# PCORnet: First Interventional Study Research Prioritization Topic Brief

**[Elizabeth A. Chrischilles, PhD; Cynthia Chuang, MD, MSc; Saman Nazarian, MD]**
**[Greater Plains Collaborative CDRN in consultation with PaTH CDRN]**

April 28-29, 2014



Questions or comments may be sent to Jason Rotter at PCORI at jrotter@pcori.org or by mail to Suite 900, 1828 L Street, NW, Washington, DC 20036.

## Contents

**Topic 1:**
**Comparative Effectiveness of New Oral Anticoagulants for Stroke Prevention in Non-valvular Atrial Fibrillation**

| Criteria | Brief Description |
|---|---|
| **Introduction** | |
| Overview/definition of topic | Atrial fibrillation is the most common cardiac arrhythmia, affecting from 1 to 2% of adults (Go et al 2001). Regardless of whether it is paroxysmal, persistent, or permanent, atrial fibrillation increases the risk of thrombotic ischemic stroke, and is the cause of 15-20% of all ischemic strokes. The risk of ischemic strokes can be reduced by 64% with anticoagulation therapy (Hart et al 2007); despite availability of efficacious anticoagulation therapy (warfarin) for decades, oral anticoagulants are underused (a 2010 systematic review of 54 studies found underuse – defined as treatment of <70% of at-risk patients – in the majority of studies; Ogilvie et al, 2010), resulting in missed opportunities to prevent ischemic stroke in patients with atrial fibrillation. While the optimal approach to increasing use of anticoagulants for stroke prophylaxis is unknown, the recent 2014 AHA/ACC/HRS Guidelines for the Management of Patients with Atrial Fibrillation recommend that antithrombotic therapy should individualized based on shared decision-making after discussion of the absolute and relative risks of stroke and bleeding, and the patient's values and preferences (AHA/ACC Task Force 2014).<br><br>The new oral anticoagulants (NOACs) targeting a single clotting enzyme, either factor Xa or thrombin, afford a potential breakthrough innovation which may be more convenient for patients to take than warfarin (Connolly et al 2009; Patel et al 2011; Fox et al 2011; Granger et al 2011). All three NOACs have been compared to warfarin and found either superior (dabigatran and apixaban) or noninferior to warfarin for reducing stroke risk. New oral anticoagulants had a favorable risk—benefit profile, with significant reductions in intracranial hemorrhage and mortality, and with similar major bleeding as for warfarin, but increased gastrointestinal bleeding. There is very recent evidence from the American College of Cardiology's National Cardiovascular Data Registry to suggest that the introduction of NOACs is resulting in an increase in the percentage of patients being anticoagulated (Jancin, 2014). However, there are important questions to answer: In patients with non-valvular atrial fibrillation, can an EHR-based shared decision-making tool increase the proportion of atrial fibrillation patients on anticoagulants, and reduce stroke outcomes? For patients in whom a new oral anticoagulant is being initiated for stroke prevention, what is the comparative effectiveness of the thrombin inhibitor dabigatran and two direct factor Xa inhibitors, rivaroxaban and apixaban, on ischemic stroke, intracranial hemorrhage, and gastrointestinal bleeding within 18 months after initiating treatment? Does comparative effectiveness vary across patient subgroups such as age, baseline stroke risk and bleeding risk? These questions require a multi-network approach because the prevalence of atrial fibrillation and its associated stroke and bleeding outcomes are not high, NOACs are still only being prescribed for the minority of anticoagulant initiators, and there is reason to believe from trial meta-analyses that how patient characteristics affect comparative effectiveness is at least as important as an average estimate of comparative effectiveness. |

**Topic 1:**
**Comparative Effectiveness of New Oral Anticoagulants for Stroke Prevention in Non-valvular Atrial Fibrillation**

