluation, are subject to intense regulatory scrutiny. Yet during routine clinical care—in situations where there is no comparative effectiveness research to guide treatment choice, so that decisions are equally arbitrary—no such constraints apply.[12] Experimentation by politicians on the delivery of health services also does not suffer from this intense regulatory scrutiny.[16]

Several justifications have been suggested for so called research exceptionalism—the phenomenon whereby more stringent rules are applied to research than to usual clinical practice, even for treatments in widespread use. One frequently raised justification is that research does not in general specifically aim to benefit the participants, but rather to generate knowledge; study participants may take the risks while others accrue the benefits.[17] However, this justification often does not apply to patients with chronic conditions, whose treatment next year may well benefit from knowledge gained in the randomised evaluations they participate in today. It is also unclear how a trial presents extra risk, where the randomisation is between two routine treatments already in widespread use, and with no evidence presently available to inform a choice between them. This asymmetrical approach to regulation can be traced back to the establishment of the Declaration of Helsinki[18] following the Nuremberg war crimes trials.[16] Informed consent is fundamental to medical ethics, but the regulations designed to prevent abuse were never intended to prevent evaluation of safety in routine practice.

Table 2 | Potential opportunities and challenges with REACT trials conducted within EHR databases

Opportunities	Challenges
Long term follow-up at low cost—EHR database and linked datasets can be used to follow study participants over the long term for major clinical outcomes and mortality	Ethical and regulatory approvals—Approval has been achieved for pilot studies; risk adapted regulatory processes may expedite approval for trials of routine treatments in future
Easy identification of eligible patients—Candidates are identified automatically through the EHR database from a pool of all patients: clinician is alerted when a patient they are treating meets eligibility criteria	Lengthy consent process—Ongoing research is necessary into the optimum length of consent processes for informed patients; current practice will adversely affect recruitment of clinicians and patients
Highly representative study populations—Randomisation at point of routine care means safety and effectiveness of intervention is assessed in usual clinical practice	Research approval at multiple local sites—Different regions have varying requirements for research approval, which is resource intensive
Representativeness is measurable—Study population can be compared to patients not enrolled in the trial	Availability of desired outcome data in EHR—Feasibility of collecting additional patient outcome data being assessed (eg, an electronic diary); REACT trials not suited for studies that require major study specific data collection
Adverse event monitoring—Daily transfer of EHR records into database: (i) analyses in trial centre of suspected unexpected serious adverse reactions; (ii) comparisons of event rates with those in patients not enrolled in trial	Data quality of EHR data—Recruitment can be restricted to patients with baseline completeness of key covariates; linkages to external data sources permits validation; outcomes can be restricted to outcomes well recorded in EHR
Evaluation of research questions of direct relevance to clinicians—Trials only of treatments already in routine use	Trial drug supplies—Research focus is on current therapies prescribed as usual by clinicians: no special supplies needed
Validation of major clinical outcomes—Confirmation of outcomes through the linkages and/or by the patient's clinician; blinded review of complete EHR by experts	Compliance with conventional good clinical practice (GCP) quality standard requirements—With electronic records, there is no difference between data held centrally and locally; a review is ongoing into optimum scrutiny methods for dispersed electronic trials
Recruitment for rarer conditions—Multiple sites offer a broader pool of potentially eligible patients	Clinician training in protocol and GCP—Online GCP training package is provided for participating GPs
Adaptive designs—Potential to incorporate minimisation during treatment allocation	Clinician time to recruit patients—New IT systems and strategies minimise time and disruption; qualitative research of participating GP feedback is ongoing
Testing of study strategies—Cluster randomisation of sites will allow evaluation of study strategies (such as method of collection of additional data)	Lack of blinding of treatment allocation—REACT trials are best suited to measuring major clinical outcomes with clear diagnostic criteria (such as death)
Fraud prevention—Newly registered patients not eligible; eligibility and recruitment checks all recorded in the trial IT system; strategy to recruit few patients at many sites	Crossover of study treatments over time—A challenge in most long term trials; crossover may be outcome of interest (indicating treatment failure); statistical techniques may partly deal with this
Fraud detection—Clinical records of participants before and after the trial are available to the trial investigators; outcomes from linked external sources not controlled by local investigators (such as hospital episodes, mortality register)	Local prescribing rules and performance indicators—GPs may operate under mandatory or incentivised prescribing rules, without any exception for research studies
Reduced loss to follow-up—Linkages will ensure that outcomes leading to hospitalisation or death will be captured, even after a patient has left study site	Poor recognition of uncertainty by clinicians—If clinicians are unaware that current practice lacks good quality evidence this may be a challenge for recruitment
Linkage of patient data to EHR—Information collected by patients (eg, using smart devices or electronic diaries) could be linked to outcome data recorded in EHR	Uncertainty faced by clinicians not recognised by researchers or funding agencies—Clinicians need to be involved in setting a relevant research agenda

In the REACT trials no new risks are introduced, but the alternative—the current situation—has demonstrable ethical problems. Good quality evidence to improve patient care cannot be reliably generated from arbitrary treatment decisions made in usual clinical practice, and patients may continue to suffer through being exposed to interventions that are later found to be inferior. Furthermore, where there is uncertainty clinical decisions are often made without fully acknowledging their arbitrariness to patients.

The extent to which research exceptionalism will restrict the benefits of the REACT trials is not yet clear. All consent forms currently cover a great deal of information normally not provided when the same treatments are routinely given outside a randomised evaluation, and are extremely time consuming to complete. UK government guidelines presently recognise that one size will not fit all with respect to the information that is required to make autonomous decisions.[19] However, the guidelines also state that all randomised trials must comply with the good clinical practice quality standard, and this includes a list of 22 different topics to be covered in the information sheet.[20] Research ethics committees may further add to this barrier, often including idiosyncratic administrative requirements, such as a duty on participants to inform a private health insurer (as happened in our trials).

We have concerns over these barriers to research on routine treatments, which will reduce recruitment of clinicians and patients. Requirements for informed consent should ideally be based on empirical evidence on what kind of process best informs participants, and be designed in collaboration with patients. However, the good clinical practice quality standard, which has come to be viewed as canonical, was based on expert opinion, and has little empirical evidence. A systematic review has found that evidence for the optimal amount of information to enhance patient understanding is inconclusive and limited.[21] UK government guidelines state that "any researcher is faced with considerable difficulty" in selecting information for informed consent, "given the disagreement on how much information potential participants in research want."[19] There are also frank contradictions. For example, the guidelines recommend that draft versions of patient information sheets should be passed to patients in disease support groups for comments. But the same guidelines also require that all informed consent procedures in trials must adhere to current good clinical practice requirements,[19] which mandate extensive content,[20] so support groups are prevented from reducing information overload, for example, should they recommend this in their comments.

This extra burden may reduce recruitment and retard research throughout clinical medicine. The largest review conducted on strategies to improve trial participation found that concerns about extra effort and workload are barriers to recruitment for both doctors and patients.[22] The review also recommended that trials should be framed and organised in ways that minimise differences between research and clinical practice, using simple and clear entry criteria, and address questions of clear relevance to clinical practice.[22]

A second major challenge of using EHR data for trials is data quality, which is of paramount importance. The REACT trials will not be suited to evaluating every type of research question. A study requiring detailed, study specific data collection at regular intervals may not be best suited to a trial using EHR data. There may also be specific outcomes that a trialist would prefer to measure that are not routinely collected in EHR. However, by definition many major outcomes are recorded in routine medical notes. Furthermore, mortality and other major clinical outcomes can now also be measured in EHR databases, and then verified across several other data sources. As an example, a heart attack in the REACT trials can be measured in the

GPRD, linked hospital data, disease registries, and death certificates (if fatal). Where there is doubt, the patient's clinician can also be asked to confirm a diagnosis for an outcome of interest.

Current progress of REACT trials

The first two REACT trials have recently been approved by the research ethics committee, along with a qualitative study that seeks feedback from GPs and patients to assess and improve the implementation. The main point of discussion by the committee was our proposed consent form. The original one page patient information draft submitted for ethical review was considered by the committee to be the "skimpiest ever" and missing much of the standard clinical trial information (the informed consent template of the UK National Research Ethics Service lists a large number of items to be covered). We resubmitted the patient information sheet, now twice the length and amended to meet only the minimum ethics committee requirements. It could be argued that the single most important consideration for informed consent in the REACT trials should be the replacement of clinicians' uncertainty with randomisation. After all, the patient could have received any of the interventions in a REACT trial by consulting another clinician.

The IT system has taken considerable time to develop and is currently undergoing testing. Once implemented, the system will provide instantaneous trial recruitment and daily analysis of EHR data that can easily be adapted to future studies. GP recruitment is also continuing. Of English GPRD practices, 42% approached have expressed interest and 15% declined (recruitment in Scotland has just started). Together with recruitment by the Primary Care Research Network, we now have over 200 interested practices, and study details (protocol and contract) have now been sent to practices.

The main challenge now will be to obtain research and development approvals from the 150 local NHS bodies that cover UK general practices. Our experience with a GPRD cluster trial[23] and pharmacogenetic study found that this takes enormous effort and time, even for low risk studies, replicated at multiple sites, and often with differing systems. Our goal of maximising representativeness is achieved by recruiting at multiple sites with few patients in each, so such fragmented and diverse local administrative systems present a challenge. Finally, the project also has undertaken a review on how best to comply with the good clinical practice quality standard, since this dispersed model with electronic data collection means that site visits for scrutiny are of very limited value.

Conclusions

EHR databases contain a wealth of information, and their utility for randomised evaluations should be fully exploited. A revolution is long overdue in the technical and research governance frameworks for testing widely used interventions whose relative merits are unknown. Narrowly restricted studies with questionable external validity need not be the norm. Our suggestion for large scale randomisation in usual clinical practice may face several challenges, some of them technical, but most of them related to research governance procedures. We hope that these barriers will be overcome, by providing proof of concept for a streamlined simple framework for undertaking REACT trials, in which recognition of widespread uncertainties about the effects of treatments will motivate clinicians and patients to participate in randomised evaluations as a matter of routine.

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TRIALS

STUDY PROTOCOL Open Access

Cluster randomised trial in the General Practice Research Database: 1. Electronic decision support to reduce antibiotic prescribing in primary care (eCRT study)

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Abstract

Background: The purpose of this research is to develop and evaluate methods for conducting cluster randomised trials in a primary care database that contains electronic patient records for large numbers of family practices. Cluster randomised trials are trials in which the units allocated represent groups of individuals, in this case family practices and their registered patients. Cluster randomised trials often suffer from the limitation that they include too few clusters, leading to problems of insufficient power and only imprecise estimation of the intraclass correlation coefficient, a key design parameter. This difficulty might be overcome by utilising databases that already hold electronic patient records for large numbers of practices. The protocol describes one application: a study of antibiotic prescribing for acute respiratory infection; a second protocol outlines an intervention in a less frequent chronic condition of public health importance, stroke.

Methods/Design: The objective of the study is to implement a cluster randomised trial to test the effectiveness of an electronic record-based intervention at achieving a reduction in antibiotic prescribing at consultations for respiratory illness in patients aged 18 and 59 years old in intervention family practices as compared with controls. Family practices will be recruited from the practices that presently contribute data to the UK General Practice Research Database (GPRD). Following randomisation, electronic prompts will be installed remotely at intervention practices to promote adherence with evidence-based standards of medical practice. The intervention was developed through qualitative research at non-intervention practices. Data for outcome assessment will be obtained from anonymised electronic patient records that are routinely collected into GPRD. This protocol outlines the proposed study designs, data sources, sample size requirements, analysis methods and dissemination plans. Ethical issues are also discussed.

Discussion: Results from this study will provide methodological evidence concerning the use of electronic patient records and databases for implementing cluster randomised trials in primary care. The study will also provide substantive findings in respect of electronic record-based interventions to reduce antibiotic prescribing in primary care.

Trial Registration: Current Controlled Trials ISRCTN 47558792.

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Background

This protocol aims to develop an application of electronic patient records to the evaluation of health interventions, including their health impacts and effectiveness. We aim to provide 'proof of concept' of the feasibility and utility of implementing cluster randomised trials utilising electronic patient records in a large national primary care database. The specific objectives of the proposal are to develop, and confirm the feasibility of, a resource efficient method for implementing cluster randomised trials in public health and health services research by implementing a cluster randomised trial in a primary care database using routinely collected electronic patient records to evaluate patient outcomes. There will be two interventions that will build on our previous research; one application is in a common acute condition - antibiotic prescribing in respiratory illness; the other is in a less frequent chronic condition of public health importance - stroke. This protocol only concerns the intervention on antibiotic prescribing in respiratory illness. The research will provide guidance for the future conduct of cluster randomised trials using electronic patient records.

In cluster randomised trials, entire areas or health service organisational units are allocated to intervention or control groups, with outcomes evaluated for individuals within each cluster [1]. Cluster randomised trials (CRTs) are increasingly utilised in public health and health services research and are especially important in the evaluation health service and public health interventions [2]. CRT designs may be used to avoid problems of contamination. CRTs also facilitate pragmatic evaluation of the effectiveness of interventions delivered in routine practice settings. In addition, CRTs allow estimation of cluster level elements associated with the efficacy of the intervention. However, compared with studies in which an equivalent number of individual subjects are allocated, CRTs generally have reduced power because of the correlation of individual responses within clusters. The extent of such clustering is not easy to anticipate [1]. Another difficulty is that only small numbers of clusters may be allocated in CRTs because recruiting, intervening in, and collecting data from clusters may be costly [3].

In this proposal, we suggest that these difficulties may be overcome, to a certain extent, by implementing CRTs within the General Practice Research Database (GPRD), a primary care database that includes records from large numbers of practices. The database will provide a sampling frame for the study, it will also provide a mechanism for the electronic capture of data that describes case-mix at baseline and outcome measures pre- and post-intervention. This will be done by randomising, intervening in, and analysing data from family practices already contributing their electronic patient records to the database. The GPRD offers an excellent pre-existing sampling frame with large numbers of practices covering 5% of the UK population [4,5]. Studies conducted in the GPRD should have good external validity, covering a range of geographical and demographic settings and levels of risk. The GPRD also offers ongoing data collection for baseline and outcome measures for all registered patients, offering the potential to implement studies with greater power at lower cost. GPRD can now be linked individually and anonymously to other National Health Service (NHS) datasets. Currently, 304 GP practices in England are participating in this linkage (about 50% of GPRD). Data from the Hospital Episode Statistics (HES) and National Death Certificates (with date and primary and secondary cause of death) will be used for this study.

The substantive application for the research is in antibiotic prescribing. The problem of resistance to antimicrobial drugs is growing and appropriate prescribing of antimicrobial drugs is of great public health importance [6]. Respiratory tract infections (RTI) account for some 300-400 consultations annually per 1000 registered patients [7] and up to 60% of all antibiotic prescribing in family practice [6]. Giving antibiotics to patients with RTIs is often motivated by a concern to meet patient expectations [8] but antibiotics do not provide clinical benefit in a majority of RTIs [6,9-11]. These illnesses are usually brief and self-limiting, complications are unusual even without antibiotics, [6,12] and antibiotics may promote the spread of resistant organisms [13]. GPRD-based research has shown that antibiotic prescribing for respiratory infections in primary care declined between 1995 and 2000, [7,14] but since 2000 antibiotic prescribing for respiratory illness has stabilised [15]. There is a need to develop and implement interventions that endorse evidence-based antibiotic prescribing in family practice [6]. The age range 18 to 59 has been selected for study because the perceived, and actual, risk of serious infective complications is lower than at the extremes of age.

Methods/Design

Objective

To implement a cluster trial in GPRD in a common acute condition. This study aims to test the effectiveness of an electronic record-based intervention at achieving a reduction in antibiotic prescribing at consultations for respiratory illness in patients aged 18 and 59 years in intervention practices as compared with controls.

Practices and allocation

Practices are being recruited through a letter of invitation from GPRD. A record will be maintained of the

numbers of practices approached, recruited and analysed. Since data for all practices are collected into GPRD, it will be feasible to compare participating and non-participating practices through analysis of anonymised data in GPRD.

GPRD practices are allocated by minimisation, stratifying for region and list size. Allocation is at KCL to ensure allocation is separated from the process of practice recruitment. Patients will be all registered patients aged 18 to 59 years. There will be no other exclusion criteria, so as to optimise both internal and external validity [16].

Intervention

Electronic prompts have been developed based on recommended clinical practice guidelines to be activated during consultations for RTI in the selected age range. The electronic prompts promote no antibiotic prescribing, or delayed antibiotic prescribing, instead of the immediate prescription of antibiotics for respiratory tract infections. The prompts specifically incorporate recommendations from the recent NICE guidelines on antibiotic prescribing in respiratory illness [6]. The research also builds on existing work that has identified barriers to reducing antibiotic prescribing [17-19] by designing prompts that briefly address common concerns (e.g. including messages providing evidence regarding likely consequences of delayed prescribing or not prescribing). During consultations with patients presenting with symptoms of respiratory tract infection, primary care professionals will see the prompts which remind them of recommended standards of care in RTI. The prompts will also provide them with supporting information and links to evidence that supports the recommendations, in a format suitable for printing out for patients when appropriate. The decision on whether to follow the treatment suggestions included in the prompt will be at the discretion of the GP. The GP will also be able to terminate display of the prompt at any time. There will be no intervention at control practices. The intervention phase will continue for 12 months at each practice.

The VISION software used by GPRD practices does not presently include any reminders on antibiotic prescribing, so the trial will compare outcomes associated with the new prompts as compared with care with no prompts.

Intervention development

Intervention requires the development of prompts that encourage primary care professional adherence with recommended processes of care. The first year of the project has included a workstream to develop appropriate interventions consistent with the initial phases of the MRC framework for complex evaluations [20]. The format and content of the messages to be used in the interventions have been developed by a multi-disciplinary grouping comprising the research team and primary care professionals. Interventions are grounded in theoretical models of behaviour change [21,22] and informed by pre-existing evidence including systematic reviews [23,24] and national clinical guidelines as well as qualitative research. The development process was used to explore the extent to which electronic prompts can be used not only to remind GPs of recommended behaviour but also to convince them it will be beneficial and assist them with implementation. Tape-recorded interviews were carried out with a maximum variety sample of GPs (N = 30) from local non-GPRD practices with a variety of characteristics, to identify factors likely to influence successful implementation, and to pilot messages that have been identified as most likely to positively influence prescribing behaviour [25]. Thematic analysis was used to determine the range of likely responses to the proposed intervention and messages, which were then iteratively modified as necessary. The development and design of the prompts are reported in detail by McDermott et al. [25]

Intervention implementation

Prompts will be downloaded automatically through the DXS Point-of-Care system. DXS (UK) Ltd collects data on usage of the information provided. In order to understand utilisation of the intervention, we will analyse fully anonymised practice-level data on usage of the electronic prompts that comprise the intervention.

Initial evaluation has shown that GPs may either begin their record of the consultation by initiating an antibiotic prescription, or by recording a medical code consistent with respiratory tract infection. The prompts are designed to be sufficiently flexible to be activated either by the start of an antibiotic prescription or by the specification of a medical code. 'Antibiotics' are defined as including all drugs in section 5.1 of the British National Formulary with the exception of anti-tuberculous and anti-leprotic drugs. Initially, prompt activation will be by means of medical codes.

Outcomes and analysis

Outcome evaluation will be through analysis of routinely-collected GPRD data during a defined study period, while historical information will be used to assess the baseline characteristics of the study patients. Information routinely collected into GPRD for all registered patients includes medical history, use of medicines, hospitalisations and other resource use, smoking history, laboratory tests, letters from specialists or hospitals. GPRD also now links patients in GPRD to the English

Hospital Episode Statistics, with detailed information on date, duration and reason for hospitalisation. Availability of data for all registered patients has potential to minimise biases from patient selection/recruitment.

Electronic patient records will be eligible for trial analyses if they describe patients who consult with acute respiratory tract infections, defined using pre-specified Read codes that identify conditions appropriate for study, and are aged 18 to 59 years at the date of the consultation. Pre-intervention GPRD analyses have already been reported [15]. Medical codes have been selected for RTIs including sub-groups of colds, rhinitis and upper respiratory infection; sore throat, pharyngitis and tonsillitis; influenza; laryngitis and tracheitis including croup and epiglottitis; acute sinusitis; otitis media and earache; acute bronchitis; and chest infection and pneumonia. The primary outcome will be the proportion of RTI consultations with antibiotics prescribed over 12 months; secondary outcomes will be age- and sex-specific rates of RTI consultation, age and sex-specific proportion of RTI consultations with antibiotics prescribed, and occurrence of RTI complications. We will use linked Hospital Episode Statistics (HES) data for English practices to evaluate hospitalisation with respiratory illness. Analyses will also be reported separately for each sub-group of RTI codes. In order to provide further insight into safety issues, family practices will be offered the opportunity to notify the study team prospectively of suspected adverse events, in fully anonymised format, during the course of the trial.

Outcomes will be measured through analysis of GPRD electronic prescribing records as described previously [14]. Antimicrobial drugs included will be those in British National Formulary chapter 5.1 excluding anti-tuberculous and anti-leprotic drugs. A maximum of one RTI consultation and antibiotic prescription on the same day will be analysed. Only first consultations within the same episode will be evaluated for the primary outcome, using a 10 day time window. Data for the intervention phase of the trial will be analysed from the intervention start date to 12 months later. Trial analyses will estimate the difference (95% confidence interval) in the proportion of RTI consultations with antibiotics prescribed between intervention and control groups after adjusting for age-group, sex, pre-intervention prescribing proportion. A cluster-level analysis will be implemented using the practice specific proportions as observations, with minimum variance weights to allow for varying numbers of consultations per practice [26].

Sample size calculation

The sample size calculation is based on a comparison between the intervention condition, in which the new prompts are present, and usual care, in which no prompts are present. A cluster-level analysis of the practice specific proportions will be implemented. The sample size calculation therefore estimates the number of clusters (practices) required for the study. In a systematic review, quality improvement interventions were associated with reductions in antibiotic prescribing of between 7% and 12% (Ranji et al., 2006). The study therefore aims to detect differences of less than 7%. The selected age-range comprises about 55% of the registered population with about 1,000 registered patients per general practitioner and about 4,500 patients per practice. In data from Gulliford et al. [15], the age-standardised rate of RTI consultations in the 18 to 59 years range was 280 per 1,000 in women and 146 per 1,000 in men in 2006. This suggests there will be about 959 RTI consultations per year, per practice. We observed 1166 consultations in 5,647 person years, [15] consistent with 932 consultations per year per practice. Assuming 10% of consultations may be second visits, there may be 850 eligible consultations per practice. The proportion of consultations with antibiotics prescribed in 2006 was approximately 39% for all RTIs, having declined from 44% in 1997 (unpublished data). We assume that the coefficient of variation of this proportion between practices is 0.23 from Ashworth et al. [14], with alpha = 0.05 and power = 0.8. From Hayes and Bennett [27] equation 4, to detect a 5% difference in the proportion of consultations at which antibiotics are prescribed, 47 practices per group will be required. To detect a 6% difference 32 practices per group will be required. The GPRD includes more than 400 practices and a recent questionnaire of 386 GPRD practices found that 68% (262) were interested in participating in clinical trials. We plan to include 50 practices per group.

Research ethics and governance

Hutton [28] suggests that consent in a cluster trial may be sought for three main reasons:

i) for the use of routinely held data;

ii) for the collection of additional data specifically for the study;

iii) for the offer or administration of an intervention.

The practices included in the present research already contribute anonymised electronic patient records to GPRD under an established governance framework. No additional data will be collected for this study at the individual patient level.

Implementing the interventions will require the randomisation of practices that are already participating in GPRD. Edwards et al. [29], and MRC [30] guidance on cluster randomised trials, distinguish two types of cluster randomised trials. Type A (or cluster-cluster) interventions are implemented for the whole cluster and consent is required at the cluster level from a guardian

or gatekeeper. This is in contrast to Type B (or cluster-individual) interventions that are implemented at the individual participant level. These require active recruitment of individual participants within practices with a requirement for informed consent at the individual participant level. In Type B studies, selection of individual participants subsequent to the randomisation of the cluster may represent a potentially serious form of bias.

In the proposed research covered by this application, the trial intervention will be implemented at the cluster (practice) level through a modification to the practice information system. In trials of cluster-level interventions, consent should be obtained from the guardian of the cluster (usually the senior partner) on behalf of the cluster members (registered patients) [29,30]. The guardian's consent is regarded as ethically justified if the expected utility associated with the trial intervention is greater than the alternative [29]. The proposed interventions will encourage primary care professionals to adhere to nationally agreed, evidence-based, standards of care. Electronic prompts will provide practitioners with additional information during the course of consultations. However, all clinical treatment decisions remain at the discretion practitioners and their patients. Although electronic prompts provide information and advice concerning recommended standards of care, practitioners and patients remain free to jointly negotiate a chosen course of action during each consultation.

Analysis of outcomes will be through the analysis of routinely collected and anonymised GPRD data at the individual patient level.

We have convened a Trial Steering Committee (TSC) and a Data Monitoring and Ethics Committee (DMEC) with Independent Chairs and two/three independent members for each committee. The study was approved by London Surrey Borders Research Ethics Committee (09-H0806-81) and by the MHRA Independent Scientific Advisory Committee on Database Research (ISAC) (08-083).

Discussion

Anticipated outcomes

This study will provide evidence concerning the feasibility of implementing CRTs using the electronic records of patients with both acute conditions. The research will specifically provide evidence concerning the effectiveness of a strategy based on electronic prompts at enhancing effectiveness of care.

Evaluation

As these studies will be among the first intervention studies implemented within GPRD, evaluation of the obstacles, barriers and facilitators to implementation of intervention research within GPRD will be an integral part of the study. We will evaluate views of staff at GPRD and practices using a questionnaire to ensure the anonymity of practices is maintained. Towards the end of the trial, an invitation email to complete an electronic evaluation questionnaire will be sent to all practices (both control and intervention groups). Fidelity of adherence with the intervention protocol, as well as feasibility and acceptability of interventions and trial participation, will be specifically addressed. Quantitative data will be supplemented by telephone interviews with a purposive sample to explore experiences of the intervention in more depth.

Reporting, dissemination and implementation

We will prepare interim reports as well as an end-of project report. We expect to publish our findings in peer-review journals and make presentations at scientific meetings and conferences. The methodology developed through this project will have wide potential for application in future research and we expect that dissemination efforts will also be facilitated by data providers including GPRD and other databases. A key output from the research will therefore be methodological advice that will identify and analyse the component tasks of implementing a cluster trial through electronic patient records.

Limitations

We recognise that the study will have limitations both with respect to the feasibility of the research and the validity of the results. One of the main purposes of the research is to evaluate the feasibility of conducting cluster trials in an electronic database. We will therefore document and report the processes of research that either facilitate or impede the conduct of these cluster trials. Cluster trials are susceptible to bias. However, the implementation of a cluster trial within an electronic database offers the opportunity to evaluate such biases because data may be analysed both for participating and non-participating practices. For example, the behaviour of professionals at control practices may be modified through their participation in the study even though they are not exposed to the intervention. This potential bias may be evaluated by comparing changes in practice at non-participating practices and participating control practices.

Abbreviations

GPRD: General Practice Research Database; HES: hospital episode statistics; KCL: King's College London; MHRA: Medicines and Healthcare products Regulatory Agency; NHS: National Health Service; RTI: respiratory tract infection.

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Authors' contributions
MG developed the idea and drafted the protocol; TvS, PL, MA, LY, JC and AG contributed to the design and implementation of the study and contributed to the protocol; AD contributed to the implementation of the study and contributed to the allocation process and analysis plan; GM was responsible for developing recruitment procedures; LM and LY with PL and MM were responsible for developing the trial interventions. All authors read and approved the final version.

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The authors declare that they have no competing interests.

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Policy Needs – Medical Product Regulatory Issues

Measuring the Incidence, Causes, and Repercussions of Protocol Amendments

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Drug development companies frequently amend finalized clinical trial protocols. Yet the incidence, causes, and impact of protocol amendments have never been quantified. Tufts Center for the Study of Drug Development (Tufts CSDD) conducted a study, in collaboration with 17 large and midsized pharmaceutical and biotechnology companies, examining more than 3,400 clinical trial protocols across development phases and therapeutic areas. Data on protocol characteristics, the number of amendments, the nature and incidence of changes per amendment, the causes of amendments, and the time and cost to implement amendments were among those analyzed. Tufts CSDD found that more than 40% of protocols were amended prior to the first subject/first visit, and one third of amendments were avoidable. Each amended protocol had an average of 2.3 amendments resulting in 4 months of incremental time to implement. Protocol amendments translate into significant unplanned expense and delays for research sponsors and unexpected burden for investigative sites. These findings underscore the substantial impact of protocol amendments on drug development efficiency and present an opportunity to realize substantial cycle time and cost savings.

Key Words
Protocol amendments; Protocol design; Protocol complexity; Protocol design changes

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INTRODUCTION

Amendments made to finalized clinical trial protocols are commonplace, but they are widely viewed as a nuisance, resulting in study delays and additional costs (1). Clinical trial protocols that have undergone a rigorous internal review and approval process are often changed for a variety of reasons, including revisions to subject eligibility criteria; requests for modification from regulatory agencies, institutional review boards (IRBs), or ethical review boards (ERBs); the addition of new countries due to poor recruitment; the availability of new safety information; the introduction of new standards of care for a given illness; or typographical errors and clarifications in procedural descriptions.

Clinical research professionals perceive protocol amendments as a major problem, but it is perhaps more accurate to view amendments as solutions to underlying problems. These include the growing pressure to collect more data during clinical trials, increasing difficulty in recruiting study volunteers, and intensifying pressures that sponsors face in initiating and completing clinical trials within ambitious time frames (2).

Despite the widespread practice of amending protocols, very little is known about the incidence and cause of amendments, and their economic and operating impact. Wise and Drury (3) found that 45% of 100 general, practice-based multicenter research protocols submitted to the ethics committee of the Royal College of General Practitioners were amended. The authors noted that on average, each of the amended protocols had 1.5 changed items. Study volunteer compensation, incomplete informed consent forms, new safety requirements for pregnant volunteers, and inadequate and imprecise scientific content were major reasons cited for amending the protocols.

A study conducted by Losch and Neuhauser (4) showed that protocol amendments related to study volunteer eligibility criteria have a significant impact on statistical methods analyses. The authors demonstrated that protocol amendments change the population sampling and diminish the power of statistical tests performed.

A 2008 study conducted by the Tufts Center for the Study of Drug Development (Tufts CSDD) found a positive association between protocol complexity and the incidence of amendments (2). Less complex protocols—those containing fewer procedures and eligibil-

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ity criteria—averaged two amendments; more complex protocols, in contrast, averaged 3.2 amendments (5).

As a follow-up to that study, and in response to the dearth of quantitative data on the incidence, causes, and impact of protocol amendments, Tufts CSDD convened a group of pharmaceutical and biotechnology companies to share protocol amendment data. The results of this study highlight the substantial impact of protocol amendments on drug sponsors and clinical sites, offer ways to better anticipate and plan for protocol amendments, and suggest opportunities to reduce, and even prevent, the use of certain protocol amendments in the future.

METHODS

Seventeen midsized and large pharmaceutical and biotechnology companies participated in this study: Amgen, Astellas, AstraZeneca, Biogen Idec, Cephalon, Forest, Genentech, Genzyme, Lilly, Merck, Millennium, Otuska, Pfizer, Roche, Schering-Plough, Sepracor, and Takeda. Representatives from these companies worked collaboratively with Tufts CSDD to develop the data collection instrument, and then engaged their staff to complete the data collection instrument.

In January and February 2010, each participating company submitted its data on protocols approved internally between January 2006 and December 2008. Protocols approved within the most recent 12 months were excluded from the study to allow enough time for protocols to accumulate amendments. Data from 3,410 protocols were submitted across a wide and representative range of therapeutic areas, providing detailed data on 3,596 amendments containing 19,345 total protocol modifications.

For this study, amendments were defined as any change to a protocol requiring internal approval followed by approval from the IRB, ERB, or regulatory authority. Only implemented amendments—that is, amendments approved both internally and by the ethics committee—were counted and analyzed in this study.

Tufts CSDD staff analyzed both protocol design characteristics and protocol amendment descriptive and impact measures. With respect to protocol design characteristics, data on the number of amendments, indication (therapeutic area and disease), molecule type, study phase, treatment duration, planned and actual study size (number of subjects, number of sites, and regions where the study was conducted), level of outsourcing (whether various study components were conducted in house, partially outsourced, or fully outsourced), and cycle time milestones (protocol finalized by sponsor; first patient, first dose; last patient, last visit; and final database lock) were collected and analyzed.

Measures on amendment incidence and impact included the total number of amendments, total changes made per amendment, and classification of each change based on which part of the protocol it affected (see Figure 1). In total, 6,855 changes were categorized. Additionally, companies provided data on key cycle time metrics related to implementing each amendment (eg, date problem first identified; date work on amendment began; date revised protocol received internal approval; date revised protocol was submitted to, and approved by, first IRB; date first patient resubmitted under revised protocol; date study halted; and date study began again); external sources used in writing the amendment and in supporting problem resolution; study volunteers enrolled (before and after amendment implementation); patient recruitment rates (before and after amendment implementation); and the cost to implement each amendment including internal resources required to prepare and execute resolution.

In assessing the reasons why amendments were written, companies were asked to subjectively categorize each protocol amendment cause. Classification categories were developed by the participating companies (see Figure 2) based on their collective internal assessments of causes. In total, companies categorized the causes for 2,768 amendments. Next the company representatives mutually agreed on rating those cause categories in terms of whether each was "completely avoidable," "somewhat avoid-

Which part(s) of the protocol did this amendment change?
(Please choose up to three of the most important changes for this amendment.)

- General information (including protocol title, affiliated names, and addresses)
- Name and description of product
- Findings from nonclinical studies
- Risks and benefits
- Route of administration, dosage, or dosage regimen
- Dosage form, packaging, or labeling
- Compliance statement
- Population description (including inclusion and exclusion criteria)
- Medications permitted before/during the trial
- Background literature
- Trial objectives and purpose
- Endpoints
- Type/design of trial
- Measures to avoid bias (including randomization and blinding)
- Duration of subject participation, treatment, or follow-up
- Stopping rules or discontinuation criteria
- Randomization codes
- Subject withdrawal criteria
- Procedures for monitoring compliance
- Efficacy assessment
- Safety assessment
- Statistical methods and analysis
- Sample size
- Trial termination criteria
- Quality control and quality assurance
- Ethics
- Data handling and record keeping
- Financing and insurance
- Publication policy
- Supplemental materials
- Typographical correction

FIGURE 1

List of areas that the amendment changed in the protocol.

able," "somewhat unavoidable," or "completely unavoidable."

Tufts CSDD conducted all data analyses using SAS 9.2 (Cary, NC). Descriptive statistics as well as correlational analyses (ie, Spearman's rho) were performed. Analyses examining the causes of amendments used only the primary or top-ranked cause; that is, companies were asked to rank order the top three causes of each amendment, but analyses only used the cause ranked most important. Mean values were compared for each measure by trial phase, therapeutic area, and whether the protocol was in progress or completed, with the last defined by the date when the final database was locked.

RESULTS

Tufts CSDD collected data from 3,410 protocols. Those that specified study phase were distributed as follows: 1,640 (54%) were phase 1 studies; 560 (18%) were phase 2 studies; 397 (13%) were phase 3 studies; and 466 (15%) were phase 3b/4 studies. In addition, data from 3,596 amendments were analyzed. For those protocols that specified study phase, 41% of amendments were associated with phase 1 study protocols, 47% with phase 2 and 3 study protocols, and the remainder with phase 4 study protocols. Companies were able to provide data for almost all protocols in the study time frame, with an additional 145 protocols and 1,149 amendments identified that met the inclusion criteria but were not submitted. Characteristics of the sample data analyzed are presented in Table 1.

Protocol data submitted are also representa-

What caused this amendment?
(Please rank up to three of the most important causes of this amendment, with 1 being the most important and 3 being the least important.)

- New data available (other than safety data)
- New safety information available
- Change in standard of care
- Regulatory agency request
- Recruitment difficulty
- Manufacturing change
- Investigator/site feedback
- Change in study strategy
- Protocol design flaw
- Inconsistency and/or error in protocol

FIGURE 2

List of amendment causes.

TABLE 1

Characteristics of Submitted Data

	Protocols		Amendments	
	n	%	n	%
Total	**3,410**		**3,596**	
Study phase				
1 Healthy volunteers	1,060	31	710	20
Patients	333	10	507	14
Unspecified	247	7	242	7
2 Proof of concept	103	3	199	6
Dose ranging	51	1	117	3
Proof of concept and dose ranging	2	0	3	0
Unspecified	404	12	577	16
3	395	12	756	21
3b/4	466	14	441	12
Therapeutic area				
Central nervous system/neuropsychological	744	22	807	22
Oncology	580	17	848	24
Endocrinology/metabolism	487	14	624	17
Cardiovascular	393	12	247	7
Anti-infective	255	7	220	6
Respiratory	174	5	102	3
Pain/anesthesia	171	5	145	4
Immunomodulation/anti-inflammatory	165	5	203	6
Genitourinary system	121	4	111	3
Gastrointestinal	94	3	71	2
Hematology	43	1	73	2
Other	109	3	114	3
Study status				
Complete[a]	1,315	39	1,266	35
In progress	468	14	812	23

[a]Complete is defined as past final database lock.

tive of typical protocols designed and administered by pharmaceutical and biotechnology companies each year. Table 2 provides the median number of sites and subjects recruited as well as the average treatment duration per protocol by clinical research phase.

AMENDMENTS AND CHANGE PER AMENDMENT PREVALENCE

More than half of the protocols required one or more amendments; 56.6% of protocols (n = 1,979) and 58.8% of completed protocols (n = 772) had at least one amendment. Com-

pleted protocols across all phases had an average of 2.3 amendments, though later-stage phase 2 and 3 protocols averaged 2.7 and 3.5 amendments respectively. Each amendment required an average of 6.9 changes to the protocol. Therapeutic areas that had the highest incidence of amendments and changes per amendment include cardiovascular and gastrointestinal protocols. Protocols for respiratory studies had a higher average number of amendments compared to the average across all therapeutic areas; endocrine, hematology, and immunomodulation studies had a higher than average incidence of changes per amendment. Pain study protocols had the lowest incidence of amendments and changes per amendment on average. A breakdown of the average number of amendments and changes per amendment by study phase and therapeutic area are presented in Tables 3 and 4.

Older protocols—those that were approved and implemented in 2006 and 2007—had a significantly higher prevalence of amendments than did protocols that were more recently approved and implemented ($P < 0.001$). Protocols with longer treatment durations also had a significantly higher incidence of amendments. Removing outliers for both variables, Tufts CSDD compared clinical time (defined as time from first dose to last patient, last visit) to the number of amendments per protocol using Spearman's rho correlational analysis. This correlation was statistically significant ($P < 0.001$). Larger protocol scope as defined by the number of investigative sites administering a given protocol was also significantly correlated ($P < 0.001$) with the number of amendments.

Participating companies were asked to indicate up to three of the most important changes made per amendment. Of the 6,855 protocol amendment changes categorized, 1,108 were modifications made to the description and eligibility criteria of the patient population under investigation, 847 noted adjustments made in the number and types of safety assessment procedures performed as one of the three most important changes, and a relatively high number, 715 changes, were alterations and edits made to general information contained in the protocol (eg, protocol title and study staff contact information). A complete list of change categories and their distribution is shown in Table 5. Differences in the distribution of changes by phase and by therapeutic area were not observed.

TABLE 2

Protocol Characteristics and Scope

Phase	Subjects per Protocol	Number of Sites	Treatment Duration (Days)
Phase 1	36	1	30
Phase 2	120	26	98
Phase 3	446	65	182
Phase 3b/4	258	35	91

All values are medians.

TABLE 3

Mean Number of Amendments and Changes per Amendment by Phase

	Number of Amendments[a]	Protocol Changes per Amendment
Phase 1	1.9	5.6
Phase 2	2.7	6.8
Phase 3	3.5	8.5
Phase 3b/4	2.6	8.3
All phases	2.3	6.9

[a]Includes only completed protocols (past final database lock) with at least one amendment.

AMENDMENT TIMING

For completed studies, 43% (n = 533) of amendments for which data were available were signed off by the sponsor before the first study volunteer had been enrolled (ie, first patient, first dose). This occurrence was most pronounced in phase 1 where more than half (52%, n = 309) of amendments occurred prior to beginning patient enrollment. In later-stage clinical trials, a smaller percentage of amendments occurred prior to study volunteer enrollment. In phases 2, 3, and 3b/4 studies, 37% (n = 101),

TABLE 4

Mean Number of Amendments, Changes per Amendment, and Changes per Protocol by Therapeutic Area

	Number of Amendments[a]	Protocol Changes per Amendment	Total Changes per Protocol
Anti-infective	2.5	4.4	8.6
Cardiovascular	2.6	10.1	18.8
Central nervous system/neuropsychological	2.2	6.8	16.9
Endocrinology/metabolism	2.2	8.0	19.1
Gastrointestinal	3.9	7.2	16.6
Genitourinary system	2.6	5.0	10.9
Hematology	2.1	9.5	14.6
Immunomodulation/anti-inflammatory	2.4	8.3	16.4
Oncology	2.3	6.7	15.9
Pain/anesthesia	1.8	3.6	6.8
Respiratory	2.9	4.2	7.4
Other	1.9	6.8	18.1
All therapeutic areas	2.3	6.9	15.3

[a]Includes only completed protocols (past final database lock) with at least one amendment.

30% (n = 56), and 38% (n = 67) of amendments, respectively, occurred before first patient, first dose.

AMENDMENT CAUSES

Companies categorized the causes of 2,795 amendments. The most commonly cited cause was the availability of new safety information (19.5%), followed closely by requests from regulatory agencies to amend the study (18.6%), and changes in the study strategy (18.4%). Protocol design flaws and difficulties recruiting study volunteers were also top-cited causes at 11.3% and 9% of categorized amendments, respectively. Table 6 provides the incidence of all 10 primary causes of amendments.

Two thirds (66%) of amendments had causes considered unavoidable, including amendments that were the result of new safety information, new regulatory requests, changes in the standard of care, or study objectives. Of all categorized amendments, one third were in categories considered partially or completely avoidable. Undetected design flaws, inconsistencies or errors in the protocol, and difficulties recruiting study volunteers were rated as amendment causes that sponsors could have better anticipated and avoided. Table 7 presents a grouping of all causes by how easily they are avoidable and preventable.

Some discrimination was observed in the average number of changes made per amendment by cause category. Amendments that were the result of adjustments to the study strategy and objectives prompted an average of 10 changes. Inconsistencies and errors contained within the protocol triggered an average of 9.4 changes per amendment. Table 6 contains the mean number of changes by cause of amendment. Of those causes that facilitated the highest number of changes per amendment, two—new safety information available and regulatory agency request to amend—were considered completely unavoidable.