| | |
|---|---|
| Relevance to patient-centered outcomes | The most common complications among patients with atrial fibrillation are heart failure and stroke (CDC, 2013). Atrial fibrillation is a major risk factor for ischemic stroke. Stroke is a devastating event. It is a major cause of disability and death worldwide. The 30-day case fatality rate after an ischemic stroke is between 8 and 15 percent (Mohr et al 2011). Even with a minor stroke, the 10-year mortality rate is double that of the general population. There is a wide array of persistent severe neurologic deficits and disability outcomes include depression, loss of mobility, impairments in social function and institutional care in approximately 25 percent of affected patients. In clinical trials with a warfarin comparator, the NOACs reduced overall mortality and intracranial bleeding but increased the rate of gastrointestinal bleeding. Patients may be concerned about the lack of an antidote for NOACs, though their short half-life may provide some reassurance. However, the short half-life may result in increased ischemic strokes among non-adherent patients. There are three different NOACs that have entered the market since 2010 and they have not been directly compared with each other. |
| **Patient-centeredness** | |
| Is the proposed research focused on questions and outcomes of specific interest to patients, their caregivers, and clinicians? | Patients who have atrial fibrillation typically require long-term management. Their needs are complex and not limited to anticoagulation. They typically have comorbidities, take multiple medications, and have frequent interaction with the healthcare system so substantial patient engagement and communication with healthcare providers may be needed for their treatment outcomes to be optimized. Patients may prefer NOACs in this setting because they are less complex to manage than warfarin. The most current atrial fibrillation management guidelines recommend at least weekly laboratory monitoring during the initiation of warfarin therapy and at least monthly once the INR level is stable (AHA/ACC Task Force 2014). This can present a burden to patients who cannot easily commute to a laboratory facility due to lifestyle, health, or geographical limitations. Since warfarin is a vitamin K antagonist, variations in an individual's diet can significantly affect warfarin's effect, further complicating management. However, some patients gain peace of mind from frequent anticoagulant testing. In a large European survey, less convenient settings for anticoagulant testing were associated with more favorable patient attitudes toward conversion to NOACs. Qualitative and quantitative research that estimated utility assessments, has established that patients' health beliefs and preferences are important factors in their decisions about anticoagulation treatment for atrial fibrillation. While patient preferences are clearly important in the decision between warfarin and NOACs, preferences about the choice between NOACs have not been investigated. It seems likely that, due to their similar dosing and monitoring, patient preferences in this decision would be focused mostly on their utility-weighted risks of stroke and bleeding outcomes. |
| **Burden on Society** | |
| Recent prevalence in populations and subpopulations | Among adults the prevalence of atrial fibrillation is 1-2% with the highest prevalence (9%) among the elderly. Due to the growing elderly population, the prevalence of atrial fibrillation is increasing and expected to increase from 5.2 million in 2010 to 12.1 million cases in 2030 (Colilla et al, 2013). Atrial fibrillation is a major risk factor for ischemic stroke, responsible for a five-fold increase in risk and accounting for 15 to 20% of ischemic strokes. |

| | |
|---|---|
| Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services | As described above, both stroke and serious bleeding outcomes can cause disability and death. |
| **Assessment of Current Options** | |
| Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options? | Without anticoagulation, the risk of ischemic stroke varies from 1%-15%, depending on the individual patient's underlying risk factors. Among 6 RCTs that included close to 3000 patients in which dose-adjusted warfarin was compared with placebo, warfarin was associated with a 64% relative risk reduction for stroke, which was an absolute risk reduction of 2.7% per year (NNT 37 for 1 year to prevent 1 stroke and NNT 12 in patients with prior stroke or TIA)(Hart et al, Ann Intern Med 2007).<br>Because the NOACs have not been compared with each other in trials, four meta-analyses have attempted to make indirect comparisons of NOACs in nonvalvular atrial fibrillation. Only one of these (Schneeweiss et al, 2012) corrected for differences in trial populations between the clinical trials. From this analysis, one of the agents, apixaban, was found to have a lower risk of major bleeding events and there was a suggestion that comparative effectiveness may vary with baseline stroke risk, though there were too few patients in each level of risk to evaluate this well. However, the relative effectiveness and safety of these drugs may be different in actual practice where adherence patterns, baseline stroke risk, and other characteristics may result in differences that can't be predicted by clinical trial results. |

**Topic 1:**
**Comparative Effectiveness of New Oral Anticoagulants for Stroke Prevention in Non-valvular Atrial Fibrillation**