AMENDMENT IMPLEMENTATION CYCLE TIME AND COST

The majority of companies were unable to provide amendment implementation cycle time and cost data and therefore these results must

TABLE 5

Distribution of Changes Made

Change Category	n	Percentage of All Changes Selected
Population description (including inclusion and exclusion criteria)	1,108	16
Safety assessment	847	12
General information (including protocol title, affiliated names, and addresses)	715	10
Type/design of trial	531	8
Route of administration, dosage, or dosage regimen	506	7
Typographical correction	425	6
Efficacy assessment	401	6
Statistical methods and analysis	310	5
Medications permitted before/during the trial	282	4
Trial objectives and purpose	258	4
Ethics	230	3
Sample size	210	3
Duration of subject participation, treatment, or follow-up	203	3
Stopping rules or discontinuation criteria	171	2
Dosage form, packaging, or labeling	138	2
Endpoints	99	1
Risks and benefits	80	1
Background literature	57	1
Data handling and record keeping	47	1
Measures to avoid bias (including randomization and blinding)	45	1
Findings from nonclinical studies	35	1
Supplemental materials	35	1
Subject withdrawal criteria	34	0
Procedures for monitoring compliance	29	0
Trial termination criteria	18	0
Name and description of product	12	0
Compliance statement	11	0
Quality control and quality assurance	9	0
Randomization codes	6	0
Publication policy	2	0
Financing and insurance	1	0

Companies could choose up to three changes for each amendment.

TABLE 6

Distribution of Primary Amendment Causes

Cause	n	Percentage	Mean Number of Protocol Changes
New safety information available	539	19.5	7.9
Regulatory agency request to amend	515	18.6	7.2
Change in study strategy	510	18.4	10
Protocol design flaw	313	11.3	5.7
Recruitment difficulty	249	9.0	4.8
Inconsistency and/or error in protocol	242	8.7	9.1
New data available	196	7.1	8.8
Investigator/site feedback	124	4.5	9.4
Change in standard of care	52	1.9	6.2
Manufacturing change	28	1.0	7.9

be viewed with caution. Based on data from approximately 59 amendments, the median total cycle time from when the protocol problem was identified to when the amendment was fully implemented—defined as first patient resubmitted under the revised protocol—was 65 days. Nearly half (46%) of this time was devoted to determining what changes needed to be made to the protocol. It took an additional 4 weeks (on average 28 days or 43% of the total cycle time) to obtain approval from senior management and the IRB before the first patient could be resubmitted under the revised protocol.

Cost data were provided for only 20 amendments. Among this small sample, the average cost to implement a single protocol amendment was $453,932. This figure does not include internal resources utilized to amend the protocol, costs, or fees associated with protocol language translation, and costs associated with resubmission to the local authority. The largest areas of amendment-associated costs were increases in investigative site fees (58% of total costs) and contract change orders with existing third party provider agreements (24%). Table 8 provides a breakdown of cost elements captured that are associated with the implementation of the 20 amendments.

DISCUSSION

The incidence of protocol amendments is high. Nearly 60% of protocols examined required at least one amendment, with the typical protocol having an average of 2.3 amendments. Based on the cycle time data gathered in this study, the results suggest that pharmaceutical and biotechnology companies are spending an additional 4 months to accommodate these 2.3 amendments. Multiply this by the number of global protocols executed per year for any given pharmaceutical company, and the cumulative unplanned delays incurred for R&D programs are staggering. At a minimum, the results of this study offer insights and refinements on project planning and budgeting expectations.

Variability in the average number of amendments and changes per amendment was observed across research phases and therapeutic areas, suggesting opportunities to minimize the number of amendments and reduce the amount of disruption each amendment causes. Initiatives should target those areas with the highest average number of amendments and changes per amendment, specifically phase 3 protocols, and protocols in cardiovascular and gastrointestinal studies.

Larger studies and those involving longer treatment durations are significantly, positively correlated with more amendments. These studies tend to be more demanding (eg, large numbers of study volunteers being recruited at more investigative sites globally) and their protocols tend to be more complex (eg, higher numbers of procedures and eligibility criteria). Protocols in

TABLE 7

Avoidable and Unavoidable Amendments

Avoidability	n	Percentage	Cause Categories
Completely avoidable	555	20	Protocol design flaw Inconsistency and/or error in the protocol
Somewhat avoidable	373	13	Recruitment difficulty Investigator/site feedback
Somewhat unavoidable	758	27	New data available (other than safety data) Change in strategy/objective Change in standard of care
Completely unavoidable	1,082	39	New safety information available Regulatory agency request to amend Manufacturing change

As a group and based on judgment, participating companies rated these cause categories in terms of whether each was completely avoidable, somewhat avoidable, somewhat unavoidable, and completely unavoidable.

these larger studies may be touched and managed by more investigative site personnel, and they may have more time in the clinical research setting to identify and modify problem areas.

Participating companies in this study note, anecdotally, that larger-scope and longer-duration studies, such as those in phase 3, encourage clinical research scientists to design more ambitious protocols, which may ultimately result in a larger number of protocol amendments. In these large-scale studies, the marginal cost of collecting additional data seems trivial in comparison with the overall study budget, and the data gathered may prove useful in deriving new insights (the "nice to have" additional data versus key data required to answer a scientific question) and in addressing future regulatory agency inquiries. But the high cost and long cycle time of amendment implementation shown in this study, combined with the incremental costs associated with higher protocol complexity and execution burden (2), suggests that the perception of trivial costs may be grossly inaccurate. Indeed, clinical research scientists need to be aware of the potential costs associated with a protocol amendment when making the decision to amend a protocol.

The most common causes of protocol amendments found in this study were regulatory agency requests, new safety information about the study drug (safety or dose related), evolving standards of care, competitive pressures, inconsistencies in the protocol design and execution process, and patient recruitment difficulties. These causes reflect the myriad considerations that clinical teams weigh to manage clinical research performance. Some of these causes also reflect judgments made, and risks taken, by clinical research management to meet tight deadlines and budget requirements. Faced with time pressures, project teams often must move forward at risk, while pending announcements

TABLE 8

Distribution of Direct Costs to Implement an Amendment

Item	n	Cost
Contract change orders to existing contracts	20	$109,523
New contracts with providers	9	$69,444
IRB fees	19	$4,384
Increase study grants/site fees	16	$265,281
Additional drug supply	10	$5,300
Total[a]		$453,932

[a]Does not include oversight, language translation, or other costs.

of new standards of care and regulatory decisions loom.

Clinical research scientists typically amend a protocol to make clarifications and enhancements to that protocol. The changes made at the time of an amendment are consistent. The largest numbers of changes are design modifications and adjustments to sampling, clinical endpoint measurements, and evaluation. One in four changes is associated with efforts to improve patient recruitment and retention rates. In the current study, 425 (6%) of amendments cited typographical errors and inconsistencies in the protocol narrative as one of the top three changes made to the protocol—changes that in many cases could have been addressed prior to protocol approval.

Our study findings strongly suggest that a large proportion of amendments can be avoided and prevented. Forty-three percent of amendments were written before the first volunteer was even enrolled in the study. Additionally, one third of cited amendment causes were deemed somewhat or completely avoidable.

The average cost per amendment measured in this study, $453,932, is substantial but should be viewed with caution as it is based on a very small sample size (n = 20). Also, the figure is a conservative estimate as it only measures certain direct costs. The figure is missing the estimated direct costs of internal and investigative site resources involved in implementing an amendment, as well as protocol language translation costs, and those costs associated with resubmission to local authorities. No indirect costs—such as those associated with development and commercialization delays—have been measured. The cost data gathered in this study are also limited in that our aggregate estimate combines all submitted cost estimates, although the types of amendments included may not be directly comparable.

It is important to note that many amendments are necessary to optimize study results and ensure patient safety and ethical treatment. According to the 2001/20/EC Directive, amendments are considered substantial and necessary when a change to the approved protocol will have significant impact on the safety or mental well-being of a clinical trial participant, the scientific quality and value of the trial, or both (6). The ultimate decision to implement a protocol amendment, however, rests with the research sponsor. As such, clinical research scientists may opt to implement protocol amendments as a conservative practice, the result of which is an unplanned impact on the clinical research study budget.

In the highly volatile and challenging economic environment in which pharmaceutical and biotechnology companies currently operate, the substantial cost and time savings realized from a reduction in avoidable amendments could be reallocated to R&D projects and mission-critical infrastructure. Moreover, the 2-month development time savings associated with the elimination of each avoidable amendment is notable, as is the substantial, incremental revenue that would result from faster product commercialization.

Many pharmaceutical and biotechnology companies have already recognized the potential economic and speed advantages that would result from reductions in the incidence of protocol amendments. Sponsor companies have established internal teams and task forces to understand the root cause of protocol amendments and to identify improvement opportunities. Some companies are focusing energy on revising protocol authoring templates to clarify and remove areas of redundancy to minimize errors and inconsistencies and to provide more instructional text for protocol authors. Companies are also evaluating and refining protocol development, feasibility, and approval processes to isolate potential amendment causes before they occur.

New approaches being pursued reflect a commitment on the part of pharmaceutical and biotechnology companies to invest more time upfront prior to protocol finalization. The rush to enroll the first patient in a study is increasingly being viewed by sponsors as a recipe for mistakes in protocol design, poor project planning, and hasty decision making.

The results of our study quantify the inci-

dence of amendments and the associated impact resulting from the amendment implementation process. In addition, this study captures the primary causes of amendments, when they occur, and the cycle time and costs associated with their resolution. There are numerous areas for subsequent research, including a more robust evaluation of the relationship between protocol complexity and amendment incidence; a robust quantification of the economics of implementing protocol amendments; an assessment of the impact of various external forces (eg, commercialization and competitive pressures) on protocol amendment frequency; and the success and failure of newly implemented sponsor practices on reducing the need to amend protocols.

The magnitude of this problem and insights into areas where protocol amendments can be avoided and prevented represents a major opportunity for pharmaceutical and biotechnology companies to improve cycle times and reduce development costs to deliver safe treatments to patients faster and more efficiently.

Acknowledgments—The authors wish to thank the 17 companies that participated in this study and contributed their valuable time and data.

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Randy Krauss has disclosed that he is a stock shareholder of Genzymem Abbott, Johnson & Johnson, and Novartis. Anne B. Cropp has disclosed that she is a stock shareholder of Pfizer, Inc. Anna L. Hindle has disclosed that she is a stock shareholder of Biogen Idec. Kenneth A. Getz, Rachael Zuckerman, and Kenneth I. Kaitin report no relevant relationships to disclose.

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Tufts Center for the Study of Drug Development
TUFTS UNIVERSITY

Impact REPORT

ANALYSIS AND INSIGHT INTO CRITICAL DRUG DEVELOPMENT ISSUES

One in five procedures generates extraneous clinical trials data

Tufts CSDD study sets benchmark for quantity and cost of less essential data

- The typical protocol has an average of 7 objectives and 13 endpoints.
- 22.3% of all procedures are considered to be non-core: 17.7% of Phase II procedures and 24.7% of Phase III procedures.
- Half of all procedures—54.3% of Phase II procedures and 47.9% of Phase III—support primary and key secondary endpoints.
- $1.1 million (18%) of a typical study budget is spent on procedures for supplementary secondary, tertiary, and exploratory endpoints, and another $1.3 million (22%) is spent on procedures supporting regulatory compliance.
- Based on the total number of active FDA-regulated Phase II and III trials conducted annually, the pharmaceutical industry spends $4 billion to $6 billion each year on procedures that generate extraneous clinical trial data.

During the past decade, Tufts CSDD studies have consistently demonstrated the inverse relationship between protocol complexity and clinical trial performance; more complex protocols are associated with longer study cycle times, poorer patient recruitment and retention rates, and a higher number of protocol amendments.

It is widely believed that clinical trial protocols contain a growing number of procedures that support supplementary, tertiary, and exploratory endpoints, generating extraneous data and imposing substantial additional costs. The impetus to collect these data is strong: sponsors collect more data to interpret findings, guide development decisions, support adherence to protocol authoring templates and design practices, and anticipate requests from regulatory agencies, purchasers, and payors. Until now, there has been no systematic study of the issue. The findings summarized here offer pharmaceutical and biotechnology companies insight into, and a framework to use in, streamlining protocol designs, improving clinical research performance, and reducing cost.

The number of total clinical procedures has grown by 57% since 2000

Phase II and Phase III Protocol Demands and Work Burden: 2000-2011

	Phase II 2000-03	Phase II 2008-11	Phase III 2000-03	Phase III 2008-11
Unique procedures	21.6	34.3	20.0	28.6
Total procedures	117.1	192.1	93.6	146.6

Source: Tufts Center for the Study of Drug Development

- Since 2000, the median number of unique and total procedures for Phase II and III protocols combined has increased by 48% and 57%, respectively.
- Typical Phase II and III protocols have a median of 192 and 147 procedures, respectively.
- Phase II protocol complexity, as measured by the number of procedures and work burden, has grown at a faster rate than Phase III protocol complexity, as sponsors look to collect more data in earlier phase studies.

Phase II and III study execution has become far more complicated since 2000

Phase II and Phase III Study Size and Scope: 2011

(Mean values per study)

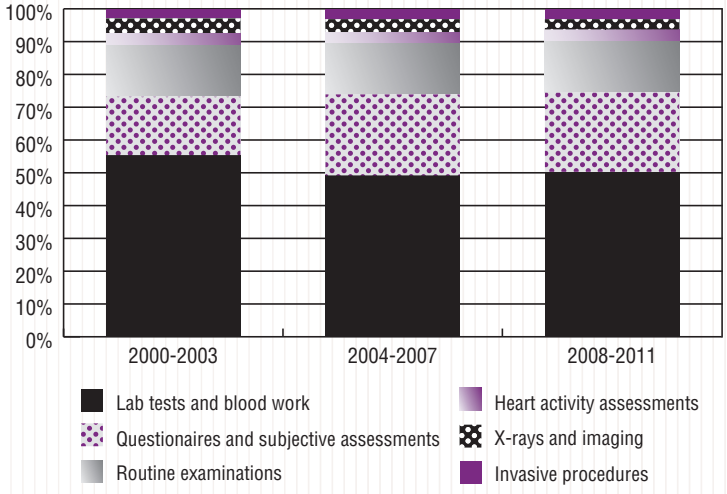
	Overall	Phase II	Phase III
No. of countries	27	18	34
No. of sites	130	42	193
No. of treatment arms	3	4	3
No. of eligibility criteria	32.8	31.4	33.8
No. of patients screened	882	287	1,300
No. of patients randomized	437	226	597
No. of data points collected	618,557	378,447	929,203

Source: Tufts Center for the Study of Drug Development

- The typical Phase III study involves nearly 200 investigative sites and 600 patients from 34 countries.
- Phase II and III studies have an average of 33 eligibility criteria per protocol.
- More than 929,000 data points are collected from an average Phase III study – nearly 2.5 times the volume of data collected from a typical Phase II program, largely due to the number of patients enrolled.

The proportion of procedure types for Phase II and III studies has been relatively consistent

Distribution of Procedures by Type for Phase II and Phase III Programs

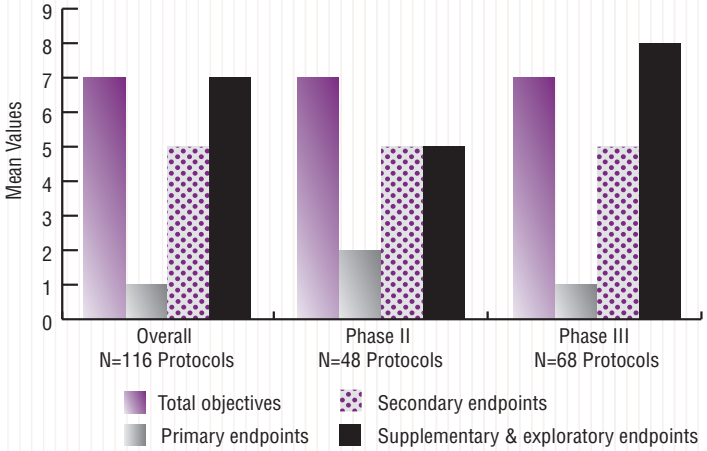


Source: Tufts Center for the Study of Drug Development

- During the past decade, the types of procedures performed as a proportion of total procedures per protocol have remained consistent with one exception: study volunteer self-assessments have increased.
- Half of all procedures performed are lab tests and blood work.
- X-ray and imaging procedures, heart activity assessments, and invasive procedures each make up a relatively small percentage of all procedures performed per protocol.

The typical clinical trial protocol has an average of 7 objectives and 13 endpoints

Protocol: Objectives and Endpoints: 2012

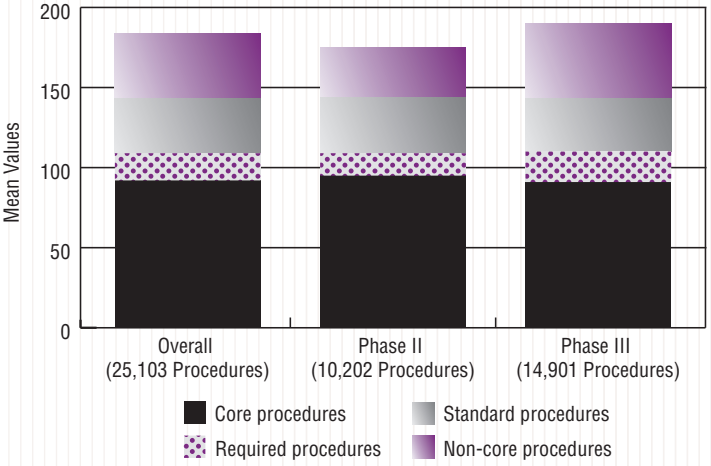


Source: Tufts Center for the Study of Drug Development

- Phase II and III protocols have 7 objectives, 1 primary, and 5 key secondary endpoints.
- The typical Phase III protocol has 8 endpoints that are supplementary secondary, tertiary, and exploratory in nature.
- The number of less essential endpoints per protocol today is nearly double the average level observed 10 years ago.

Half of all protocol procedures are considered core and 22.3% are deemed non-core

Procedure Distribution by Endpoint Type: 2012

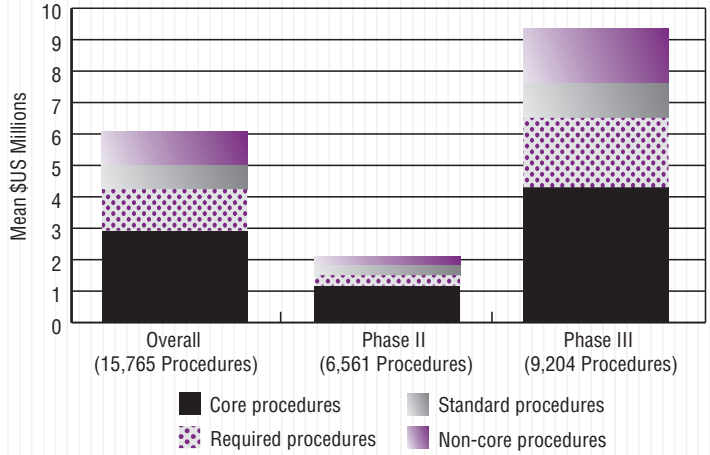


Source: Tufts Center for the Study of Drug Development

- 54.3% of Phase II procedures and 47.9% of Phase III procedures support core—that is, primary and key secondary—endpoints.
- 17.7% of Phase II procedures and 24.7% of Phase III procedures support supplementary, tertiary, and exploratory endpoints, and collect extraneous data.
- Approximately 10% of all procedures per protocol support Good Clinical Practice-International Conference on Harmonization (GCP-ICH) compliance requirements.

$1.1 million per study budget is spent on direct costs to administer non-core procedures

Distribution of Total Direct Study Procedure Costs by Type: 2012



Source: Tufts Center for the Study of Drug Development

- $1.1 million (18%) of a study budget is spent on the direct cost to administer non-core procedures.
- For the typical Phase III study, $4.3 million (46%) is spent on the direct cost to administer core procedures; $1.7 million (18.5%) and $2.2 million (24%) are spent, respectively, on non-core procedures and on those required to comply with GCP-ICH.
- Based on the total number of active, global, FDA-regulated Phase II and III studies conducted in 2011, the pharmaceutical and biotechnology industry spends $4 billion to $6 billion annually in direct costs to administer non-core procedures.

About this study

The study, conducted November 2011 through May 2012, collected input from 15 mid-sized and large pharmaceutical and biotechnology companies conducting clinical trials globally. Each company performed an extensive review of their protocols. In all, 116 unique Phase II and III protocols completed since 2009, having at least one procedure tied to a primary endpoint, were analyzed. Procedures added as part of the implementation of a protocol amendment were also classified. To minimize unusual and atypical protocol designs, pediatric, medical device, and orphan drug studies were excluded, as were protocols of extension studies. A total of 25,103 individual protocol procedures were evaluated and classified by research professionals from each of the participating companies, with each protocol procedure classified according to the objective and endpoint it supported as indicated in the clinical study report and the statistical analysis plan. For each protocol, direct costs for procedures were aggregated by classification group (i.e., core, required, standard, and non-core) and multiplied by the number of evaluable patients.

Ken Getz, MBA and Stella Stergiopoulos, BA—both at the Tufts Center for the Study of Drug Development—were the principal investigator and project manager, respectively, on this study.

Definition of terms

Clinical trial — A type of clinical study that tests a hypothesis. Clinical studies, in general, investigate any of a broad range of issues relating to drug development.

Core protocol procedures — Those that support primary and/or secondary study objectives or primary or key secondary and safety endpoints.

Required protocol procedures — Those that support screening requirements and compliance-related activity, including drug dispensing, informed consent form review, and study drug return.

Standard protocol procedures — Those commonly performed during initial and routine study participant visits, including medical history, height and weight measurement, adverse event assessment, and concomitant medication review.

Non-core protocol procedures — Those that support ancillary secondary, tertiary, and exploratory endpoints, and safety and efficacy procedures not associated with a study endpoint or objective.

Protocol — A plan detailing the methodology of a clinical trial.