| | |
|---|---|
| What could new research contribute to achieving better patient-centered outcomes? | There are multiple barriers to initiation of anticoagulant therapy for providers and patients, one of which is assessment of stroke and bleeding risk in an individual patient. There is a subset of patients with atrial fibrillation for whom the stroke risk is low (<2% per year), and the risk of bleeding with anticoagulation outweighs the benefits, requiring physicians to risk stratify atrial fibrillation patients prior to initiation of anticoagulation therapy. Despite only modest predictive performance (Apostolakis S et al, 2012; Fang et al, 2008; VanStaa et al, 2011), risk estimation tools are the only alternative to implicit clinical judgment. A recent study found physician estimates of stroke and bleeding risk do not correspond well to estimates from stroke and bleeding risk estimation tools in patients with atrial fibrillation (Steinberg et al, Circulation 2014). An unanswered question is whether point-of-care delivery to providers of a tool for shared decision-making that includes risk assessment can increase shared-decision making about anticoagulation and more individualized, patient-centered decisions about stroke prevention.<br><br>The differences between NOACs are likely to be smaller than the difference between warfarin and NOACs and clearly less than the difference between no anticoagulation and any anticoagulation. Quantitative information about outcomes of NOACs in routine practice is likely to be valuable to patients who need to make decisions about taking an anticoagulant and differences between individual NOACs will be useful when it comes to deciding which NOAC to take. |
| Have recent innovations made research on this topic especially compelling? | Before 2010, when dabigatran was approved, vitamin K antagonists (predominantly warfarin) were the mainstay of stroke prevention among patients with atrial fibrillation. Although warfarin reduces stroke risk by approximately 64% (Hart et al, Ann Intern Med 2007), only about half of patients take it and only half of those are well-managed (Go et al, 1999). The new oral anticoagulants (NOAC) dabigatran, rivaroxaban, and apixaban, have each been found superior or noninferior compared with warfarin in clinical trials and offer a potential advantage for patients who will not take or are unlikely to be effectively managed on warfarin. However, in the first year after dabigatran was introduced, treatment rates for atrial fibrillation did not increase, and by the fourth quarter of 2012 only 15% of patients were on a NOAC, perhaps reflecting availability and uncertainty about the effects in real-world usage. Because of the short half-life of the NOAC drugs, a single missed dose can lead to an increased risk of stroke. Dabigatran and apixaban are dosed twice daily compared with once daily dosing for rivaroxaban and warfarin. On the safety side, unlike warfarin, there is no antidote for NOACs should bleeding occur. The pharmacokinetic and pharmacodynamic differences between the available NOACs may result in different risk-benefit profiles between the drugs in real-world usage. |
| How widely does care now vary? | Anticoagulation appears to be under-used in general (see above) and whether to initiate anticoagulation has been found to be a preference-sensitive decision. The NOACs are too new to have much if any published evidence about variation in uptake, though formulary differences are likely to introduce variation in use of individual agents. Though there are promising potential advantages of the NOACs, this is controversial and the observation that adoption of these agents has been slow suggests that this controversy is affecting patient care. |

**Topic 1:**
**Comparative Effectiveness of New Oral Anticoagulants for Stroke Prevention in Non-valvular Atrial Fibrillation**

| | |
|---|---|
| What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)? | Apart from the published controlled trials, there is one ongoing trial with epoxaban. There are ongoing observational analyses that will provide quantitative information about outcomes among new users of warfarin and NOACs in routine care and which will therefore provide context for the results of this trial.<br>While a few studies have examined the use of a patient decision aid for antithrombotic therapy in atrial fibrillation, they are generally small studies, designed to help patients with deciding between warfarin and aspirin (prior to NOACs), and were not integrated into the EHR (Protheroe et al. BMJ 2000, Man-Son-Hing et al JAMA 1999, Thomson et al, BMJ 2006) |
| **Potential for New Information to Improve Care and Patient-Centered Outcomes** | |
| How likely is it that new CER on this topic would provide better information to guide clinical decision making? | The topic would generate 3 key pieces of information that will inform better clinical decision-making: (1) a quantitative estimate of outcome rates among patients treated with NOACs in routine practice; (2) precise relative benefit-risk data for the three drugs; and (3) quantitative information about how much the relative benefits and risks change with advanced age, baseline stroke risk, and bleeding risk. None of this information is presently available. In addition to the randomized trial results, it would be of interest to conduct exploratory cohort analyses (using EHR data) of warfarin new users and NOAC new users who have opted out of the randomized trial. This would provide benchmark outcome rates with which to anchor the rates from the trial. Alternatively, to directly address the important problem of general underuse of anticoagulation, a randomized behavioral intervention trial could be conducted in which patients with nonvalvular atrial fibrillation who are not yet anticoagulated would be identified and randomized to having their providers receive or not receive an EHR alert with accompanying shared decision-making and risk assessment tool. |
| What are the facilitators and barriers that would affect the implementation of new findings in practice? | The NOACs are more expensive than warfarin and formulary management may also create differential cost advantages to one NOAC vs. another. This could affect the calculus and result in different decisions than if the decision were based purely on relative safety and effectiveness. A major facilitator would be if eligibility criteria could be kept to a minimum in the trial so that the estimates would be relevant to routine practice. Involving stakeholders such as insurers and health system CEOs would be a facilitator. Analyzing EHR data to understand the differences between people who are started on warfarin vs a NOAC would help understand whether there are subgroups to whom the results of the trial should not be generalized and uncover settings in which prescribers seem reluctant to initiate NOAC agents. |
| How likely is it that the results of new research on this topic would be implemented in practice right away? | For the randomized comparison between NOACs, the intervention is simple and no training would be required to implement the results. The American College of Cardiology Foundation/American Heart Association Practice Guideline on management of atrial fibrillation provides an important vehicle for dissemination. For a randomized study of an EHR-based tool to facilitate shared-decision making about antithrombotic therapy in atrial fibrillation. EPIC and Cerner would be logical partners to make the tool available to their clients. |

**Topic 1:**
**Comparative Effectiveness of New Oral Anticoagulants for Stroke Prevention in Non-valvular Atrial Fibrillation**

| | |
|---|---|
| Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies? | The information provided by this project would remain relevant for several years. Obviously, new drugs that enter the market after the trial is initiated could not be studied. For example, another NOAC, epoxaban, is entering Phase III testing for use in non-valvular atrial fibrillation. However, the decision to offer and prescribe anticoagulation in atrial fibrillation will always be relevant, regardless of what may become the newest agents for anticoagulation in the future. |
| **Feasibility of the clinical trial within health systems** | |
| Does this trial meet the requisite technical, governance and regulatory constraints described below*? | TECHNICAL CONSTRAINTS:<br><u>Ability to capture required data elements</u><br>The eligibility criteria, interventions, and outcomes are all measurable with data that are routinely recorded in electronic health record systems. Stroke risk stratification can also be determined by EHR data (CHA2DS2-VASc score includes congestive heart failure diagnosis, hypertension diagnosis, age, diabetes, stroke or TIA or thromboembolism diagnosis, vascular disease diagnosis, sex). Algorithms also exist that allow billing data to be used for each of these data elements in lieu of EHR data.<br><br><u>Standardized terminologies</u><br>Eligibility, intervention, and outcome measures use standardized nomenclatures. EHR systems that do not include National Drug Codes, typically use or can be cross-walked to a widely available drug coding nomenclature such as RxNorm, Rx Terms, Multum, or First Databank. ICD9 or 10 diagnosis and procedure codes indicative of chronic dialysis or kidney transplantation can be used to identify severe renal impairment, though laboratory data would be even better (Creatinine clearance <15). Ischemic stroke, intracranial hemorrhage, and GI bleeding each have claims-based coding algorithms using ICD9/10 with high positive predictive values. These should translate well to EHR systems.<br><br>PCORI networking software and standardized queries could be used to facilitate identification of potential participants.<br><br>REGULATORY AND GOVERNANCE CONTRAINTS<br>This topic brief has received approval of the two CDRNs who are submitting the topic |

**Topic 1:**
**Comparative Effectiveness of New Oral Anticoagulants for Stroke Prevention in Non-valvular Atrial Fibrillation**

| | |
|---|---|
| Is the trial characterized by operational simplicity? | The study question requires a multi-network approach because the prevalence of atrial fibrillation is not high (1-2 percent), NOACs are still being prescribed for the minority of anticoagulant initiators, (in the fourth quarter of 2012, 14.9% of patients with nonvalvular atrial fibrillation were receiving a NOAC compared with 44.3% receiving warfarin) and there is reason to believe that how patient characteristics affect comparative effectiveness is at least as important as an average estimate of comparative effectiveness.<br><br>To determine whether this question can be answered in a trial that is operationally simple and clinically relevant, we applied the PRECIS framework as a guide. Our assessments are provided in this box and the next. We evaluated study A (comparative effectiveness of NOACs) and study B (comparative effectiveness of an EHR tool).<br><br>Simplicity of interventions and Expertise – For both studies, the interventions would be applied by the full range of practitioners (cardiologists, primary care providers), regardless of their expertise, with only ordinary attention to dose setting and side effects. Oral anticoagulants are most often initiated in an outpatient setting which avoids the challenges of recruiting and enrolling patients during an acute care inpatient stay. The NOAC interventions (study A) are dosed similarly and do not require therapeutic assays for monitoring. The interventions are simple to implement: the physicians are in the act of writing a prescription for a NOAC anyway and randomization will determine which prescription is written. No additional provider training is needed and no patient education beyond what would ordinarily be supplied is required. The clinician who is prescribing a NOAC will either prescribe a specific NOAC (thereby opting out of the study for this patient) or indicate that the choice of NOAC can be randomized. For the study B (randomization of an EHR-based tool to facilitate shared-decision making about anticoagulation) the design would be operationally simple if good usability of the tool can be confirmed prior to the study.<br><br>Practitioner adherence to study intervention - This is a strength of the study question because the practitioners are not being asked to adhere to any study protocol. Study A is stronger in this regard because they are simply prescribing the initiation of a NOAC which they intended to do anyway. For study B they will be receiving an EHR-based tool at the point of care but could choose to not use it. If physicians choose to not use the tool, the magnitude of effect on outcomes will be dampened. |