About the Tufts Center for the Study of Drug Development

The Tufts Center for the Study of Drug Development at Tufts University provides strategic information to help drug developers, regulators, and policy makers improve the quality and efficiency of pharmaceutical development, review, and utilization. Tufts CSDD conducts a wide range of in-depth analyses on pharmaceutical issues and hosts symposia, workshops, and public forums.

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CLINICAL TRIALS

SENSIBLE GUIDELINES CONFERENCE

Clinical Trials 2008; **5**: 75–84

Sensible approaches for reducing clinical trial costs

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Background Over the past decade, annual funding for biomedical research has more than doubled while new molecular entity approvals have declined by one third.

Objective To assess the value of practices commonly employed in the conduct of large-scale clinical trials, and to identify areas where costs could be reduced without compromising scientific validity.

Methods In the qualitative phase of the study, an expert panel recommended potential modifications of mega-trial designs and operations in order to maximize their value (cost versus scientific benefit tradeoff). In the quantitative phase, a mega-trial economic model was used to assess the financial implications of these recommendations. Our initial chronic disease trial design included 20,000 patients randomized at 1000 sites. Each site was assigned 24 monitoring visits and a $10,000 per patient site payment. The case report form (CRF) was 60 pages long, and trial duration was assumed to be 48 months.

Results The total costs of the initial trial design were $421 million ($US 2007). Following the expert panel's recommendations, we varied study duration, CRF length, number of sites, electronic data capture (EDC), and site management components to determine their individual and combined effects upon total trial costs. The use of EDC and modified site management practices were associated with significant reductions in total trial costs. When reductions in all five trial components were combined in a streamlined pharmaceutical industry design, a 59% reduction in total trial costs resulted. When we assumed an even more streamlined trial design than has typically been considered for regulatory submissions in the past, there was a 90% reduction in total trial costs.

Conclusion Our results suggest that it is possible to reduce substantially the cost of large-scale clinical trials without compromising the scientific validity of their results. If implemented, our recommendations could free billions of dollars annually for additional clinical studies. Research in the setting of clinical trials should be conducted to refine these findings. *Clinical Trials* 2008; **5**: 75–84. http://ctj.sagepub.com

Introduction

The randomized clinical trial has been heralded as one of the great medical innovations of the twentieth century [1,2]. The use of this research method a has significantly advanced the quality of health care, and prevented millions of premature deaths [1,3].

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Over the past decade, funding for all biomedical research in the United States has more than doubled, from $37.1 billion in 1994 to $94.3 billion in 2003, and funding for phase 1–4 clinical trials by the pharmaceutical industry and National Institutes of Health has increased from 37 to 64% of their biomedical research expenditures [4]. However, Food and Drug Administration approvals of new molecular entities dropped from 35.5 to 23.3 entities per year over the same period [5]. The result has been a doubling of the capitalized costs per approved new drug, or a 7.4% annual increase above price inflation [6,7]. These reductions in clinical research productivity have prompted thought leaders to question the value of many practices routinely used in conducting clinical trials, and to call for research into more efficient and less bureaucratic ways of conducting them [3,8].

While our experience in assessing the value of clinical trial practices may be limited, we do have extensive experience in assessing the value of medical technologies [9,10]. Nearly 35 years ago, Archie Cochrane wrote that to determine whether a medical technology is 'worth it' (his test of efficiency), we must necessarily compare the benefits derived through its use to the resources it consumes [11]. Large, multi-center clinical trials have become standard technology for evaluating medical therapies prior to regulatory approval or as post-registration commitments. In the present study, we sought to assess the value of practices currently employed in the conduct of these clinical trials and identified areas within them that could be modified to reduce costs without compromising scientific validity.

Methods

Researchers associated with the UK's Medical Research Council recently proposed a framework for the design and evaluation of complex health care interventions (i.e., those with multiple, interconnected components) [12]. We assessed the value of clinical trial components using elements from the framework's second, or modeling, phase. Activities in this phase fall between the theoretical and exploratory trial phases, and are concerned with identifying components of the medical technologies and hypothesizing the mechanisms by which they relate to important outcomes. Simulation is frequently used to gain a greater understanding of the intervention's components and how they might interact with each other. Our approach contained two stages: a qualitative stage during which an expert panel made recommendations as to how the design and operation of clinical trials could be modified to increase the value of these studies; and a quantitative stage during which we used a mega-trial economic model to assess the financial implications of these recommendations.

Expert panel

As part of a Conference in early 2007 to develop sensible guidelines for the conduct of clinical trials, we convened a group with special expertise in the design and management of mega-trials [13]. Our group membership included representatives from academia, industry, and site management organizations. Through a structured discussion process we sought to identify the scientific objectives of clinical trials (their benefits) and to identify factors associated with their structure and conduct that could be changed without compromising the overall scientific objectives of the trials. Our group also made recommendations for configuring these factors to optimize clinical trial value.

Recommendation modeling

We then tested our recommendations by using an existing model from the Duke Clinical Research Institute to simulate the total costs of conducting a hypothetical mega-trial. Our initial chronic disease trial design, which we called the full-cost pharmaceutical industry model, called for 20,000 patients to be randomized at 1000 sites. The duration of enrollment and follow-up were assumed to be 48 months and the case report form (CRF) was 60 pages in length. We assumed 24 monitoring visits per site with a $10,000 per patient site payment. Using techniques previously described, we varied key trial components to test the effects of our recommendations in terms of reducing total clinical trial costs [14,15]. Our initial simulations assumed a pharmaceutical industry trial designed for regulatory submission and conducted under an investigational new drug (IND) application. In a second set of simulations, we assumed an even more streamlined design than has typically been considered for regulatory submission. Our simulation results are presented as changes (dollar value and percent) in total trial costs and as changes in major cost components. We present cost changes both as percents of total trial costs and as percents of total trial costs less site payments.

Results

Framing the efficiency question

The first step in assessing the value of clinical trial components is to determine the scientific objective (benefit) to be achieved from investments in an individual clinical trial. Then the determination can be made as to whether the inclusion/exclusion of specific quantities of trial components add to or detract from the attainment of that objective. Several possible scientific objectives for clinical trials were defined by our expert panel (Figure 1).

Each definition has slightly different implications for what, how many, and in which configuration components will be included in clinical trials. From the society's perspective, investments in clinical trials will have value to the extent that the therapies they evaluate succeed in reducing patient morbidity and/or mortality, and in improving the patients' quality of life (Objective 5). Presumably, one could then calculate a cost-effectiveness ratio to estimate the incremental cost per quality adjusted life year gained through the use of a specific component (say 20 versus 2 monitoring visits per site) in an individual clinical trial. However, any hypothesized linkages between clinical trial components and long-term patient outcomes would be speculative at best and difficult to verify empirically. The same problem exists when the scientific objective selected is reducing the time to peak therapeutic value (Objective 3) or increasing the number of effective therapies available to patients (Objective 4).

During our expert panel's discussions, academics were more comfortable with the objective of increasing the reliability and generalizability of trial results (Objective 1) as a scientific objective for clinical trials: industry representatives also recognized the need to attain regulatory approval for the therapy being evaluated (Objective 2). In a rational world, there would be no difference between the resources required to achieve regulatory approval and those required for achieving reliable and generalizable results without compromising patient safety. However, experience suggests that this may not be the case. Thus, to the extent that these differences exist, they may present opportunities to adjust, or clarify, regulatory requirements. For the purposes of the present study, we agreed to use as our scientific objective the increase of reliability and generalizability of clinical trial results.

(1) Increase the reliability and generalizability of clinical trial results

(2) Increase the chance of regulatory approval and widespread use

(3) Reduce the time to peak therapeutic value

(4) Increase the number of effective therapies available to patients

(5) Reduce patient morbidity and mortality, and improve quality of life

Figure 1 Clinical trial scientific objectives

Expert panel recommendations

Three themes for improving the value of clinical trials evolved from our expert panel's discussion. These included: (1) increasing the ability of sites to be top performers; (2) using computer systems to improve site management and monitoring, and (3) streamlining and enhancing clinical trial operations (Figure 2).

Site capabilities

Three issues were identified that could potentially influence the participation of sites in clinical trials; increasing site workloads, the competition for patients among trials, and the need for better-performing sites. Our panel concluded that adopting a site-focus in the design and operations of trials would reduce unnecessary work and make it easier for sites to participate in studies. Ways to accomplish this site focus include; designing trials that fit existing clinical practice workflows, designing CRFs and electronic data capture (EDC) systems around clinical practice routines so that they are easy to complete, and limiting CRF length so that data that are unnecessary and difficult to obtain are not collected. These measures should reduce the number of protocol-mandated tests and procedures that are not covered by health insurance. Lastly, the experts suggested that appropriate site compensation formulas should be developed. There was a perception among the panel that sites are able to estimate accurately their costs for performing tasks that can be scheduled, but typically underestimate the costs of non-scheduled tasks such as queries. Therefore, the payments made to sites may not represent an appropriate sum to cover the costs involved, and this should be assessed.

As the number of trials increases, a competition for patients has developed. This has led to a scarcity of patients in many therapeutic areas and may disproportionately impact government-sponsored trials, which typically have less funding than trials sponsored by industry. Proposed solutions include making trials more attractive to sites (as discussed

(1) Increasing Site Capabilities

(a) Increasing workload

- Adopt a site-focus in the design and operations of trials
- Design trials to fit clinical practice workflows to increase overall trial feasibility
- Design case report forms and electronic data capture systems around clinical practice routines
- Limit case report form length
- Grant appropriate compensation to trial sites

(b) Competition for patients

- Make trials more attractive to sites (see section above)
- Allow patients to have multiple trial enrollments

(c) Need to increase performance

- Select Sites that best meet protocol requirements
- Site Development

(2) Computer Systems for Site Monitoring

(a) Centralize source document verification

(b) Use Statistical programs to monitor data anomalies

(c) Remote monitoring via conference calls and in-house data monitoring

(3) Streamline and Enhance Operations

(a) Develop one level of evidence standard for government and commercial trials

(b) Adopt current levels of evidence in government sponsored trials

(c) Evaluate cost-effectiveness of current practices with further research

(4) Unresolved issues

(a) Event (end-point) Adjudication

(b) Noninsured Trials (indemnity for health care and liability for trial)

Figure 2 Expert panel recommendations

in the previous paragraph) and enrolling patients in multiple trials. Currently, multiple trial enrollments are limited by the misperception that regulatory procedures preclude patient inclusion in more than one trial (even though multiple comparisons within factorial trials are commonplace). Regulatory authorities should clarify this point and stipulate that enrollment in a concurrent trial is acceptable provided that it does not adversely impact the patient's participation in the initial trial or compromise patient safety.

While coordinating centers would prefer to include only top performing sites in their

studies, this is not always possible. The following four strategies were identified by our panel as having the potential to improve site performance. First, coordinating centers could focus on fitting sites to protocols. For example, a site may be an excellent performer on heart failure trials but only a mediocre performer on hypertension trials. Top performing sites could be better identified by prospectively selecting sites based upon their performance on similar protocols and requiring that sites run eligibility lists from clinical databases to assess their potential for enrollment in a particular trial. Second, coordinating centers could work on developing good sites. This could be accomplished by evaluating site performance over time, developing education programs to set site expectations, and requiring periodic feedback reports to monitor site performance. Third, existing clinical research networks such as those in the United Kingdom, Europe, and the United States could provide a mentoring environment for sites to develop the skills and capacity necessary to support high quality clinical research. Participation by sites in this type of research relationship may serve to prepare them for participation in other trials that do not provide a high level of support. Fourth, simulation can be used to standardize site training. As investigator meetings may occur before a study's CRF and EDC system are finalized, computer simulations can play a valuable role in providing initial training for site personnel. They can also provide supplemental training when protocols/CRFs change and when new personnel join a site's project team.

Computer systems for site monitoring

Site visits typically involve two types of activities; monitoring of the clinical trial for quality control, and conducting site education and training. Previous studies have shown that source document verification and data validity checking can be performed very efficiently using statistical programs to monitor data [16]. Our panel recommended that source document verification be centralized, where appropriate, with minimal verification performed at local trial sites (primarily in the initial stage of trial execution). Statistical programs could be used to monitor data for anomalies, or identify sites where trial conduct appears problematic. Thus, depending on the trial protocol, on-site monitoring might be limited to a selected set of records from those sites in which anomalies were detected.

Similarly, coordinating center site managers could have more frequent site contact and better serve their sites with central data monitoring and periodic conference calls than with time-consuming and costly on-site visits. Our panel recommended that coordinating centers should consider separating current site visit functions by centralizing monitoring activities as much as possible. However, the experts also recognized that there were other, potentially important, benefits of site visits: they motivate local staff and also help to maintain personal contact with key individuals at each site. The experts' view was that, while monitoring functions of site visits could often be satisfactorily handled by central processes, some form of personal contact with individual sites remains important.

Clinical trial operations enhancement

Frequently, regulatory agencies require different levels of evidence for industry-sponsored compared to government/charity-sponsored trials. Yet the results of these trials are considered equivalent with respect to judging the safety and efficacy of the intervention. Our expert panel recommended that there be one level-of-evidence standard for all trials and that it be similar to the one currently used in government/charity-sponsored trials. This would minimize differences between the resource use considered necessary for obtaining reliable results and the use required for regulatory approval. The panel also recognized a need to evaluate the cost-effectiveness of clinical trial practices, as practitioners need evidence of the cost versus benefit of current practices when making decisions regarding future trial designs and operations. It was thought that such research could begin with the evaluation of big ticket items and the assessment of cost differences between different methods of performing similar trial functions. Some of the potential research questions are outlined in Figure 3. There also is a need to develop linkages between clinical trial processes and the achievement of scientific objectives: for industry there is the need to include in these calculations the risk of failing regulatory approval and the time to peak sales.

Unresolved issues

The panel did not make recommendations regarding adjudication and insurance costs for institutions conducting investigator-initiated trials. Adjudication is an area that some have identified as having minimal value with regard to improving

the accuracy of clinical trial results [8]. The panel recommended that an economic analysis be performed to compare the benefits of adjudication with its costs (both the costs associated with centralized adjudication as well as costs for sites to collect and prepare the required documentation). The panel also recognized the additional costs and risks for non-profit educational institutions when conducting investigator initiated trials. These frequently involve therapies that are of particular interest in developing countries, and institutions are required to hold specific insurance for each country. These insurance needs include indemnity for health care and liability insurance for the trial. Difficulties in obtaining these insurances can result in a reduction in the overall number of investigator-initiated studies that are conducted worldwide.

Clinical trial economic simulations

Using our initial assumption set, the estimated total costs of our full-cost pharmaceutical industry trial would be $421 million, with 40% attributable to coordinating center costs and 60% to non-coordinating center costs. Of note, site payments were 48% of the total costs, while other costs (primarily for airfare, hotels, and meetings) were 12% of the total costs. We then varied five clinical trial components identified by our expert panel to determine their independent effects upon total trial costs.

Study duration

Previous research has shown that the time allocated to planning is relatively constant across

1. Monitoring: methods and intensity
   (a) 100% SDV versus SDV in a random sample
   (b) Central monitoring only versus central monitoring plus local monitoring in centers where there appear to be problems
2. The benefits and costs of site visits:
   (a) For setting up the center
   (b) For maintaining recruitment and data quality
   (c) For close-out
3. The benefits and costs of investigator meetings
4. Adjudication:
   (a) Central adjudication versus no adjudication
   (b) Adjudicate only 'suspected events' and screen out false positives versus screen all records for false negatives as well
5. Measures to improve data quality
   (a) Data entry: double versus single entry
   (b) Paper CRF versus Electronic Data capture
   (c) Short versus long CRF
6. Methods of documenting consent
   (a) Paper versus 'electronic signature / fingerprint' methods

Figure 3 Research questions about identifying efficient and effective processes in managing clinical trials

trials [14]. This is important: since these activities occur before sites begin enrolling patients, reducing planning time might be a way to reduce the time to approval without impacting subsequent activities. For our hypothetical clinical trial, we calculated the relative costs of reducing the simulated pharmaceutical industry trial planning duration from a typical 6 months to 4 months. We also varied the enrollment period from a typical 24 months to 18 months in order to gauge the impact of accelerated enrollment upon total trial costs. Reducing the planning phase by 2 months reduced total trial costs by 0.4% (0.8% after excluding site payments), and reducing enrollment by 6 months reduced total costs by 1.6% (3.0% after excluding site payments) (Table 1). While the effect upon overall trial costs was modest, reducing the duration of the trial may have other benefits; such as the reduction of time to regulatory approval and marketing, which may provide a significant public health benefit as well as a financial benefit for the pharmaceutical company sponsoring the trial.

Case report form length

Case report form length is frequently used as a surrogate for clinical trial complexity [3,14,17]. We varied the number of CRF pages from 60 to 20 in our analyses in our pharmaceutical industry simulation. Reducing the CRF by 40 pages reduced total trial costs by 3.5% (6.7% after excluding site payments) (Table 1). Thus, while reducing CRF pages did result in cost savings, this reduction was only modest as well. Some panel members suggested even more radical reductions in CRF length and data processing requirements (e.g., by substituting clinic visits with assessment by postal questionnaires or telephone follow-up methods), which could lead to additional cost savings and efficiencies. There is good evidence that shortening questionnaires increases response rate, and hence data quality [18]. In some countries, it is possible to collect data on major clinical outcomes (e.g., hospitalizations and deaths) through electronic health record linkage systems and central registries of deaths, which could be highly cost effective and also provide independent verification of patient outcome. The use and value of such systems for clinical trials, especially to facilitate long-term follow-up of safety and efficacy, has recently been demonstrated in the UK [19,20].

Number of sites

Previous studies also have associated the number of sites with clinical trial complexity [3,14].

Table 1 Economic simulations

		Trial components						Streamlined industry model	
	Full cost industry model	Planning	Enrollment	CRF length	Number of sites	EDC	Site management	$10,000 per Patient Site Payment	$5,000 Per Patient Site Payment
		6>4 months	24>18 months	60>20 pages	1000>750				
Total costs	$421.5*	$419.8	$414.8	$406.8	$385.9	$380.2	$332.5	$272.4	$171.4
Cost reduction		$1.7	$6.7	$14.7	$35.6	$41.3	$89.0	$149.1	$250.1
Percent cost reduction		0.4%	1.6%	3.5%	8.4%	9.8%	21.1%	35.4%	59.3%
After site payment		0.8%	3.0%	6.7%	16.2%	18.8%	40.6%	67.9%	67.9%
Percent cost reduction									

*$ in US 2007 Millions.

We varied the number of sites from 1000 to 750 in our pharmaceutical industry simulations and found that total trial costs were reduced by 8.4% (16.2% after excluding site payments) (Table 1). This reduction, too, is considered modest.

Electronic data capture

The use of EDC in large-scale cardiovascular trials has been cited as a means for speeding up the pace of trials and enabling earlier close-out. We assessed the influence of EDC versus a paper CRF upon total trial costs and found that the use of EDC reduced total trial costs in our pharmaceutical industry trial simulations by 9.8% (18.8% after excluding site payments) (Table 1). These differences were largely driven by an anticipated 2 month reduction in study close out time, as well as by the elimination of query processing, data entry, and medical coding at the coordinating center. Although EDC would increase site time for data entry, it would also decrease time associated with managing queries. Thus, we assumed no change in the site payment amount associated with switching from a paper CRF to EDC.

Modified site management

Current site management practices have been highlighted as a primary factor contributing to the increasing costs of clinical trials [3,8,14]. We assessed the incremental effect on total clinical trial costs of replacing a traditional site management strategy with one that involved chiefly remote monitoring. In this comparison, we reduced on-site evaluation visits from 50 to 10% of sites, site visits per site from 24 to 4 visits, on-site closeout visits from 100 to 0%, and on-site source document verification from 100 to 10%. This combined strategy resulted in a 21.1% reduction in total trial costs in our pharmaceutical industry simulations (40.6% after excluding site payments) (Table 1).

Cumulative reductions

If all of the proposed changes in clinical trial components were implemented, we found there would be a 35.4% reduction in total costs of our hypothetical pharmaceutical industry mega-trial, with the largest reduction occurring in coordinating center costs (Table 1, Figure 4). Implementing modified site management, moving to EDC, and reducing the number of sites had the greatest impact upon total trial costs; whereas, reducing trial duration and reducing CRF length had less

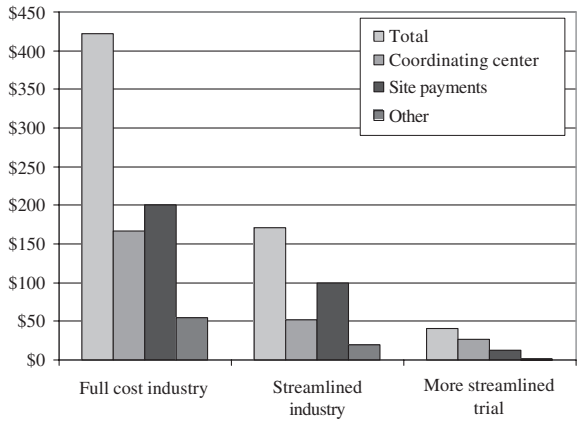

Figure 4 Cost comparison: full cost pharmaceutical industry, streamlined pharmaceutical industry, and more streamlined trial models. $ in US millions

economic impact. However, many of these changes in clinical trial design and management (e.g., CRF length and modified site management) also would be associated with significant reductions in site workload. Assuming the per patient site payment could be reduced to $5,000 as a result of these site-based efficiencies, total trial costs in our pharmaceutical industry simulation could be reduced by an additional 24%. When combined with the reductions in non-site costs described above, this yields an overall 59% reduction in total trial costs for the streamlined pharmaceutical industry model (difference = $250 million, from $421 to $171 million).