**Topic 1:**
**Comparative Effectiveness of New Oral Anticoagulants for Stroke Prevention in Non-valvular Atrial Fibrillation**

| | |
|---|---|
| Does the trial make use of EHR to identify patients and measure outcomes? | Simplicity of participant eligibility criteria and recruitment - Because the primary question is about relative effects in routine care settings, the proposed trial would apply few selection criteria, i.e. in study A all patients with non-valvular atrial fibrillation whose physicians intend to prescribe a NOAC will be eligible to be enrolled, regardless of their anticipated risk, responsiveness, comorbidities or past compliance. Patients would be screened for eligibility via EHR including labeled warnings, precautions and contraindications to any of the NOACs. These include interacting drugs (P-gp and strong CYP3A4 inhibitors and inducers) severe renal impairment , and prior intra-cerebral or gastro-intestinal major bleeding events, which are readily identifiable through the EHR. The same characteristics that make the study A intervention relatively simple to implement and monitor (i.e., the physician and patient have decided to initiate a NOAC) make recruitment time-sensitive (if patient consent is needed prior to randomization). Thus there will be operational issues that need to be addressed to optimize recruitment and enrollment, but these challenges would need to be addressed for any individually randomized trial involving initiation of a prescription. A general approach would be for an alert to be sent to a study coordinator when a clinician indicates randomization is appropriate. For study B, patients who are not currently anticoagulated would be randomized to have their providers receive or not receive an EHR-based notification and tool to facilitate shared-decision making for anticoagulation. As for study A, patients would be screened for eligibility via EHR and recruitment would be time-sensitive.<br><br>Simplicity of follow-up and relevance and validity of outcomes - No formal follow-up visits of study individuals are needed. The outcomes - hospital admission for ischemic stroke, intracranial hemorrhage, and gastrointestinal bleeding - all have good case definitions with high positive predictive values from administrative/claims data that bode well for ascertainment in EHRs. Although overall mortality is also an important outcome, and should be obtainable through linkage, the EHR-assessed outcomes are important enough to justify a trial with these outcomes only. The primary outcome is an objectively measured, clinically meaningful outcome to the study participants. The outcome does not rely on central adjudication and is one that can be assessed under usual conditions (e.g., special tests or training are not required).<br><br>Patient compliance/adherence - To be pragmatic, there should be unobtrusive (or no) measurement of compliance. No special strategies to maintain or improve compliance would be used. Linkage to prescription dispensing records could provide an unobtrusive measurement of compliance. CDRNs that are not health systems will have less complete data on prescription dispensings and this is a limitation. A one-time assessment of patient-reported adherence might be considered for descriptive purposes. |

# References

Apostolakis S, Lane DA, Guo Y, Buller H, Lip GY. Performance of the HEMORR(2)HAGES, ATRIA, and HAS-BLED bleeding risk-prediction scores in patients with atrial fibrillation undergoing anticoagulation: the AMADEUS (evaluating the use of SR34006 compared to warfarin or acenocoumarol in patients with atrial fibrillation) study. J Am Coll Cardiol. 2012 Aug 28;60(9):861-7

Colilla, Susan, et al. "Estimates of current and future incidence and prevalence of atrial fibrillation in the US Adult population." *The American journal of cardiology* 112.8 (2013): 1142-1147.

Connolly SJ, Ezekowitz MD, Yusuf S, et al**.** Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139–1151

Fang MC, Go AS, Chang Y, Borowsky L, Pomernacki NK, Singer DE. Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular atrial fibrillation. J Am Coll Cardiol. 2008;51:810–815.

Fox KA, Piccini JP, Wojdyla D, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. *Eur Heart J*. 2011;32(19):2387–2394

Go, Alan S., Elaine M. Hylek, Kathleen A. Phillips, YuChiao Chang, Lori E. Henault, Joe V. Selby, and Daniel E. Singer. "Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study." *Jama* 285, no. 18 (2001): 2370-2375.

Go et al. Warfarin use among ambulatory patients with nonvalvular AF (ATRIA). Ann Intern Med 1999, 131.

Granger CB, Alexander JH, McMurray JJ et al Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365:981–992.

Hart, Robert G., Lesly A. Pearce, and Maria I. Aguilar. "Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation." *Annals of internal medicine* 146.12 (2007): 857-867.

Jancin B. Off-label use of novel anticoagulants accelerates. Cardiology News Digital Network. April 10, 2014.

**Topic 1:**
**Comparative Effectiveness of New Oral Anticoagulants for Stroke Prevention in Non-valvular Atrial Fibrillation**

January CT, Wann LS, Alpert JS, Calkins H, Cleveland JC, Cigarroa JE, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/ HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation 2014;129:

Man-Son-Hing, Malcolm, et al. "A patient decision aid regarding antithrombotic therapy for stroke prevention in atrial fibrillation: a randomized controlled trial." *Jama* 282.8 (1999): 737-743.

Mohr JP, Wolf PA, Grotta JC et al. Chapter 15 Mortality after ischemic stroke *In* Stroke: Pathophysiology, Diagnosis, and Management (5th ed); 2011, Elsevier.