More streamlined trial model

The scenarios described above assume a pharmaceutical industry clinical trial model. However, some previous clinical trials sponsored by governments and charities (often in collaboration with industry) have adopted an even more streamlined model. Accordingly, we developed another trial model to test the extent to which costs could be reduced if such approaches were adopted more widely. In this model, we assumed our 20,000 patients would be enrolled at 100 sites that had previously worked with our coordinating center, allowing the elimination of on-site evaluation, close-out visits, and source document verification. We also assumed a focused design with a five-page CRF, one page for enrollment and baseline data collection, and four pages containing only three questions each for annual follow-up contact. Given the resulting reduction in site workload, we assumed a $650 per patient site

payment would be appropriate ($250 for enrollment and collecting baseline data and $100 each for annual follow-up contacts). Under this scenario, there would be a 90% reduction in total trial costs from the full cost pharmaceutical industry scenario (difference = $381 million, from $421 to $40 million) (Figure 4).

Discussion

Our results suggest that it is possible to reduce significantly the costs of clinical trials without adversely impacting their scientific objectives. The resulting cost savings would provide increased funding so that additional therapies could be tested and made available for patient care.

During the past decade, the productivity of pharmaceutical clinical trials has steadily eroded. During this time, the costs per new molecular entity approved increased at a rate of 7% per year after adjustment for inflation, resulting in a doubling of the capitalized cost per drug approved [6,7]. This dramatic cost increase has been associated with a 34% reduction in the number of new drugs approved each year [5]. Continued escalation of clinical trial costs will most likely further decrease the number of new therapies that are available for patient care. We believe that the implementation of our expert panel's recommendations has the potential to make billions of dollars available annually for clinical research and to reverse current trends in declining clinical research productivity.

Clearly, all recommendations by our panel will not have the same financial effect. Implementing a modified site management strategy that largely replaces on-site with remote monitoring could in itself reduce clinical trial costs in our pharmaceutical industry simulation by more than 20%, while potentially increasing the quality of monitoring activities and the overall quality of trial results. Implementing EDC (where appropriate) and reducing the number of sites by 25% could together achieve levels of cost reductions similar to those possible through modified site management. Selectively pruning the number of sites, as long as it does not reduce the representative nature of the population, would appear to be a particularly advantageous cost saver as 10–15% of sites participating in a clinical trial do not enroll a single patient, and 20–25% enroll <5% of the total trial population [21]. Additional reductions in total trial costs in our pharmaceutical industry simulation were achieved through reductions in site workloads, which were associated with the modifications to overall trial design and operation described above. When per-patient site payments were adjusted to account for the reductions in site-based workload, the savings achieved were about one-quarter of the total trial costs.

Our pharmaceutical industry model results build upon those of Eisenstein *et al*. [14] who found that site-related expenses (site management and site payments) were >65% of total trial costs. This earlier study found that total trial costs could be reduced by >40% through reductions in CRF length, monitoring visits, and site payment amounts. In the present study, our expert panel recommended more aggressive trial management strategies that were associated with a 59% reduction in total trial costs using our pharmaceutical industry model and a 90% reduction using our more streamlined trial model. Thus, the potential for cost reduction is greater than previously estimated and more than sufficient to offset the ongoing escalation in clinical trial costs.

While our pharmaceutical industry model simulations estimated changes in coordinating center-related costs, we did not have adequate models to estimate their impact on the costs incurred by sites and patients participating in our hypothetical clinical trial. To the extent that our $10,000 and $5,000 per patient site payment amounts are under- or overestimates of the amount that would be required in an actual pharmaceutical industry clinical trial, we have under- or overestimated the total costs of our trial. Additionally, we have not estimated the costs of patient participation in this clinical trial. While patients are not paid for their participation, their time does have value and may be a consideration in their decision to participate in a clinical trial. Trials designed around clinical workflows and routines would make it easier and more attractive for sites and their patients to participate in clinical studies.

In our more streamlined trial model, we demonstrated that the use of a less complex design that has not typically been considered for regulatory submissions could reduce the costs of conducting clinical trials to <10% of those in our full cost pharmaceutical industry scenario. These results are paralleled in the 20,000 patient UK Heart Protection study. This study was conducted at 69 hospitals in a single country over a period of 7 years (1995–2002) using a one-page CRF at a cost of about $40 million [22]. The results of that trial have been used subsequently as the basis of regulatory approval for widening the indication for statin therapy, as well as the modification of international therapeutic guidelines. To the extent that these less complex trial features can be incorporated into the

pharmaceutical industry based model, even more dramatic cost savings might be realized. More streamlined trial designs do, however, benefit from safety data collected in previous clinical trials of the therapies they investigate. This may limit the extent to which elements of this approach can be applied to new mega-trials. Even so, it is likely that the reduced pharmaceutical industry design still involves the collection of far more information than is needed to achieve its scientific objective.

Conclusions

While our results are based in part on speculations, they are derived from the combined experience of our expert panel, and many of our proposed methods have been tested in actual clinical trials. While all clinical trials may not be able to achieve cost savings of the magnitude seen in our simulations, we believe that our results are compelling and adequately set the stage for further research in the setting of actual clinical trials. This step will allow our interventions to be honed and adapted to the exigencies of various trial settings.

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Biographies and Meeting Logistics

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LARGE SIMPLE TRIALS AND KNOWLEDGE GENERATION IN A LEARNING HEALTH SYSTEM

Planning Committee biographies

David L. DeMets, PhD (Co-Chair) Professor and Chair of the Department of Biostatistics and Medical Informatics at the University of Wisconsin - Madison. Since receiving his PhD in 1970 from the University of Minnesota, he has been very active in the design, conduct, and analysis of clinical trials in several disease areas. Following a postdoctoral appointment at the National Institutes of Health (1970-72), he spent 10 years (1972-1982) at the National Heart, Lung and Blood Institute at the National Institutes of Health where he became chief of the Biostatistics Research Branch. He has co-authored a text, Fundamentals of Clinical Trials. Dr. DeMets is a recognized international leader in statistical research and methods for the analysis of clinical trials. He has collaborated in the development of statistical methods for the sequential analysis of outcome data and the design of clinical trials. He has extensive national and international clinical trial experience and has served on and chaired numerous NIH and industry sponsored Data Safety and Monitoring Committees for clinical trials in diverse disciplines. He served on the Board of Scientific Counselors of the National Cancer Institute and Board of Directors of the American Statistical Association, as well as having been President of the Society for Clinical Trials and President of the Eastern North American Region (ENAR) of the Biometric Society. He is a fellow of the American Statistical Association, the International Statistics Institute and the American Association for the Advancement of Science. Dr. DeMets served on the Human Subjects Committee (1982-1987) and on the following UW committees since 1990: Ad hoc Committee on Conflict of Interest (1992-1993); Tenure Track Promotions Committee (1995-1998) and Biomedical Industry Relations Committee (1996-1998). In addition he has served on the Search Committees for: UWCCC Director (1994-1997), Associate Dean for Research (Chair) (1995-1996), Associate Dean for Administration (Chair)(1995-1996), Section of Cardiology Chief (1998-1999) and Preventive Medicine Chair (1999-2000). Graduate School committees include the Committee on Training Research Ethics (Chair) 1993-1996 & 1998-2000 and the Health Sciences Information Technology Committee 1999-2003.

Richard E. Kuntz, MD, MSc (Co-Chair) is Senior Vice President and Chief Scientific, Clinical and Regulatory Officer of Medtronic, Inc. In this role, which he assumed in August 2009, Kuntz oversees the company's global regulatory affairs, health policy and reimbursement, clinical research activities, ventures and new therapies, strategy and innovation, corporate development, and acquisitions, integrations and divestitures functions. Kuntz joined Medtronic in October 2005, as Senior Vice President and President of Medtronic Neuromodulation, which encompasses the company's products and therapies used in the treatment of chronic pain, movement disorders, spasticity, overactive bladder and urinary retention, benign prostatic hyperplasia, and gastroparesis. In this role he was responsible for the research, development, operations and product sales and marketing for each of these therapeutic areas worldwide. Kuntz brings to Medtronic a broad background and expertise in many different areas of healthcare. Prior to Medtronic he was the Founder and Chief Scientific Officer of the Harvard Clinical Research Institute (HCRI), a university-based contract research organization which coordinates National Institutes of Health (NIH) and industry clinical trials with the United States Food and Drug Administration (FDA). Kuntz has directed over 100 multicenter clinical trials and has authored more than 200 original publications. His major interests are traditional and alternative clinical trial design and biostatistics. Kuntz also served as Associate Professor of Medicine at Harvard Medical School, Chief of the Division of Clinical Biometrics, and an interventional cardiologist in the division of cardiovascular diseases at the Brigham and Women's Hospital in Boston, MA. Kuntz graduated from Miami University, and received his medical degree from Case Western Reserve University School of Medicine. He completed his residency in internal medicine at the University of Texas

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William H. Crown, PhD is group president of health economics and outcomes research and late phase research for Optum. From 1982 to 1995, he was a faculty member at the Florence Heller Graduate School, Brandeis University, where he taught graduate courses in statistics and conducted research on the economics of aging and long-term care policy. Prior to joining Optum, Crown was vice president of outcomes research and econometrics at Medstat, where he conducted numerous retrospective database analyses of the burden of illness associated with various diseases — particularly respiratory and mental health conditions. Crown's work in the area of depression was one of the first applications of econometric techniques in outcomes research to control for the effects of selection bias when using retrospective data. He has 24 years' experience conducting health policy and income maintenance research for private-sector and public-sector clients. Crown is the author or co-author of four books and more than 90 referenced journal articles, book chapters, and other publications.

Jeffrey M. Drazen, MD joined the *New England Journal of Medicine* (NEJM) as editor-in-chief in July of 2000. At NEJM, Dr. Drazen's responsibilities include oversight of all editorial content and policies. His editorial background includes service as an associate editor or editorial board member for the *Journal of Clinical Investigation*, the *American Journal of Respiratory Cell and Molecular Biology*, and the *American Journal of Medicine*. A specialist in pulmonology, Dr. Drazen maintains an active research program. Dr. Drazen has published more than 300 articles on topics such as lung physiology and the mechanisms involved in asthma. In 1999, he delivered the Amberson Lecture, the major research address at the annual meeting of the American Thoracic Society. In 2000, he received the Chadwick Medal from the Massachusetts Thoracic Society for his contributions to the study of lung disease. Dr. Drazen is the Distinguished Parker B. Francis Professor of Medicine at Harvard Medical School, professor of physiology at the Harvard School of Public Health, and a senior physician at Brigham and Women's Hospital. In 2003, he was elected as a member of the Institute of Medicine. Dr. Drazen has served on numerous committees for the National Institutes of Health, including the Respiratory and Applied Physiology Study Section; the Lung Biology and Pathology Study Section; the Pulmonary Disease Advisory Council; the National Heart, Lung, and Blood Institute Advisory Council; the Public Access Working Group; and the National Heart, Lung, and Blood Institute's Division of Lung Disease Executive Planning Committee. He has also served on the Veterans' Administration National Research Advisory Committee. He currently serves on the Global Initiative for Asthma Science Committee, the World Health Organization's Scientific Advisory Group on Clinical Trials Registration, and co-chairs the Institute of Medicine's Forum on Drug Discovery, Development, and Translation. Dr. Drazen earned his bachelor's degree and graduated summa cum laude from Tufts University. He received his medical degree from Harvard Medical School and completed his internship and residency at Peter Bent Brigham Hospital in Boston. Dr. Drazen has received honorary degrees from the University of Ferrara, Italy, and the National and Kapodistrian University of Athens, Greece. A native of Missouri, Dr. Drazen lives with his wife in Winchester, Massachusetts. They are the parents of two grown sons.

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Judith M. Kramer, MD, MS is trained in clinical pharmacy (BS, MS) and is board certified in general internal medicine, having practiced internal medicine in the community for 5 years. For the past 21 years, she has been involved in clinical research. She worked for 10 years at Burroughs Wellcome Co. where she was Vice-President and Director of U.S. Clinical Research. In that capacity, she oversaw 220 employees and was responsible for the scientific administration of antiviral, oncology, neurology/psychiatry, cardiovascular, and pulmonary/critical care clinical research. During that time she supervised the preparation of 7 full original new drug applications (NDAs) and 14 INDs. From 1997 to 2006 Dr. Kramer was Chief Medical Officer at DCRI and in that role provided guidance and consultation on the formation of the regulatory affairs and quality assurance functions at DCRI. Dr. Kramer is currently the Executive Director of a public–private partnership, the Clinical Trials Transformation Initiative (CTTI). She oversees all activities and operations of the partnership under the direction of the Chair and Co-Chair, Dr. Robert M. Califf, Vice Chancellor for Clinical Research at Duke University, and Dr. Rachel Behrman, Director of the FDA's Office of Critical Path Programs. The goal of CTTI is to improve and modernize the operational performance of the clinical research enterprise by convening experts in the field and undertaking projects to identify existing issues related to current practice, design models for improvement, test the new procedures and compare them to previously existing systems, and develop recommendations to inform policy makers.

Michael Lauer, MD is the director of the Division of Cardiovascular Sciences at the National Heart, Lung, and Blood Institute (NHLBI), part of the National Institutes of Health (NIH). In this position, Dr. Lauer provides leadership for the Institute's national program for research on the causes, prevention, and treatment of cardiovascular (basic, clinical, population, and health sciences) diseases. Dr. Lauer joined the NHLBI in July 2007. Dr. Lauer's primary research interests include cardiovascular clinical epidemiology and comparative effectiveness, with a focus on diagnostic testing. He also has a strong background in leadership of the cardiovascular community and longstanding interests in medical editing—for seven years he was a contributing editor for Journal of the American Medical Association (JAMA) — and human subjects protection. Prior to joining the NHLBI, Dr. Lauer served as the director of the Cleveland Clinic Foundation Exercise Laboratory and vice chair of the clinic's Institutional Review Board. He also served as co-director of the Coronary Intensive Care Unit and director of clinical research in the clinic's department of cardiology. Dr. Lauer earned his Bachelor of Science degree in biology, summa cum laude, from Rensselaer Polytechnic Institute in 1983 and his Doctor of Medicine, magna cum laude, from Albany Medical College in 1985. Following internal medical training at the Massachusetts General Hospital, Harvard Medical School, he completed a clinical fellowship in cardiology at the Boston Beth Israel Hospital, Harvard Medical School. His

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Sally Okun, RN, MMHS a member of the Research and Development Team at PatientLikeMe, Inc., is the Head of Health Data Integrity and Patient Safety for the company. In that role she is responsible for the site's medical ontology and the integrity of patient reported data. In addition, she developed and currently oversees the operational activities of the PatientsLikeMe Drug Safety and Pharmacovigilance Platform. Ms. Okun received her nursing diploma from the Hospital of St. Raphael School of Nursing, her baccalaureate degree in nursing from Southern Connecticut State University, and her Master's degree from The Heller School for Social Policy & Management at Brandeis University. In 2010 she was accepted as a fellow for the National Library of Medicine Fellowship in Biomedical Informatics at the Marine Biology Laboratory in Woods Hole, MA. Prior to joining PatientsLikeMe Okun was an independent consultant through her firm Caretography, LLC. In addition to private practice with patients and families facing life-changing illnesses she participated in numerous multi-year clinical, research, and education projects focused on palliative care, including: "Promoting Excellence in End-of-Life Care for Persons with Serious Mental Illness" with the MA Department of Mental Health; the "TOOLKIT Project Resource Guide: Measurement to Improve Quality of Care at Life's End" at Brown University; and "Palliative Care Education and Practice: An Intensive Course for Physician and Nurse Educators" at Harvard Medical School Center for Palliative Care; and the Center for Life Care Planning & Support, a program of Hospice & Palliative Care of Cape Cod. Ms. Okun was a national facilitator for "Healing Conversations: Effective Communication in Breast Cancer Care", a program developed by Novartis Pharmaceuticals Corporation and PRG Corporation. She served as a Senior Consultant with Weatherbee Resources, Inc. a firm dedicated to serving the hospice industry with regulatory compliance and clinical excellence. She served as an expert witness for Medicare Hospice Fraud and Abuse investigations initiated by the Department of Justice and the Office of Inspector General. Ms. Okun serves on the Compassionate Caregiver Annual Award Selection Committee of the Schwartz Center for Compassionate Care and previously served as a facilitator for Schwartz Center Rounds® at numerous locations including the innovative telephonic rounds with Aetna's National Medical Services Case Management.

John J. Orloff, MD is the Chief Medical Officer and Senior Vice President, Global Development, for Novartis Pharmaceuticals. In this position, Dr. Orloff is responsible for providing strategic and scientific leadership for all processes within Global Development, and for representing Novartis externally in various forums interfacing with the scientific, academic, and health policy communities. In addition, Dr. Orloff serves as Chair of the Pharma Portfolio Stewardship Board (PSB), which oversees safety and risk management plans for products within Pharma. Dr. Orloff has held a number of roles with increasing responsibility at Novartis, including Section Head for Bone Metabolism in Clinical Development, Vice President and Therapeutic Area Head of the Arthritis, Bone Metabolism, and Women's Health division within Clinical Development and Medical Affairs, and most recently as Head of US Medical and Drug Regulatory Affairs. Dr. Orloff graduated from Dartmouth College, received his medical degree from the University of Vermont, and completed specialty training in Endocrinology and Metabolism at Yale University, where he served on the faculty as an Associate Professor of Medicine before moving on to Merck Research Labs to lead clinical programs in bone metabolism.

Eric D. Peterson MD, MPH, FAHA, FACC is a professor of medicine in the Division of Cardiology at Duke University Medical Center. He is also an associate director of the Duke Clinical Research Institute. Dr. Peterson served as vice chair for Quality in the Department of Medicine (DUMC) from 2004-2010. His formal research training includes an MPH from Harvard University with special emphasis in biostatistics, health economics, and decision analysis. Dr. Peterson is a leader in quality research, with over 600 peer-reviewed publications in the field. Dr. Peterson is also the principal investigator for the NIH/AHRQ Duke Centers for Education and Research on Therapeutics (CERTs), Society of Thoracic Surgeons (STS) National Cardiac Surgery Database, Data Coordinating Center for both the American College of Cardiology's National Cardiac Database (ACC-NCDR), and the American Heart Association's Get With the Guidelines Data (AHA GWTG). He is the PI and center director for the American Heart Association's Pharmaceutical Roundtable Outcomes Center (one of four nation-wide) as well as director of the coordinating center for the NHLBI's Centers for Cardiovascular Outcomes Research. Dr. Peterson participates on multiple national committees including chair of the AHA Quality of Care and Outcomes Research Interdisciplinary Working Group; chair of the AHA Strategic Planning Committee, ACC/AHA Performance Measures Task Force; ACCF Appropriateness Criteria Implementation Working Group; the VA's Quality Enhancement Research Initiative (QUERI) Executive Committee, oversight board of the Massachusetts Data Analysis Center (MASS-DAC), the National Quality Forum Technical Advisory Panel for Priorities, Goals and a Measurement Framework: Efficiency and Episodes of Care; the Institute of Medicine (IOM) Committee on Redesigning Insurance Benefits, Provider Payments and Accountability Programs to Promote Quality of Health Care Delivery, the IOM Committee on Secondhand Smoke Exposure and Acute Coronary Events, and Co-Chair of the National Quality Forum Outpatient Imaging Efficiency Project Steering Committee. Dr. Peterson is also a member of the American Society for Clinical Investigation (ASCI) Council. He received the DukeMed Scholar Award in 2007. In April 2010 he was awarded, the Fred Cobb, MD Distinguished Professor of Medicine. He is also a contributing editor on the *Journal of the American Medical Association*.

Richard Platt, MD, MSc is Professor and Chair of the Harvard Medical School Department of Population Medicine at the Harvard Pilgrim Health Care Institute. He is principal investigator of the FDA's Mini-Sentinel program, of contracts with FDA's Center for Drugs Evaluation and Research and Center for Biologics Evaluation and Research to conduct post-marketing studies of drugs' and biologics' safety and effectiveness. Dr. Platt is also principal investigator of a CDC Prevention Epicenter, a CDC Center of Excellence in Public Health Informatics, and an Agency for Healthcare Research and Quality (AHRQ) HMO Research Network DEcIDE Center. He chaired the FDA's Drug Safety and Risk Management Advisory Committee, is a member of the Association of American Medical Colleges' Advisory Panel on Research. Dr. Platt was co-chair of the Board of Scientific Counselors of the Centers for Disease Control and Prevention's (CDC) Center for Infectious Diseases. Additionally, he chaired the National Institutes of Health study section, Epidemiology and Disease Control 2, and the CDC Office of Health Care Partnerships steering committee.

Joe V. Selby, MD, MPH is the first Executive Director of the Patient-Centered Outcomes Research Institute (PCORI). A family physician, clinical epidemiologist and health services researcher, he has more than 35 years of experience in patient care, research and administration. He will identify strategic issues and opportunities for PCORI and implement and administer programs authorized by the PCORI Board of Governors. Building on the work of the Board and interim staff, Selby will lead the organizational development of PCORI, which was established by Congress through the 2010 Patient Protection and Affordable Care Act. In addition to creating an organizational structure to carry out a national research agenda, Selby will lead PCORI's external communications, including work to establish effective two-way communication channels with the public and stakeholders about PCORI's work. Selby joined PCORI from Kaiser Permanente, Northern California, where he was Director of the Division of Research for 13 years and oversaw a department of more than 50 investigators and 500 research staff working on more than 250 ongoing studies. He was with Kaiser Permanente for 27 years. An accomplished researcher, Selby has authored more than 200 peer-reviewed articles and continues to conduct research, primarily in the areas of diabetes outcomes and quality improvement. His publications cover a spectrum of topics, including effectiveness studies of colorectal cancer screening strategies; treatment effectiveness, population management and disparities in diabetes mellitus; primary care delivery and quality measurement. Selby was elected to membership in the Institute of Medicine in 2009 and was a member of the Agency for Healthcare Research and Quality study section for Health Care Quality and Effectiveness from 1999-2003. A native of Fulton, Missouri, Selby received his medical degree from Northwestern University and his master's in public health from the University of California, Berkeley. He was a commissioned officer in the Public Health Service from 1976-1983 and received the Commissioned Officer's Award in 1981. He serves as Lecturer in the Department of Epidemiology and Biostatistics, University of California, San Francisco School of Medicine, and as a Consulting Professor, Health Research and Policy, Stanford University School of Medicine. Selby was appointed PCORI executive director on May 16, 2011, and formally begins his duties on July 1, 2011.

Rachel E. Sherman, MD, MPH is the Associate Director for Medical Policy, Center for Drug Evaluation and Research, U.S. Food and Drug Administration. She is responsible for developing, implementing, and coordinating medical policy programs and strategic initiatives, including regulation of prescription drug promotion and advertising through the Center's Division of Drug Marketing, Advertising, and Communications. Dr. Sherman provides leadership and scientific guidance and advice in clinical trial implementation and facilitates the development and implementation of Agency policy related to human subject protection and good clinical practices through the development of regulations, guidance documents, and procedures related to medical policy issues. Key activities involve leveraging resources and expertise from within FDA and from industry, academia, and other federal agencies to achieve Agency goals. Dr. Sherman is leading the Agency's implementation of the Sentinel Initiative and the development and implementation of biosimilars policy. Dr. Sherman began her career with FDA in the Division of Antiviral Drug Products in CDER in 1989. During her tenure there, both as a medical reviewer and team leader, she played a pivotal role in the rapid development of new agents to treat HIV and other viral diseases. Since 1998, she has held a series of senior management positions in the Agency, including Deputy Office Director for the Office of Drug Evaluation I, Deputy Office Director of the Office of Medical Policy in CDER, and Associate Commissioner for Clinical Programs. From 2003 until her return to CDER in 2009, Dr. Sherman directed the Office of Critical Path Programs in the Office of the Commissioner, leading FDA's Critical Path Initiative, an Agency initiative to spur innovation and foster efforts to modernize the way FDA-regulated products are developed, evaluated, manufactured, and used. Dr. Sherman is a board certified internist and infectious disease subspecialist. She received her A.B in mathematics from Washington University, her M.D. from Mt. Sinai School of Medicine, and her M.P.H. from The Johns Hopkins School of Hygiene and Public Health.

José M. Vega, MD is Vice President of Amgen Global Safety. In his current role, Dr. Vega is responsible for leading the company's global safety and pharmacovigilance efforts. He joined Amgen in 2003 and served as Senior Director, Medical Sciences, where he led the Proof of Concept Group in Early Development responsible for the development and validation of clinical pharmacodynamic biomarkers across all therapeutic

areas. From February 2004 through July 2004 he also had responsibility for the Nephrology/Anemia Therapeutic Area in Global Clinical Development. From January 2005 through July 2008, Dr. Vega led the General Medicine Therapeutic Area in Global Development with oversight for all Phase 2 - 4 clinical development programs at Amgen in the areas of Nephrology, Metabolic Disorders, Neuroscience, and Cardiovascular. Prior to joining Amgen, Dr. Vega was at Merck Research Laboratories for 7 years, first as Associate Director and then as Director in Clinical Pharmacology and for 2 years as Senior Director in Clinical Drug Metabolism. Previous to Merck he practiced and taught at the Massachusetts General Hospital and the Harvard Medical School as a Staff Emergency Dept. Physician for 5 years and as part of an academic primary care and internal medicine practice for 2 years. During his career he has served in various capacities on many medical and industry committees and has been co-author on numerous published articles in scientific and medical journals. From 2004 to 2007 he served as industry representative on the FDA Gastrointestinal Drugs Advisory Committee. Since 2008 Dr. Vega has represented Amgen on the Steering Committee of the Clinical Trials Transformation Initiative (CTTI) and served as team co-leader of the CTTI SAE Reporting Project. Dr. Vega received his MD, AM, and AB from Harvard University.

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LARGE SIMPLE TRIALS AND KNOWLEDGE GENERATION IN A LEARNING HEALTH SYSTEM

Speaker Biographies

Robert M. Califf, MD is Vice Chancellor for Clinical and Translational Research at Duke and leads the Duke Translational Medicine Institute, an organization focused on translating scientific discoveries into improved health outcomes. Before leading the DTMI, he was founding director of the Duke Clinical Research Institute, a premier academic research organization now part of the DTMI. Under his leadership, the DCRI grew into an organization with more than 1000 employees and an annual budget of over $100 million; the DTMI currently has a budget of over $300 million. Born in 1951 in Anderson, SC, Dr. Califf attended high school in Columbia, where he played on the 1969 AAAA SC championship basketball team. He attended Duke both as an undergraduate and for medical school, completing his residency at UCSF before returning to Duke for a cardiology fellowship. An international leader in cardiovascular medicine, health outcomes, healthcare quality, and medical economics, he is among the most frequently cited authors in medicine. Dr. Califf is married to Lydia Carpenter Califf; they have three children and one grandchild. He enjoys spending time with his family, working on his golf game, listening to music, and cheering on the Duke men's and women's basketball teams.

Niteesh K. Choudhry, MD, PhD is an internist and health services researcher whose work focuses on the clinical and economic consequences of using evidence-based therapies for the management of common chronic conditions. He is particularly interested in the design and evaluation of novel strategies to overcome barriers to treatment initiation and long-term medication adherence. His work employs a broad range of methods including randomized policy evaluations, cost-effectiveness modeling, claims analyses, and surveys and he regularly collaborates with large health insurers and employers to conduct his research. He has published over 125 peer-articles in leading medical and policy journals and has won awards from AcademyHealth, the Society of General Internal Medicine, the International Society of Pharmacoeconomics and Outcomes Research, and the National Institute of Health Care Management for his research. Dr. Choudhry is an Associate Professor at Harvard Medical School and Associate Physician in the Division of Pharmacoepidemiology and Pharmacoeconomics and the Hospitalist Program at Brigham and Women's Hospital. He attended McGill University, received his M.D. and completed his residency training in Internal Medicine at the University of Toronto and then served as Chief Medical Resident for the Toronto General and Toronto Western Hospitals. He did his Ph.D. in Health Policy at Harvard University, with a concentration in statistics and the evaluative sciences, and was a Fellow in Pharmaceutical Policy Research at Harvard Medical School. His work is funded by the Robert Wood Johnson Foundation, the Commonwealth Fund, the Aetna Foundation, CVS Caremark, the Agency for Healthcare Quality and Research and others. Dr. Choudhry practices inpatient general internal/hospital medicine and has won numerous awards for teaching excellence.

Elizabeth A. Chrischilles, PhD, professor in the Department of Epidemiology, holds the Marvin A. and Rose Lee Pomerantz Chair in Public Health in the University of Iowa College of Public Health. Dr. Chrischilles is Principal Investigator of the Iowa Developing Evidence to Inform Decisions about Effectiveness (Iowa DEcIDE) Center and co-investigator on a pragmatic trial in the NIH Common Fund's Health Care Systems Research Collaboratory. She is also involved in cluster-randomized trials of team management interventions, prospective follow-up of prognostic cohorts, linkage of claims data to

prospective registries and cohorts, and leading a research team that is investigating multiple uses of an internet-based personal health record designed with older adults.

P.J. Devereaux, MD, PhD, FRCP(C) obtained his MD from McMaster University. After medical school he completed a residency in internal medicine at the University of Calgary and a residency in cardiology at Dalhousie University. He then completed a PhD in Clinical Epidemiology at McMaster University. Dr. Devereaux holds a Heart and Stroke Foundation of Ontario Career Investigator Award. He is the Head of Cardiology and the Perioperative Cardiovascular Clinical Program at the Juravinski Hospital and Cancer Centre. He is also the Scientific Leader of the Perioperative Medicine and Surgical Research Group at the Population Health Research Institute. The focus of his clinic research is vascular complications around the time of surgery. He is undertaking several large international RCTs and observational studies addressing this issue. Dr. Devereaux has published over 150 peer reviewed papers and 40 editorials, book chapters, and commentaries.

Ruth R. Faden, PhD, MPH is the Philip Franklin Wagley Professor of Biomedical Ethics and Director of the Johns Hopkins Berman Institute. She is also a Senior Research Scholar at the Kennedy Institute of Ethics, Georgetown University. Dr. Faden is the author and editor of many books and articles on biomedical ethics and health policy including *Social Justice: The Moral Foundations of Public Health and Health Policy* (with Madison Powers), *A History and Theory of Informed Consent* (with Tom L. Beauchamp), *AIDS, Women and the Next Generation* (Ruth Faden, Gail Geller and Madison Powers, eds.), and *HIV, AIDS and Childbearing: Public Policy, Private Lives* (Ruth Faden and Nancy Kass, eds.). Dr. Faden is a member of the Institute of Medicine and a Fellow of the Hastings Center and the American Psychological Association. She has served on numerous national advisory committees and commissions, including the President's Advisory Committee on Human Radiation Experiments, which she chaired. She is a co-founder of the Hinxton Group, a global community committed to advancing ethical and policy challenges in stem cell science, and the Second Wave project, an effort to ensure that the health interests of pregnant women are fairly represented in biomedical research and drug and device policies. Dr. Faden was the recipient of Lifetime Achievement Awards from the American Society for Bioethics and Humanities and from Public Responsibility in Medicine and Research (PRIMR) in 2011. Dr. Faden's current research focuses on questions of social justice in public policy and global health. She also works on ethical challenges in biomedical science and in women's health. Dr. Faden's work in social justice is concentrated on justice theory and national and global challenges in learning health care systems, health systems design and priority setting, and access to the benefits of global investments in biomedical research.

Ryan E. Ferguson, ScD, MPH is the Acting Director of the VA Cooperative Studies Program Coordinating Center in Boston, MA, where he is involved in the conduct of large multi-center randomized clinical trials. He also currently serves as the program director for the VA's Point of Care Research Initiative. Dr. Ferguson joined the Cooperative Studies Program in 2001 and has since focused on clinical trial methodologies for conducting pragmatic comparative effectiveness trials. In addition to the conduct of trials, his research interests include general clinical trials methodology, Bayesian statistics, renal epidemiology, molecular and genetic epidemiology, and translational research. Dr. Ferguson's published work includes first authored publications, abstracts, presentations and a book chapter (currently in-press). Dr. Ferguson is on faculty at Boston University School of Public Health where he is Assistant Professor of Epidemiology. He is also a member of the Society for Clinical Trials, the Society for Epidemiologic Research, and the American Statistical Association.

Kenneth A. Getz is the Director of Sponsored Research Programs and Research Assistant Professor at the Tufts Center for the Study of Drug Development where he studies R&D management practices; pharmaceutical and biotechnology company operating models; and global investigative site, outsourcing, and study volunteer practices, trends and policies. Ken is also the chairman of CISCRP – a nonprofit

organization that he founded to educate and raise public awareness of the clinical research enterprise -- and the founder and owner of CenterWatch, a leading publisher in the clinical trials industry. A well-known speaker at conferences, symposia, universities and corporations, Ken has published extensively in peer-review journals, the trade press, and books. He holds a number of board appointments in the private and public sectors, is on the editorial boards of *Contemporary Clinical Trials*, *Research Practitioner*, the *Drug Information Journal, Pharmaceutical Medicine* and writes a column for *Applied Clinical Trials* that was a 2010 Neal Award finalist. Ken received an MBA from the J.L. Kellogg Graduate School of Management at Northwestern University and a bachelor's degree, Phi Beta Kappa, from Brandeis University. Prior to founding CenterWatch, Ken worked for over seven years in management consulting where he assisted biopharmaceutical companies develop and implement business strategies to improve clinical development performance.

Alan S. Go, MD completed his Internal Medicine training and a General Internal Medicine fellowship in clinical research at the University of California, San Francisco (UCSF) before joining the Kaiser Permanente Northern California Division of Research in 1998. He is currently Chief, Cardiovascular and Metabolic Conditions Section; Director, Comprehensive Clinical Research Unit; and Regional Medical Director of Clinical Trials through the Kaiser Permanente Northern California Division of Research. He is also Associate Professor in the Departments of Epidemiology, Biostatistics, and Medicine at UCSF and Consulting Professor in the Department of Health Research and Policy at the Stanford University School of Medicine. Dr. Go is also Chair of the American Heart Association Epidemiology and Prevention Council's Statistics and Stroke Statistics Committee. Dr. Go is a clinical epidemiologist, outcomes researcher, and clinical trialist in the areas of cardiovascular and renal disease. He also leads several large multi-center cohort studies in these areas, including the NHLBI-sponsored Cardiovascular Research Network (CVRN), a research consortium of 14 health plans in the US. He is Principal Investigator of the ATRIA-CVRN Study of >34,000 adults with incident atrial fibrillation and the CVRN PRESERVE cohort of >30,000 adults with heart failure and documented systolic function. Dr. Go also leads several prospective cohort studies including the NIDDK-sponsored Assessment, Serial Assessment, and Subsequent Sequelae of Acute Kidney Injury (ASSESS-AKI) Study and Chronic Renal Insufficiency Cohort (CRIC) Study. Dr. Go's current research interests include optimizing stroke prevention strategies for atrial fibrillation; epidemiology and outcomes of heart failure with preserved vs. reduced systolic function; improving quality of care for primary and secondary prevention of cardiovascular diseases; genetics of cardiovascular diseases; and delineating the roles of acute kidney injury and chronic kidney disease in influencing cardiovascular and renal-related adverse events.

Christopher B. Granger, MD, FACC, FAHA is a Professor of Medicine in the Division of Cardiology at Duke University and Director of the Cardiac Care Unit for the Duke University Medical Center. Dr. Granger is a Fellow of the American College of Cardiology, the American Heart Association, and of the European Society of Cardiology. He is Associate Editor of the *American Heart Journal* and serves on the editorial board of the *Journal of the American College of Cardiology*. He is a cardiology section author for *Current Medical Diagnosis and Treatment*. He serves on the publication oversight committee of the American Heart Association and he is chairman of the Advisory Working Group of the American Heart Association Mission: Lifeline program. He is a member of the 2011 ACC/AHA STEMI Guidelines Committee. He has served on FDA advisory committees on an *ad hoc* basis. He is on the Board of External Experts of the National Heart, Lung and Blood Institute (NHLBI). Dr. Granger's primary research interest is in the conduct and methodology of large randomized clinical trials in heart disease; he has co-authored more than 400 peer-reviewed manuscripts. He currently serves on a number of clinical trial steering committees and data safety monitoring committees. He has coordinated the Duke Clinical Research Institutes' activities in many clinical trials evaluating acute MI reperfusion and antithrombotic strategies in acute coronary syndromes and in atrial fibrillation. Dr. Granger is co-chairman of the Steering Committee of the ARISTOTLE trial assessing an oral factor Xa inhibitor for stroke prevention

in atrial fibrillation. In addition, he is co-director of the Reperfusion of Acute MI in Carolina Emergency Departments (RACE) projects, North Carolina state-wide programs to improve reperfusion care for acute myocardial infarction and care for cardiac arrest.

Rosemarie Hakim, PhD is a senior research advisor at the Centers for Medicare & Medicaid Services. She has worked extensively with CMS staff and with the public on coverage with evidence development and CMS' clinical trial policy. She currently works with researchers to develop projects related to coverage, CED, and post coverage analyses using CMS claims and registry data. She has developed and overseen multiple studies that have used CMS data. She has a doctorate in epidemiology from the Johns Hopkins Bloomberg School of Public Health and has extensive experience in observational study design and analysis, clinical trial design and analysis and evidence development.

Peter Held MD, PhD, FACC is currently a Medical Science Director leading an AstraZeneca effort to improve the conduct and delivery of the company's large clinical outcome studies. He is currently responsible for a number of global ongoing or planned such studies in the cardiovascular and in the respiratory field. He has long experience from, and interest in, the methodology and conduct of both traditionally run and simplified trials. During the late 1980´s he spent time at the NHLBI as a visiting scientist and project officer, involved in the planning and conduct of mortality/morbidity trials in heart failure and atherosclerosis. Since 1993 he has been employed by AstraZeneca R&D, based in Gothenburg, Sweden. He has designed and led many global clinical development programs with a large number of new chemical entities, leading to successful demonstration of benefit and resulting in regulatory approvals. A scholar from the Universities of Uppsala, Linköping and Göteborg, Sweden, he received his MD and PhD during the mid 1980´s. He specialised in cardiology and internal medicine and was appointed associate professor of cardiology in 1989. Adjunct professor of clinical CV research at the University of Gothenburg 2001-2010.

Rebecca Daniels Kush, PhD is Founder, President and CEO of the Clinical Data Interchange Standards Consortium (CDISC), a non-profit standards developing organization (SDO) with a mission to develop and support global, platform-independent standards that enable information system interoperability to improve medical research and related areas of healthcare and a vision of *"Informing patient care and safety through higher quality medical research"*. Dr. Kush has over 25 years of experience in the area of clinical research, including positions with the U.S. National Institutes of Health, academia, a global CRO and biopharmaceutical companies in the U.S. and Japan. She earned her doctorate in Physiology and Pharmacology from the University of California San Diego (UCSD) School of Medicine. She is lead author on the book: eClinical Trials: Planning and Implementation and has authored numerous publications for journals, including New England Journal of Medicine and Science Translational Medicine. She has developed a Prescription Education Program for elementary and middle schools and was named in PharmaVoice in 2008 as one of the 100 most inspiring individuals in the life-sciences industry. Dr. Kush has served on the Board of Directors for the U.S. Health Information Technology Standards Panel (HITSP), Drug Information Association (DIA) and currently Health Level 7 (HL7), and she was a member of the advisory committee for the WHO International Clinical Trials Registry Platform. Dr. Kush served on the appointed Planning Committee for the HHS/ONC-sponsored Workshop Series on the "Digital Infrastructure for the Learning Health System" for the National Academy of Sciences Institute of Medicine (IOM) and has presented at other IOM meetings. She is a member of the National Cancer Advisory Board IT Workgroup and was invited to represent research as an appointed member of the U.S. Health Information Technology (HIT) Standards Committee. Dr. Kush has developed a course "A Global Approach to Accelerating Medical Research" and has been a keynote speaker at numerous conferences in this arena in Europe, U.S., Brazil, Japan, China, Korea and Australia.

Carole M. Lannon, MD, MPH is board-certified in pediatrics and internal medicine, and has a master's in epidemiology. She is nationally-recognized for her expertise in improvement science and systems improvement. She is Director, Learning Networks Core, James M. Anderson Center for Health Systems Excellence at Cincinnati Children's Hospital Medical Center (CCHMC), Professor of Pediatrics at the University of Cincinnati, and Senior Quality Advisor for the American Board of Pediatrics. Dr. Lannon is the design and implementation lead for several results-oriented, outcomes-focused improvement networks, including the Ohio Perinatal Quality Collaborative and the National Pediatric Cardiology Quality Improvement Collaborative. Dr. Lannon is principal investigator of the pediatric Center for Education and Research in Therapeutics (CERTs), funded by the Agency for Health Care Research and Quality. She is former Associate Editor of the Journal of Quality and Safety in Healthcare. She played a lead role in the design and start-up of improvement initiatives for the American Academy of Pediatrics and the National Initiative for Children's Healthcare Quality.

Deven McGraw is the Director of the Health Privacy Project at CDT. The Project is focused on developing and promoting workable privacy and security protections for electronic personal health information. Ms. McGraw is active in efforts to advance the adoption and implementation of health information technology and electronic health information exchange to improve health care. She was one of three persons appointed by Kathleen Sebelius, the Secretary of the U.S. Department of Health & Human Services (HHS), to serve on the Health Information Technology (HIT) Policy Committee, a federal advisory committee established in the American Recovery and Reinvestment Act of 2009. She also served on two key workgroups of the American Health Information Community (AHIC), the federal advisory body established by HHS in the Bush Administration to develop recommendations on how to facilitate use of health information technology to improve health. Specifically, she co-chaired the Confidentiality, Privacy and Security Workgroup and was a member of the Personalized Health Care Workgroup. She also served on the Policy Steering Committee of the eHealth Initiative and now serves on its Leadership Committee. She is also on the Steering Group of the Markle Foundation's Connecting for Health multi-stakeholder initiative. Ms. McGraw has a strong background in health care policy. Prior to joining CDT, Ms. McGraw was the Chief Operating Officer of the National Partnership for Women & Families, providing strategic direction and oversight for all of the organization's core program areas, including the promotion of initiatives to improve health care quality. Ms. McGraw also was an associate in the public policy group at Patton Boggs, LLP and in the health care group at Ropes & Gray. She also served as Deputy Legal Counsel to the Governor of Massachusetts and taught in the Federal Legislation Clinic at the Georgetown University Law Center. Ms. McGraw graduated magna cum laude from the University of Maryland. She earned her J.D., magna cum laude, and her L.L.M. from Georgetown University Law Center and was Executive Editor of the *Georgetown Law Journal*. She also has a Master of Public Health from Johns Hopkins School of Hygiene and Public Health.