Ogilvie IM, Newton N, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. Am J Med 2010;123:638-45.

Patel MR, Mahaffey KW, Garg J. ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365:883–891.

Protheroe, Joanne, et al. "The impact of patients' preferences on the treatment of atrial fibrillation: observational study of patient based decision analysisCommentary: patients, preferences, and evidence." *Bmj* 320.7246 (2000): 1380-1384.

Schneeweiss SS, Gagne JJ, Patrick AR, Choudhry NK, Avorn J. Comparative efficacy and safety of new oral anticoagulants in patients with atrial fibrillation. Circulation: Cardiovascular Quality and Outcomes. 2012;5:480-6.

Steinberg BA, Kim S, Thomas L, et al. Lack of concordance between empirical scores and physician assessments of stroke and bleeding risk in atrial fibrillation: Results from the outcomes registry for better informed treatment of atrial fibrillation (ORBIT-AF) registry. Circulation. 2014, published online ahead of print at:
http://circ.ahajournals.org/content/early/2014/03/20/CIRCULATIONAHA.114.008643

Thomson, Richard G., et al. "A patient decision aid to support shared decision-making on anti-thrombotic treatment of patients with atrial fibrillation: randomised controlled trial." *Quality and safety in Health Care* 16.3 (2007): 216-223.

Van Staa TP, Setakis E, Di Tanna GL, Lane DA, Lip GY. A comparison of risk stratification schemes for stroke in 79,884 atrial fibrillation patients in general practice. J Thromb Haemost. 2011;9:39–48.

# PCORnet: 1st Interventional Study Research Prioritization Topic Brief

**Paul Moore, MD**
**Russell Rothman, MD MPP**
**Mid-South CDRN**
**Vanderbilt University**

April 28-29, 2014



Questions or comments may be sent to Jason Rotter at PCORI at jrotter@pcori.org or by mail to Suite 900, 1828 L Street, NW, Washington, DC 20036.

## Topic 2: Role of Spacers in Asthma

| Criteria | Brief Description |
|---|---|
| **Introduction** | |
| Overview/ definition of topic | An estimated 22 million Americans have Asthma, including over 6.5 million children. Asthma is the most common chronic disease of childhood, and the National Asthma Education and Prevention Program of the National Heart, Lung, and Blood Institute (NHLBI) has developed consensus guidelines for asthma management. The Expert Panel has recommended that long-term control medications be taken daily on a long-term basis to achieve and maintain control of persistent asthma. The most effective long-term-control medications are those that attenuate the underlying inflammation characteristic of asthma, and inhaled corticosteroids are the most potent and consistently effective long-term control medication for asthma.<br>The proposed research question focuses on whether the optimal use of a metered dose inhaler (MDI) with a spacer device or the use of a dry powder inhaler (DPI) improves asthma control in children or adults with asthma who are using inhaled corticosteroids. This proposal also evaluates the use of technology to increase proper inhaled steroid device usage through ongoing education and prompts for adherence.<br>Although inhaled corticosteroids are the most potent and consistently effective long-term medication for asthma, delivery of this medication can be challenging, and with optimal technique, at best only about 22% of drug is delivered to the lung. A minority of patients and clinicians know the proper way to use these spacers or drug delivery devices. With incorrect usage, little to none of the active drug may reach the lung. Delivery devices, in conjunction with patient technique, are the primary determinants of the dose delivered to the lungs of the patient. Currently many patients are prescribed steroids using MDIs with or without the use of a spacer to improve delivery. In addition, newer devices have been recently introduced that use a dry powder inhaler (DPI) to deliver the steroid, and there is great variation among children and adults in technique. Unlike swallowing a pill, learning how to use any of these devices correctly is challenging.<br>A pragmatic trial that randomizes patients to one of four arms could help to understand the value of MDIs with spacers or DPIs and the role of an educational intervention for asthma management. Patients with persistent asthma would be randomized to either 1) standard provision of steroid MDI with spacer, 2) provision of steroid MDI with spacer and enhanced asthma education and monitoring with internet intervention, 3) provision of DPI device of equivalent steroid dose, or 4) provision of DPI of equivalent steroid dose plus enhanced asthma education and monitoring with internet intervention. Primary outcomes would be patient reported asthma quality of life, medication adherence, clinic visits, emergency room visits, and hospitalizations.<br>This question is of specific interest to patients, caregivers, and clinicians, as proper training in the use of spacers and other delivery devices is limited in the outpatient setting, and improved adherence to spacer or the use of other devices for steroid intake may contribute to increased efficacy of inhaled corticosteroids in maintaining asthma control. In addition, many insurers do not cover spacing devices, and determining their utility is therefore of great importance to support coverage if they are effective. |