Robert E. Ratner, MD is Chief Scientific & Medical Officer for the American Diabetes Association, the nation's largest voluntary health organization leading the fight to Stop Diabetes®. Dr. Ratner joined the Association in May 2012 and provides leadership and oversight of scientific and medical activities including research, clinical affairs, program recognition and certification, medical information and professional education. In this capacity, he oversees the Association's support of a broad range of professional education activities and the development of the American Diabetes Association Clinical Practice Recommendations, clinical consensus reports and expert opinions. In 2011, the Association provided $34.6 million in research funds, funding more than 400 grants at 139 leading U.S. research institutions. Prior to joining the American Diabetes Association, Dr. Ratner was a Professor of Medicine at Georgetown University Medical School and Senior Research Scientist at the MedStar Health Research Institute in metropolitan Washington, DC. He recently completed a sabbatical as a Robert Wood Johnson Foundation Health Policy Fellow, having served as the study director for the Institute of Medicine Comparative Effectiveness Research Priorities Committee, and a program examiner for health

reform in the Health Division of the U.S. Office of Management and Budget. He received his MD from Baylor College of Medicine in Houston, Texas where he also completed his Internal Medicine training. He underwent fellowship training in Endocrinology and Metabolism at Harvard Medical School and the Joslin Diabetes Center in Boston. He recently completed six years of service on the Steering Committee of the National Diabetes Education Program (NDEP), representing the American Diabetes Association. He has served on the Board of Directors of the National Certification Board for Diabetes Education and the American Association of Diabetes Educators, and is Past-President of the Washington Area Affiliate of the American Diabetes Association. He has served as the Chair of the Government Relations Committee and the Pregnancy Council of the American Diabetes Association. He was a Principle Investigator for the Diabetes Prevention Program (DPP) and DPP Outcomes Study of the National Institutes of Health (NIH) and served on the Steering Committee for the project nationwide. At Georgetown University, he served on the University Research Committee, and co-chaired the Joint Oversight Committee for Clinical Research. He was an Associate Editor of the *Journal of Clinical Endocrinology and Metabolism*. His research interests include diabetes therapeutics and complications, with an emphasis on translational efforts from controlled trials into community-based practice. He is the author of more than 130 original scientific articles and 20 book chapters.

Nancy Roach founded Fight Colorectal Cancer (Fight CRC) in 2005, nine years after her mother-in-law was diagnosed with colorectal cancer. Recognizing the need for an advocacy organization, she established Fight CRC to provide focus, infrastructure and support for colorectal cancer survivors, caregivers and those touched by the disease. Since then, Ms. Roach has played a vital role in championing the need for a cure for colon and rectal cancer, through screening, awareness and research. Her efforts as an advocate have supported education and support for patients as well as the research community. Her leadership and passion has fostered a community of advocates supporting state and federal policies that have led to increased colorectal cancer research opportunities across the country. Over the last four years, Fight Colorectal Cancer has directed more than $250,000 in research funding to young investigators. Ms. Roach currently serves as the chair of the Board of Directors and serves on the National Cancer Institute (NCI) Board of Scientific Counselors and the Clinical Trial and Translational Research Advisory Committee. She is on the Executive Committee on the Clinical Trials Transformation Initiative, an FDA-Duke public-private partnership, and is a past chair of its finance committee. She has been involved with cooperative groups and SPORES, and currently serves on the NCI Colon Task force. She served on the Department of Defense Congressionally Directed Medical Research Program Integration Panel in 2010, the first year the colorectal cancer research was funded by the program. She is a past chair of the NCI Patient Advocate Steering Committee, and received the NCI Director's Service Award when she stepped down. She has also received the Preventing Colorectal Cancer Champion Award and the Colon Cancer Alliance Sapphire Visionary Award in recognition of her efforts on behalf of patients. She has spoken on behalf of patients at meetings such as the American Association for Cancer Research, the Friends of Cancer Research/Brookings Institute Conference on Clinical Research, and the Oxford University-Duke University-McMaster University Sensible Guidelines for Clinical Trials.

Kate Ryan, MPA is the Senior Program Coordinator at the National Women's Health Network. In this role, she is responsible for developing and implementing a program of legislative and regulatory advocacy that focuses on reducing women's exposure to unnecessary drug and medical treatment risks. Kate leads advocacy efforts to increase research on women's health and increase women's participation in clinical trials and health research. Through work with the National Institute of Child Health and Human Development and the Food and Drug Administration, Kate brings women's voices to the health policy debates in Washington, DC and the states, and advocates for a health care system that is accessible to all and meets the needs of diverse women. Prior to joining the NWHN, Kate worked in the Capitol Hill office of U.S. Representative Joe Sestak (D-PA), where she worked on health care reform, the

women's issues portfolio, and managed a variety of constituent services programs. Before moving to Washington, DC, Kate volunteered in Ghana with the Alliance for Reproductive Health Rights to monitor and assess availability of, and access to, women's sexual and reproductive health services under the Ghanaian National Health Insurance Scheme. As part of this work, Kate also monitored Ghana's progress on Millennium Development Goals 4 & 5 – to reduce child mortality and improve maternal health. Kate received her MPA in International Public & Non-Profit Management and Policy Analysis with a focus in women's rights from the NYU Wagner Graduate School of Public Service.

Lewis G. Sandy, MD is Senior Vice President, Clinical Advancement, UnitedHealth Group (a Fortune 25 diversified health and well-being company dedicated to helping people live healthier lives). At UnitedHealth Group he focuses on clinical innovation, payment/delivery reforms to modernize our health care system, and physician collaboration. He also is a Principal in the UnitedHealth Center for Health Reform and Modernization, with a focus on payment/delivery innovation and policy. From 2003 to 2007, he was EVP and Chief Medical Officer of UnitedHealthcare, UnitedHealth Group's largest business focusing on the employer/individual health benefits market. From 1997 to 2003, he was EVP of The Robert Wood Johnson Foundation. At RWJF, he was responsible for the Foundation's program development and management, strategic planning and administrative operations. Prior to this, Dr. Sandy was a program VP of the Foundation, focusing on the Foundation's workforce, health policy, and chronic care initiatives. An internist and former health center medical director at the Harvard Community Health Plan in Boston, Massachusetts, Dr. Sandy received his B.S. and M.D. degrees from the University of Michigan and an M.B.A. degree from Stanford University. A former RWJF Clinical Scholar and Clinical Fellow in Medicine at the University of California, San Francisco, Dr. Sandy served his internship and residency at the Beth Israel Hospital in Boston. He is a Senior Fellow of the University of Minnesota School of Public Health, Department of Health Policy and Management.

Elsie M. Taveras, MD, MPH is an Associate Professor of Population Medicine at Harvard Medical School and Associate Professor of Pediatrics at Children's Hospital Boston. She received her bachelor of science and medical doctor degrees at New York University in New York City. After receiving her M.D., she did her internship, residency, and chief residency, at the Boston Combined Residency Program in Pediatrics, a joint program of Children's Hospital Boston and Boston Medical Center. In 2001, Dr. Taveras joined the Harvard Pediatric Health Services Research Fellowship Program and received her Master's in Public Health with a concentration in clinical effectiveness from the Harvard School of Public Health. Dr. Taveras is the Co-Director of the Obesity Prevention Program at the Department of Population Medicine. Dr. Taveras is also on staff at Children's Hospital Boston where she directs a multidisciplinary childhood obesity prevention clinic in General Pediatrics. Dr. Taveras' main focus of research is understanding determinants of obesity in children and adolescents and developing interventions across the lifecourse to prevent obesity in children, especially in underserved populations. Dr. Taveras' publications have examined diet, activity, sleep, and weight determinants in later childhood, and early life origins of obesity in young children.

Tjeerd van Staa, MD, PhD, MSc, MA studied medicine and received his degree in 1987 at the Erasmus University of Rotterdam, the Netherlands. After several years of working as a practising physician, he joined the pharmaceutical industry and worked as an epidemiologist and was also the European Qualified Person for Drug Safety. During this time, he obtained a MSc in Epidemiology (McGill University, Canada) and was awarded a PhD in Pharmacoepidemiology at Utrecht University in 1999. He has also a MA in Medical Law and Ethics. In 2006, he joined the Medicines and Health products Regulatory Agency as Director of Research of the Clinical Practice Research Datalink (the General Practice Research Database is part of CPRD). He has published over 130 peer-reviewed articles and is a well-recognised speaker in the field of pharmacoepidemiology, pharmacovigilance and osteoporosis. He has been awarded several academic affiliations (Utrecht University, the Netherlands;

Medical Research Council, Southampton, UK) and is Honorary Professor at the London School of Hygiene & Tropical Medicine. Van Staa is the recipient of the 2005 *Iain I Boyle Award* of the European Calcified Tissue Society (a monetary price awarded to the scientist who has made significant contributions to bone disease research (http://www.ectsoc.org/). His current research activities concern the implementation of randomised clinical trials that use routinely collected electronic health records (as outlined in a recent article in the British Medical Journal). Two cluster trials (randomising practices) and a large pharmacogenetic study within GPRD are close to completion. Van Staa is also involved in the implementation of multiple linkages of GPRD to other health care datasets, including cancer and registries, cardiovascular disease registries, air pollution and bowel screening data. Visualisation and evaluation of data quality are other research interests.

James B. Young, MD is Professor of Medicine and Executive Dean, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University and Chairman, Endocrinology and Metabolism Institute. He is also Physician Director of Institutional Relations and Development and a Medical Director of the Kaufman Center for Heart Failure. He holds the George and Linda Kaufman Chair and is the Study Chairman of the NIH, FDA, and CMS Interagency Registry for Mechanical Circulatory Assist Support (INTERMACS). He has a joint appointment to the Clinic's Multi-organ Transplant Center. Dr. Young is certified as a Diplomat of the American Board of Internal Medicine as well as the subspecialty of Cardiovascular Disease and holds medical licensure from the states of California, Illinois, Ohio, Pennsylvania and Texas. Dr. Young spent his early years in the San Francisco Bay Area and then attended the University of Kansas, where he received his Bachelor of Arts degree with Honors in Biology and was a resident of Stephenson Scholarship Hall. He matriculated to Baylor College of Medicine in Houston, Texas, where he was awarded his Medical Doctor degree with honors in 1974 and was elected to the Alpha Omega Alpha medical honor society. Dr. Young remained in Houston at the Baylor Affiliated Hospitals to complete his clinical training, joining the faculty, and becoming a Professor of Medicine with Tenure in 1992. He was the Clinical Coordinator and Scientific Director for Dr. Michael E. DeBakey's Multi-organ Transplant Center at The Methodist Hospital and Baylor College of Medicine. He subsequently relocated to the Cleveland Clinic, Cleveland, Ohio, in 1995 when he became Head of the Section of Heart Failure and Cardiac Transplant Medicine in the Department of Cardiovascular Disease. In 1998 Dr. Young, along with his surgical colleague Dr. Patrick McCarthy, created the Kaufman Center for Heart Failure at the Cleveland Clinic. Dr. Young's research activities began during his residency and fellowship training when he was a Lipid Research Clinic (LRC) physician. He subsequently focused his efforts on heart failure, mechanical circulatory support, and cardiac transplant therapeutics including early experiences with dopamine receptor agonists, angiotensin-converting enzyme inhibitors, beta blockers, calcium channel blockers, angiotensin receptor blockers, many new immunosuppressants, and a variety of parenteral inotropes and vasodilators. He has collaborated extensively with his basic science research associates focusing on 'translational' research with respect to the molecular biology of cardiac remodeling, allograft arteriopathy, and transplanted heart rejection. Dr. Young served as the United States Principal or Co-Principal Investigator for the HOPE, RESOLVED, SPICE, VMAC, MIRACLE-ICD, RED-HF, ACCLAIM, ONTARGET, TRANSCEND, and CHARM multi-center clinical trials. He has participated in over 150 clinical trials as an investigator. Dr. Young has published almost 600 manuscripts and several textbooks. Professionally, Dr. Young is most proud of his contributions to the development and administration of donor organ procurement programs, his efforts to secure recognition for the newly emerging cardiology subspecialty of "Heart Failure and Cardiac Transplant Medicine", his collaborations with basic and clinical scientists, his contributions to a unique medical school curriculum, and the programs that he helped develop in Houston and Cleveland.

Bram Zuckerman, MD is a graduate of the Boston University Medical School. He completed post-graduate training in internal medicine at Baltimore City Hospital and cardiology at the Johns Hopkins program. Prior to joining FDA in 1992, he was involved in basic research in hemodynamics at the University of Colorado Medical School and practiced noninvasive and invasive cardiology in Denver, Colorado and Northern Virginia. He joined the FDA Division of Cardiovascular Devices (DCD) as a Medical Officer in 1992 and has been actively involved in development and review of clinical trials for many new cardiovascular devices. In May 2001 he was appointed a Deputy Director in DCD. He was appointed to his current position as Director of the FDA Division of Cardiovascular Devices in September 2002.

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LARGE SIMPLE TRIALS AND KNOWLEDGE GENERATION IN A LEARNING HEALTH SYSTEM

Speaker Biographies

Robert M. Califf, MD is Vice Chancellor for Clinical and Translational Research at Duke and leads the Duke Translational Medicine Institute, an organization focused on translating scientific discoveries into improved health outcomes. Before leading the DTMI, he was founding director of the Duke Clinical Research Institute, a premier academic research organization now part of the DTMI. Under his leadership, the DCRI grew into an organization with more than 1000 employees and an annual budget of over $100 million; the DTMI currently has a budget of over $300 million. Born in 1951 in Anderson, SC, Dr. Califf attended high school in Columbia, where he played on the 1969 AAAA SC championship basketball team. He attended Duke both as an undergraduate and for medical school, completing his residency at UCSF before returning to Duke for a cardiology fellowship. An international leader in cardiovascular medicine, health outcomes, healthcare quality, and medical economics, he is among the most frequently cited authors in medicine. Dr. Califf is married to Lydia Carpenter Califf; they have three children and one grandchild. He enjoys spending time with his family, working on his golf game, listening to music, and cheering on the Duke men's and women's basketball teams.

Niteesh K. Choudhry, MD, PhD is an internist and health services researcher whose work focuses on the clinical and economic consequences of using evidence-based therapies for the management of common chronic conditions. He is particularly interested in the design and evaluation of novel strategies to overcome barriers to treatment initiation and long-term medication adherence. His work employs a broad range of methods including randomized policy evaluations, cost-effectiveness modeling, claims analyses, and surveys and he regularly collaborates with large health insurers and employers to conduct his research. He has published over 125 peer-articles in leading medical and policy journals and has won awards from AcademyHealth, the Society of General Internal Medicine, the International Society of Pharmacoeconomics and Outcomes Research, and the National Institute of Health Care Management for his research. Dr. Choudhry is an Associate Professor at Harvard Medical School and Associate Physician in the Division of Pharmacoepidemiology and Pharmacoeconomics and the Hospitalist Program at Brigham and Women's Hospital. He attended McGill University, received his M.D. and completed his residency training in Internal Medicine at the University of Toronto and then served as Chief Medical Resident for the Toronto General and Toronto Western Hospitals. He did his Ph.D. in Health Policy at Harvard University, with a concentration in statistics and the evaluative sciences, and was a Fellow in Pharmaceutical Policy Research at Harvard Medical School. His work is funded by the Robert Wood Johnson Foundation, the Commonwealth Fund, the Aetna Foundation, CVS Caremark, the Agency for Healthcare Quality and Research and others. Dr. Choudhry practices inpatient general internal/hospital medicine and has won numerous awards for teaching excellence.

Elizabeth A. Chrischilles, PhD, professor in the Department of Epidemiology, holds the Marvin A. and Rose Lee Pomerantz Chair in Public Health in the University of Iowa College of Public Health. Dr. Chrischilles is Principal Investigator of the Iowa Developing Evidence to Inform Decisions about Effectiveness (Iowa DEcIDE) Center and co-investigator on a pragmatic trial in the NIH Common Fund's Health Care Systems Research Collaboratory. She is also involved in cluster-randomized trials of team management interventions, prospective follow-up of prognostic cohorts, linkage of claims data to

prospective registries and cohorts, and leading a research team that is investigating multiple uses of an internet-based personal health record designed with older adults.

P.J. Devereaux, MD, PhD, FRCP(C) obtained his MD from McMaster University. After medical school he completed a residency in internal medicine at the University of Calgary and a residency in cardiology at Dalhousie University. He then completed a PhD in Clinical Epidemiology at McMaster University. Dr. Devereaux holds a Heart and Stroke Foundation of Ontario Career Investigator Award. He is the Head of Cardiology and the Perioperative Cardiovascular Clinical Program at the Juravinski Hospital and Cancer Centre. He is also the Scientific Leader of the Perioperative Medicine and Surgical Research Group at the Population Health Research Institute. The focus of his clinic research is vascular complications around the time of surgery. He is undertaking several large international RCTs and observational studies addressing this issue. Dr. Devereaux has published over 150 peer reviewed papers and 40 editorials, book chapters, and commentaries.

Ruth R. Faden, PhD, MPH is the Philip Franklin Wagley Professor of Biomedical Ethics and Director of the Johns Hopkins Berman Institute. She is also a Senior Research Scholar at the Kennedy Institute of Ethics, Georgetown University. Dr. Faden is the author and editor of many books and articles on biomedical ethics and health policy including *Social Justice: The Moral Foundations of Public Health and Health Policy* (with Madison Powers), *A History and Theory of Informed Consent* (with Tom L. Beauchamp), *AIDS, Women and the Next Generation* (Ruth Faden, Gail Geller and Madison Powers, eds.), and *HIV, AIDS and Childbearing: Public Policy, Private Lives* (Ruth Faden and Nancy Kass, eds.). Dr. Faden is a member of the Institute of Medicine and a Fellow of the Hastings Center and the American Psychological Association. She has served on numerous national advisory committees and commissions, including the President's Advisory Committee on Human Radiation Experiments, which she chaired. She is a co-founder of the Hinxton Group, a global community committed to advancing ethical and policy challenges in stem cell science, and the Second Wave project, an effort to ensure that the health interests of pregnant women are fairly represented in biomedical research and drug and device policies. Dr. Faden was the recipient of Lifetime Achievement Awards from the American Society for Bioethics and Humanities and from Public Responsibility in Medicine and Research (PRIMR) in 2011. Dr. Faden's current research focuses on questions of social justice in public policy and global health. She also works on ethical challenges in biomedical science and in women's health. Dr. Faden's work in social justice is concentrated on justice theory and national and global challenges in learning health care systems, health systems design and priority setting, and access to the benefits of global investments in biomedical research.

Ryan E. Ferguson, ScD, MPH is the Acting Director of the VA Cooperative Studies Program Coordinating Center in Boston, MA, where he is involved in the conduct of large multi-center randomized clinical trials. He also currently serves as the program director for the VA's Point of Care Research Initiative. Dr. Ferguson joined the Cooperative Studies Program in 2001 and has since focused on clinical trial methodologies for conducting pragmatic comparative effectiveness trials. In addition to the conduct of trials, his research interests include general clinical trials methodology, Bayesian statistics, renal epidemiology, molecular and genetic epidemiology, and translational research. Dr. Ferguson's published work includes first authored publications, abstracts, presentations and a book chapter (currently in-press). Dr. Ferguson is on faculty at Boston University School of Public Health where he is Assistant Professor of Epidemiology. He is also a member of the Society for Clinical Trials, the Society for Epidemiologic Research, and the American Statistical Association.

Kenneth A. Getz is the Director of Sponsored Research Programs and Research Assistant Professor at the Tufts Center for the Study of Drug Development where he studies R&D management practices; pharmaceutical and biotechnology company operating models; and global investigative site, outsourcing, and study volunteer practices, trends and policies. Ken is also the chairman of CISCRP – a nonprofit

organization that he founded to educate and raise public awareness of the clinical research enterprise -- and the founder and owner of CenterWatch, a leading publisher in the clinical trials industry. A well-known speaker at conferences, symposia, universities and corporations, Ken has published extensively in peer-review journals, the trade press, and books. He holds a number of board appointments in the private and public sectors, is on the editorial boards of *Contemporary Clinical Trials*, *Research Practitioner*, the *Drug Information Journal, Pharmaceutical Medicine* and writes a column for *Applied Clinical Trials* that was a 2010 Neal Award finalist. Ken received an MBA from the J.L. Kellogg Graduate School of Management at Northwestern University and a bachelor's degree, Phi Beta Kappa, from Brandeis University. Prior to founding CenterWatch, Ken worked for over seven years in management consulting where he assisted biopharmaceutical companies develop and implement business strategies to improve clinical development performance.

Alan S. Go, MD completed his Internal Medicine training and a General Internal Medicine fellowship in clinical research at the University of California, San Francisco (UCSF) before joining the Kaiser Permanente Northern California Division of Research in 1998. He is currently Chief, Cardiovascular and Metabolic Conditions Section; Director, Comprehensive Clinical Research Unit; and Regional Medical Director of Clinical Trials through the Kaiser Permanente Northern California Division of Research. He is also Associate Professor in the Departments of Epidemiology, Biostatistics, and Medicine at UCSF and Consulting Professor in the Department of Health Research and Policy at the Stanford University School of Medicine. Dr. Go is also Chair of the American Heart Association Epidemiology and Prevention Council's Statistics and Stroke Statistics Committee. Dr. Go is a clinical epidemiologist, outcomes researcher, and clinical trialist in the areas of cardiovascular and renal disease. He also leads several large multi-center cohort studies in these areas, including the NHLBI-sponsored Cardiovascular Research Network (CVRN), a research consortium of 14 health plans in the US. He is Principal Investigator of the ATRIA-CVRN Study of >34,000 adults with incident atrial fibrillation and the CVRN PRESERVE cohort of >30,000 adults with heart failure and documented systolic function. Dr. Go also leads several prospective cohort studies including the NIDDK-sponsored Assessment, Serial Assessment, and Subsequent Sequelae of Acute Kidney Injury (ASSESS-AKI) Study and Chronic Renal Insufficiency Cohort (CRIC) Study. Dr. Go's current research interests include optimizing stroke prevention strategies for atrial fibrillation; epidemiology and outcomes of heart failure with preserved vs. reduced systolic function; improving quality of care for primary and secondary prevention of cardiovascular diseases; genetics of cardiovascular diseases; and delineating the roles of acute kidney injury and chronic kidney disease in influencing cardiovascular and renal-related adverse events.