**Topic 2: Role of Spacers in Asthma**

| | |
|---|---|
| Relevance to patient-centered outcomes | Patient-centered outcomes are the mainstay of efforts to achieve and maintain control of persistent asthma. In the current NHLBI guidelines, assessment and monitoring is the first of four essential components to asthma management. The tools of assessment and monitoring focus on a reduction in impairment and risk. In this context, impairment is defined as the frequency and intensity of symptoms and functional limitations the patient is experiencing or has recently experienced, and risk is defined as the likelihood of an asthma exacerbation, progressive decline in lung function, reduced lung growth, or an adverse effect from medication.<br>Patient centered outcomes that can benefit from improved delivery of inhaled steroids in patients with asthma can include reduction in severity of symptoms, improvement in asthma control and quality of life, improvement in spirometry, diminished airway hyperresponsiveness, prevention of exacerbations, and reduction in systemic corticosteroid courses, ED care, hospitalizations, and deaths due to asthma. |
| **Patient-centeredness** | |
| Is the proposed research focused on questions and outcomes of specific interest to patients, their caregivers, and clinicians? | The proposed research question focuses on whether optimal usage of different delivery devices (MDI plus Spacer or DPI) improves asthma control in patients using inhaled corticosteroids. This proposal also examines the role of technology to provide ongoing education and prompts for adherence to increase medication adherence. Although inhaled corticosteroids are the most potent and consistently effective long-term medication for asthma, delivery of this medication can be challenging. Delivery devices, in conjunction with patient technique, are the primary determinants of the dose delivered to the lungs of the patient and subsequent clinical benefit.<br>This question is of specific interest to patients, caregivers, and clinicians, as proper training for the use of spacer devices is limited in the outpatient primary care setting, and improved adherence to spacer or the use of other devices for steroid intake may contribute to increased efficacy of inhaled corticosteroids in maintaining asthma control. This could lead to improved patient outcomes including improved asthma quality of life, medication adherence, and reduced clinic visits, emergency room visits, and hospitalizations. |
| **Burden on Society** | |
| Recent prevalence in populations and subpopulations | An estimated 22 million Americans have asthma; 6.5 million are under 18. Asthma is the most common chronic disease of childhood, the most frequent cause of childhood disability, and the most frequent reason for hospitalization of children in North America. Asthma prevalence approaches 10% among children in the United States. |
| Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services | Over the past decade, there has been little progress in decreasing asthma mortality, with approximately 4,000 deaths per year in the United States due to asthma, and worldwide there were reported to be 255,000 deaths in 2005. Moreover, asthma prevalence continues to increase worldwide and in the U.S., with annual costs as high as $56 billion in the U.S. alone. Economic assessments of asthma included in recent reviews indicate that decreased productivity at work and school represent a considerable proportion of the disease burden. Asthma results in 497,000 hospitalizations and 1.8 million emergency room visits. Childhood asthma accounts for 12.8 million missed school days each year, and 10.1 million lost work days for adults. Significant asthma disparities exist, with higher rates of mortality reported among Latino and African-American populations. |

**Topic 2: Role of Spacers in Asthma**

| **Assessment of Current Options** | |
|---|---|
| Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options? | A number of recent systematic reviews have highlighted the role of spacer devices and educational interventions in targeting medications to the airways and improving medication adherence. The relative benefit of the use of spacer devices in children has been well established, as well as the harm that results from lack of proper medication delivery. Although the efficacy is known, effectiveness is not well established and education may be part of the reason for poor adherence. There are no systematic reviews on the use of technology in augmenting use of spacer devices in children with asthma. |
| What could new research contribute to achieving better patient-centered outcomes? | Asthma related outcomes including quality of life, daily respiratory symptoms, work productivity, and ED visits/hospitalizations can be improved by increasing proper delivery of inhaled steroids. The use of technology may be particularly helpful, as traditional office-based education has resulted in improper technique and poor adherence. |
| Have recent innovations made research on this topic especially compelling? | Traditional retrospective self-report of asthma assessment has limitations related to recall bias and social desirability effects. Individualized ecological momentary assessment of adherence using mobile devices provides a valuable method of measuring adherence that is integrated within the daily lifestyles of patients, provides unique information on quantitative and qualitative patterns of adherence and triggers, while providing accurate data. The diverse functionality of mobile phones allows the integration of voice data, text messaging, and/or multimedia communications for monitoring symptoms and adherence. The mobile assessment of asthma adherence compliments the widely used Asthma Control Test. |
| How widely does care now vary? | There is significant variation in prescribing, education, and adherence to spacer devices and in prescription of different modes of inhaled corticosteroid delivery (such as MDI alone vs MDI plus spacer vs DPI). |
| What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)? | There are currently 32 trials on Clinical Trials.gov listing spacer device as part of asthma management, and the number of trials that incorporate spacer use emphasizes the critical role of spacers in asthma management. However, these trials are focused on either comparison of new spacer devices under development, or the use of spacers in combination with specific medications. Despite the importance of spacer use, there have been no studies assessing an intervention to enhance use, adherence, and impact on patient-centered outcomes |
| **Potential for New Information to Improve Care and Patient-Centered Outcomes** | |