Christopher B. Granger, MD, FACC, FAHA is a Professor of Medicine in the Division of Cardiology at Duke University and Director of the Cardiac Care Unit for the Duke University Medical Center. Dr. Granger is a Fellow of the American College of Cardiology, the American Heart Association, and of the European Society of Cardiology. He is Associate Editor of the *American Heart Journal* and serves on the editorial board of the *Journal of the American College of Cardiology*. He is a cardiology section author for *Current Medical Diagnosis and Treatment*. He serves on the publication oversight committee of the American Heart Association and he is chairman of the Advisory Working Group of the American Heart Association Mission: Lifeline program. He is a member of the 2011 ACC/AHA STEMI Guidelines Committee. He has served on FDA advisory committees on an *ad hoc* basis. He is on the Board of External Experts of the National Heart, Lung and Blood Institute (NHLBI). Dr. Granger's primary research interest is in the conduct and methodology of large randomized clinical trials in heart disease; he has co-authored more than 400 peer-reviewed manuscripts. He currently serves on a number of clinical trial steering committees and data safety monitoring committees. He has coordinated the Duke Clinical Research Institutes' activities in many clinical trials evaluating acute MI reperfusion and antithrombotic strategies in acute coronary syndromes and in atrial fibrillation. Dr. Granger is co-chairman of the Steering Committee of the ARISTOTLE trial assessing an oral factor Xa inhibitor for stroke prevention

in atrial fibrillation. In addition, he is co-director of the Reperfusion of Acute MI in Carolina Emergency Departments (RACE) projects, North Carolina state-wide programs to improve reperfusion care for acute myocardial infarction and care for cardiac arrest.

Rosemarie Hakim, PhD is a senior research advisor at the Centers for Medicare & Medicaid Services. She has worked extensively with CMS staff and with the public on coverage with evidence development and CMS' clinical trial policy. She currently works with researchers to develop projects related to coverage, CED, and post coverage analyses using CMS claims and registry data. She has developed and overseen multiple studies that have used CMS data. She has a doctorate in epidemiology from the Johns Hopkins Bloomberg School of Public Health and has extensive experience in observational study design and analysis, clinical trial design and analysis and evidence development.

Peter Held MD, PhD, FACC is currently a Medical Science Director leading an AstraZeneca effort to improve the conduct and delivery of the company's large clinical outcome studies. He is currently responsible for a number of global ongoing or planned such studies in the cardiovascular and in the respiratory field. He has long experience from, and interest in, the methodology and conduct of both traditionally run and simplified trials. During the late 1980´s he spent time at the NHLBI as a visiting scientist and project officer, involved in the planning and conduct of mortality/morbidity trials in heart failure and atherosclerosis. Since 1993 he has been employed by AstraZeneca R&D, based in Gothenburg, Sweden. He has designed and led many global clinical development programs with a large number of new chemical entities, leading to successful demonstration of benefit and resulting in regulatory approvals. A scholar from the Universities of Uppsala, Linköping and Göteborg, Sweden, he received his MD and PhD during the mid 1980´s. He specialised in cardiology and internal medicine and was appointed associate professor of cardiology in 1989. Adjunct professor of clinical CV research at the University of Gothenburg 2001-2010.

Rebecca Daniels Kush, PhD is Founder, President and CEO of the Clinical Data Interchange Standards Consortium (CDISC), a non-profit standards developing organization (SDO) with a mission to develop and support global, platform-independent standards that enable information system interoperability to improve medical research and related areas of healthcare and a vision of *"Informing patient care and safety through higher quality medical research"*. Dr. Kush has over 25 years of experience in the area of clinical research, including positions with the U.S. National Institutes of Health, academia, a global CRO and biopharmaceutical companies in the U.S. and Japan. She earned her doctorate in Physiology and Pharmacology from the University of California San Diego (UCSD) School of Medicine. She is lead author on the book: eClinical Trials: Planning and Implementation and has authored numerous publications for journals, including New England Journal of Medicine and Science Translational Medicine. She has developed a Prescription Education Program for elementary and middle schools and was named in PharmaVoice in 2008 as one of the 100 most inspiring individuals in the life-sciences industry. Dr. Kush has served on the Board of Directors for the U.S. Health Information Technology Standards Panel (HITSP), Drug Information Association (DIA) and currently Health Level 7 (HL7), and she was a member of the advisory committee for the WHO International Clinical Trials Registry Platform. Dr. Kush served on the appointed Planning Committee for the HHS/ONC-sponsored Workshop Series on the "Digital Infrastructure for the Learning Health System" for the National Academy of Sciences Institute of Medicine (IOM) and has presented at other IOM meetings. She is a member of the National Cancer Advisory Board IT Workgroup and was invited to represent research as an appointed member of the U.S. Health Information Technology (HIT) Standards Committee. Dr. Kush has developed a course "A Global Approach to Accelerating Medical Research" and has been a keynote speaker at numerous conferences in this arena in Europe, U.S., Brazil, Japan, China, Korea and Australia.

Carole M. Lannon, MD, MPH is board-certified in pediatrics and internal medicine, and has a master's in epidemiology. She is nationally-recognized for her expertise in improvement science and systems improvement. She is Director, Learning Networks Core, James M. Anderson Center for Health Systems Excellence at Cincinnati Children's Hospital Medical Center (CCHMC), Professor of Pediatrics at the University of Cincinnati, and Senior Quality Advisor for the American Board of Pediatrics. Dr. Lannon is the design and implementation lead for several results-oriented, outcomes-focused improvement networks, including the Ohio Perinatal Quality Collaborative and the National Pediatric Cardiology Quality Improvement Collaborative. Dr. Lannon is principal investigator of the pediatric Center for Education and Research in Therapeutics (CERTs), funded by the Agency for Health Care Research and Quality. She is former Associate Editor of the Journal of Quality and Safety in Healthcare. She played a lead role in the design and start-up of improvement initiatives for the American Academy of Pediatrics and the National Initiative for Children's Healthcare Quality.

Deven McGraw is the Director of the Health Privacy Project at CDT. The Project is focused on developing and promoting workable privacy and security protections for electronic personal health information. Ms. McGraw is active in efforts to advance the adoption and implementation of health information technology and electronic health information exchange to improve health care. She was one of three persons appointed by Kathleen Sebelius, the Secretary of the U.S. Department of Health & Human Services (HHS), to serve on the Health Information Technology (HIT) Policy Committee, a federal advisory committee established in the American Recovery and Reinvestment Act of 2009. She also served on two key workgroups of the American Health Information Community (AHIC), the federal advisory body established by HHS in the Bush Administration to develop recommendations on how to facilitate use of health information technology to improve health. Specifically, she co-chaired the Confidentiality, Privacy and Security Workgroup and was a member of the Personalized Health Care Workgroup. She also served on the Policy Steering Committee of the eHealth Initiative and now serves on its Leadership Committee. She is also on the Steering Group of the Markle Foundation's Connecting for Health multi-stakeholder initiative. Ms. McGraw has a strong background in health care policy. Prior to joining CDT, Ms. McGraw was the Chief Operating Officer of the National Partnership for Women & Families, providing strategic direction and oversight for all of the organization's core program areas, including the promotion of initiatives to improve health care quality. Ms. McGraw also was an associate in the public policy group at Patton Boggs, LLP and in the health care group at Ropes & Gray. She also served as Deputy Legal Counsel to the Governor of Massachusetts and taught in the Federal Legislation Clinic at the Georgetown University Law Center. Ms. McGraw graduated magna cum laude from the University of Maryland. She earned her J.D., magna cum laude, and her L.L.M. from Georgetown University Law Center and was Executive Editor of the *Georgetown Law Journal*. She also has a Master of Public Health from Johns Hopkins School of Hygiene and Public Health.

Robert E. Ratner, MD is Chief Scientific & Medical Officer for the American Diabetes Association, the nation's largest voluntary health organization leading the fight to Stop Diabetes®. Dr. Ratner joined the Association in May 2012 and provides leadership and oversight of scientific and medical activities including research, clinical affairs, program recognition and certification, medical information and professional education. In this capacity, he oversees the Association's support of a broad range of professional education activities and the development of the American Diabetes Association Clinical Practice Recommendations, clinical consensus reports and expert opinions. In 2011, the Association provided $34.6 million in research funds, funding more than 400 grants at 139 leading U.S. research institutions. Prior to joining the American Diabetes Association, Dr. Ratner was a Professor of Medicine at Georgetown University Medical School and Senior Research Scientist at the MedStar Health Research Institute in metropolitan Washington, DC. He recently completed a sabbatical as a Robert Wood Johnson Foundation Health Policy Fellow, having served as the study director for the Institute of Medicine Comparative Effectiveness Research Priorities Committee, and a program examiner for health

reform in the Health Division of the U.S. Office of Management and Budget. He received his MD from Baylor College of Medicine in Houston, Texas where he also completed his Internal Medicine training. He underwent fellowship training in Endocrinology and Metabolism at Harvard Medical School and the Joslin Diabetes Center in Boston. He recently completed six years of service on the Steering Committee of the National Diabetes Education Program (NDEP), representing the American Diabetes Association. He has served on the Board of Directors of the National Certification Board for Diabetes Education and the American Association of Diabetes Educators, and is Past-President of the Washington Area Affiliate of the American Diabetes Association. He has served as the Chair of the Government Relations Committee and the Pregnancy Council of the American Diabetes Association. He was a Principle Investigator for the Diabetes Prevention Program (DPP) and DPP Outcomes Study of the National Institutes of Health (NIH) and served on the Steering Committee for the project nationwide. At Georgetown University, he served on the University Research Committee, and co-chaired the Joint Oversight Committee for Clinical Research. He was an Associate Editor of the *Journal of Clinical Endocrinology and Metabolism*. His research interests include diabetes therapeutics and complications, with an emphasis on translational efforts from controlled trials into community-based practice. He is the author of more than 130 original scientific articles and 20 book chapters.

Nancy Roach founded Fight Colorectal Cancer (Fight CRC) in 2005, nine years after her mother-in-law was diagnosed with colorectal cancer. Recognizing the need for an advocacy organization, she established Fight CRC to provide focus, infrastructure and support for colorectal cancer survivors, caregivers and those touched by the disease. Since then, Ms. Roach has played a vital role in championing the need for a cure for colon and rectal cancer, through screening, awareness and research. Her efforts as an advocate have supported education and support for patients as well as the research community. Her leadership and passion has fostered a community of advocates supporting state and federal policies that have led to increased colorectal cancer research opportunities across the country. Over the last four years, Fight Colorectal Cancer has directed more than $250,000 in research funding to young investigators. Ms. Roach currently serves as the chair of the Board of Directors and serves on the National Cancer Institute (NCI) Board of Scientific Counselors and the Clinical Trial and Translational Research Advisory Committee. She is on the Executive Committee on the Clinical Trials Transformation Initiative, an FDA-Duke public-private partnership, and is a past chair of its finance committee. She has been involved with cooperative groups and SPORES, and currently serves on the NCI Colon Task force. She served on the Department of Defense Congressionally Directed Medical Research Program Integration Panel in 2010, the first year the colorectal cancer research was funded by the program. She is a past chair of the NCI Patient Advocate Steering Committee, and received the NCI Director's Service Award when she stepped down. She has also received the Preventing Colorectal Cancer Champion Award and the Colon Cancer Alliance Sapphire Visionary Award in recognition of her efforts on behalf of patients. She has spoken on behalf of patients at meetings such as the American Association for Cancer Research, the Friends of Cancer Research/Brookings Institute Conference on Clinical Research, and the Oxford University-Duke University-McMaster University Sensible Guidelines for Clinical Trials.

Kate Ryan, MPA is the Senior Program Coordinator at the National Women's Health Network. In this role, she is responsible for developing and implementing a program of legislative and regulatory advocacy that focuses on reducing women's exposure to unnecessary drug and medical treatment risks. Kate leads advocacy efforts to increase research on women's health and increase women's participation in clinical trials and health research. Through work with the National Institute of Child Health and Human Development and the Food and Drug Administration, Kate brings women's voices to the health policy debates in Washington, DC and the states, and advocates for a health care system that is accessible to all and meets the needs of diverse women. Prior to joining the NWHN, Kate worked in the Capitol Hill office of U.S. Representative Joe Sestak (D-PA), where she worked on health care reform, the

women's issues portfolio, and managed a variety of constituent services programs. Before moving to Washington, DC, Kate volunteered in Ghana with the Alliance for Reproductive Health Rights to monitor and assess availability of, and access to, women's sexual and reproductive health services under the Ghanaian National Health Insurance Scheme. As part of this work, Kate also monitored Ghana's progress on Millennium Development Goals 4 & 5 – to reduce child mortality and improve maternal health. Kate received her MPA in International Public & Non-Profit Management and Policy Analysis with a focus in women's rights from the NYU Wagner Graduate School of Public Service.

Lewis G. Sandy, MD is Senior Vice President, Clinical Advancement, UnitedHealth Group (a Fortune 25 diversified health and well-being company dedicated to helping people live healthier lives). At UnitedHealth Group he focuses on clinical innovation, payment/delivery reforms to modernize our health care system, and physician collaboration. He also is a Principal in the UnitedHealth Center for Health Reform and Modernization, with a focus on payment/delivery innovation and policy. From 2003 to 2007, he was EVP and Chief Medical Officer of UnitedHealthcare, UnitedHealth Group's largest business focusing on the employer/individual health benefits market. From 1997 to 2003, he was EVP of The Robert Wood Johnson Foundation. At RWJF, he was responsible for the Foundation's program development and management, strategic planning and administrative operations. Prior to this, Dr. Sandy was a program VP of the Foundation, focusing on the Foundation's workforce, health policy, and chronic care initiatives. An internist and former health center medical director at the Harvard Community Health Plan in Boston, Massachusetts, Dr. Sandy received his B.S. and M.D. degrees from the University of Michigan and an M.B.A. degree from Stanford University. A former RWJF Clinical Scholar and Clinical Fellow in Medicine at the University of California, San Francisco, Dr. Sandy served his internship and residency at the Beth Israel Hospital in Boston. He is a Senior Fellow of the University of Minnesota School of Public Health, Department of Health Policy and Management.

Elsie M. Taveras, MD, MPH is an Associate Professor of Population Medicine at Harvard Medical School and Associate Professor of Pediatrics at Children's Hospital Boston. She received her bachelor of science and medical doctor degrees at New York University in New York City. After receiving her M.D., she did her internship, residency, and chief residency, at the Boston Combined Residency Program in Pediatrics, a joint program of Children's Hospital Boston and Boston Medical Center. In 2001, Dr. Taveras joined the Harvard Pediatric Health Services Research Fellowship Program and received her Master's in Public Health with a concentration in clinical effectiveness from the Harvard School of Public Health. Dr. Taveras is the Co-Director of the Obesity Prevention Program at the Department of Population Medicine. Dr. Taveras is also on staff at Children's Hospital Boston where she directs a multidisciplinary childhood obesity prevention clinic in General Pediatrics. Dr. Taveras' main focus of research is understanding determinants of obesity in children and adolescents and developing interventions across the lifecourse to prevent obesity in children, especially in underserved populations. Dr. Taveras' publications have examined diet, activity, sleep, and weight determinants in later childhood, and early life origins of obesity in young children.

Tjeerd van Staa, MD, PhD, MSc, MA studied medicine and received his degree in 1987 at the Erasmus University of Rotterdam, the Netherlands. After several years of working as a practising physician, he joined the pharmaceutical industry and worked as an epidemiologist and was also the European Qualified Person for Drug Safety. During this time, he obtained a MSc in Epidemiology (McGill University, Canada) and was awarded a PhD in Pharmacoepidemiology at Utrecht University in 1999. He has also a MA in Medical Law and Ethics. In 2006, he joined the Medicines and Health products Regulatory Agency as Director of Research of the Clinical Practice Research Datalink (the General Practice Research Database is part of CPRD). He has published over 130 peer-reviewed articles and is a well-recognised speaker in the field of pharmacoepidemiology, pharmacovigilance and osteoporosis. He has been awarded several academic affiliations (Utrecht University, the Netherlands;

Medical Research Council, Southampton, UK) and is Honorary Professor at the London School of Hygiene & Tropical Medicine. Van Staa is the recipient of the 2005 *Iain I Boyle Award* of the European Calcified Tissue Society (a monetary price awarded to the scientist who has made significant contributions to bone disease research (http://www.ectsoc.org/). His current research activities concern the implementation of randomised clinical trials that use routinely collected electronic health records (as outlined in a recent article in the British Medical Journal). Two cluster trials (randomising practices) and a large pharmacogenetic study within GPRD are close to completion. Van Staa is also involved in the implementation of multiple linkages of GPRD to other health care datasets, including cancer and registries, cardiovascular disease registries, air pollution and bowel screening data. Visualisation and evaluation of data quality are other research interests.

James B. Young, MD is Professor of Medicine and Executive Dean, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University and Chairman, Endocrinology and Metabolism Institute. He is also Physician Director of Institutional Relations and Development and a Medical Director of the Kaufman Center for Heart Failure. He holds the George and Linda Kaufman Chair and is the Study Chairman of the NIH, FDA, and CMS Interagency Registry for Mechanical Circulatory Assist Support (INTERMACS). He has a joint appointment to the Clinic's Multi-organ Transplant Center. Dr. Young is certified as a Diplomat of the American Board of Internal Medicine as well as the subspecialty of Cardiovascular Disease and holds medical licensure from the states of California, Illinois, Ohio, Pennsylvania and Texas. Dr. Young spent his early years in the San Francisco Bay Area and then attended the University of Kansas, where he received his Bachelor of Arts degree with Honors in Biology and was a resident of Stephenson Scholarship Hall. He matriculated to Baylor College of Medicine in Houston, Texas, where he was awarded his Medical Doctor degree with honors in 1974 and was elected to the Alpha Omega Alpha medical honor society. Dr. Young remained in Houston at the Baylor Affiliated Hospitals to complete his clinical training, joining the faculty, and becoming a Professor of Medicine with Tenure in 1992. He was the Clinical Coordinator and Scientific Director for Dr. Michael E. DeBakey's Multi-organ Transplant Center at The Methodist Hospital and Baylor College of Medicine. He subsequently relocated to the Cleveland Clinic, Cleveland, Ohio, in 1995 when he became Head of the Section of Heart Failure and Cardiac Transplant Medicine in the Department of Cardiovascular Disease. In 1998 Dr. Young, along with his surgical colleague Dr. Patrick McCarthy, created the Kaufman Center for Heart Failure at the Cleveland Clinic. Dr. Young's research activities began during his residency and fellowship training when he was a Lipid Research Clinic (LRC) physician. He subsequently focused his efforts on heart failure, mechanical circulatory support, and cardiac transplant therapeutics including early experiences with dopamine receptor agonists, angiotensin-converting enzyme inhibitors, beta blockers, calcium channel blockers, angiotensin receptor blockers, many new immunosuppressants, and a variety of parenteral inotropes and vasodilators. He has collaborated extensively with his basic science research associates focusing on 'translational' research with respect to the molecular biology of cardiac remodeling, allograft arteriopathy, and transplanted heart rejection. Dr. Young served as the United States Principal or Co-Principal Investigator for the HOPE, RESOLVED, SPICE, VMAC, MIRACLE-ICD, RED-HF, ACCLAIM, ONTARGET, TRANSCEND, and CHARM multi-center clinical trials. He has participated in over 150 clinical trials as an investigator. Dr. Young has published almost 600 manuscripts and several textbooks. Professionally, Dr. Young is most proud of his contributions to the development and administration of donor organ procurement programs, his efforts to secure recognition for the newly emerging cardiology subspecialty of "Heart Failure and Cardiac Transplant Medicine", his collaborations with basic and clinical scientists, his contributions to a unique medical school curriculum, and the programs that he helped develop in Houston and Cleveland.

Bram Zuckerman, MD is a graduate of the Boston University Medical School. He completed post-graduate training in internal medicine at Baltimore City Hospital and cardiology at the Johns Hopkins program. Prior to joining FDA in 1992, he was involved in basic research in hemodynamics at the University of Colorado Medical School and practiced noninvasive and invasive cardiology in Denver, Colorado and Northern Virginia. He joined the FDA Division of Cardiovascular Devices (DCD) as a Medical Officer in 1992 and has been actively involved in development and review of clinical trials for many new cardiovascular devices. In May 2001 he was appointed a Deputy Director in DCD. He was appointed to his current position as Director of the FDA Division of Cardiovascular Devices in September 2002.

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

ROUNDTABLE ON VALUE & SCIENCE-DRIVEN HEALTH CARE

IOM Workshop on Large Simple Trials and Knowledge Generation in a Learning Health System

Workshop Logistics

The Keck Center of The National Academies
500 5th St, NW Washington, DC 20001
Room 100
November 26-27, 2012

The Roundtable on Value & Science-Driven Health Care is looking forward to your participation on November 26-27, 2012. If you have any questions regarding workshop logistics, please contact our office at jcsanders@nas.edu or 202-334-3889.

LOCATION:
The workshop will begin at **1pm on November 26th** and will end at **5pm on November 27th**. Breakfast will be served on site beginning at **8:00am** on November 27th, with the agenda commencing at 8:30am. While ***the agenda for this meeting has not been finalized***, these times provide an accurate estimation for travel planning purposes. The Keck Center is located at **500 5th St NW, Washington, DC 20001**.

GROUND TRANSPORT
The workshop site is approximately 5 miles from Washington National Airport and approximately 30 miles from Dulles International Airport. Taxis are most easily hailed on E or F Streets.

The **Gallery Place/Chinatown Metro station (YELLOW and GREEN lines)** is two blocks away, and only a 15-minute ride from Washington National Airport. Exit the station by following signs to Seventh and F Streets/Arena.

The **Judiciary Square Metro station (RED line)** is located one block away from the workshop site. Exit the station by following signs to the Building Museum (F Street) exit, between Fourth and Fifth Streets NW.