**Topic 2: Role of Spacers in Asthma**

| | |
|---|---|
| How likely is it that new CER on this topic would provide better information to guide clinical decision making? | Although inhaled corticosteroid prescriptions have been used as a measure of outpatient adherence, there have been no tools to assess use and adherence of spacer devices or the value of using these devices with an MDI instead versus a DPI. Better information about adherence to spacer plus MDI or DPI device would guide clinicians not only in providing the optimal therapeutic approach for inhaled steroid use and the role of education on promoting proper use to promote optimal outcomes. |
| What are the facilitators and barriers that would affect the implementation of new findings in practice? | A key facilitator to implementing these findings into practice is that there is broad recognition for the use of inhaled corticosteroids as first-line treatment for persistent asthma. A primary barrier is that there is limited education in many primary care settings and in the home, where families are faced with the task of how use the MDI plus spacers or DPI on their own. The use of technology through mobile devices not only reinforces proper technique but also provides a mechanism to improve adherence. |
| How likely is it that the results of new research on this topic would be implemented in practice right away? | There is significant interest in improved asthma control by primary care providers and subspecialists. The benefits of improved asthma outcomes with patient-focused self education would drive providers to reinforce use and focus on other aspects of care. The use of mobile technology provides a particularly compelling way to implement immediate changes to practice. |
| Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies? | Use of spacer devices has been part of asthma treatment for decades, but the focus on merely prescribing medications has often not been done in parallel with proper education for the spacer or delivery devices needed for drug delivery. |
| **Feasibility of the clinical trial within health systems** | |

**Topic 2: Role of Spacers in Asthma**

| | |
|---|---|
| Does this trial meet the requisite technical, governance and regulatory constraints described below*? | Yes. |
| Is the trial characterized by operational simplicity? | This trial could meet several criteria for operational simplicity:<br>• Patients can be identified through the EHR by searching for ICD-9 criteria for asthma, medication lists for inhaled steroid therapy and other asthma medications.<br>• Patients or Parents of Children could potentially be recruited and consented electronically. Randomization to study drug could also occur centrally/electronically.<br>• Health care providers would need to agree to prescribing the assigned treatment strategy and discussing risks/benefits of this treatment with the patient. We anticipate that this would be reasonable, since the treatment options are all part of usual care.<br>• As a pragmatic trial, health care providers would have the ability to alter treatment over time, as they chose, and in accordance with their usual practices.<br>• Outcome data could be collected through extraction of key variables from the EMR, as well as claims data for adherence to inhaled corticosteroid use. In addition, web-based surveys could be used to collect patient reported outcomes over time.<br>• For the education component, a web or mobile phone-based educational intervention could be designed and delivered from one central site. Several existing models already exist that could be adapted for this use. |
| Does the trial make use of EHR to identify patients and measure outcomes? | **Yes.**<br>• Individuals with asthma are easily identified with EHR; there are well-validated algorithms for identifying these individuals based on ICD codes and medication disbursements.<br>• Several of the outcomes of interest are measured as usual care or are processes of care (e.g. ED visits, hospitalization). The recording of *quality of life, medication adherence, and other patient reported outcomes* could be collected through web or mobile phone. |

## What are the benefits of spacer use and asthma education in asthma?

**Topic 2: Role of Spacers in Asthma**

## References


1. Asthma Facts, http://www.acaai.org/press/Pages/asthma-facts.aspx, accessed 4/14/2014
2. Expert Panel Report 3 (EPR3): Guidelines for the Diagnosis and Management of Asthma, NHLBI, 2007, http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf, accessed 4/14/2014
3. Mulvaney SA, Ho YX et al. Assessing adolescent asthma symptoms and adherence using mobile phones. J Med Internet Res. 2013 Jul 17;15(7):e141. doi: 10.2196/jmir.2413.
4. Cates CJ, Lasserson TJ, Regular treatment with formoterol versus regular treatment with salmeterol for chronic asthma: serious adverse events. Cochrane Database Syst Rev. 2012;3:Cd007695. PMID 22419326
5. Cates CJ, Welsh EJ, Rowe BH, Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. Cochrane Database Syst Rev. 2013;9:Cd000052. PMID 24037768
6. Edmonds ML, Milan SJ, Camargo CA, Jr., et al., Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. Cochrane Database Syst Rev. 2012;12:Cd002308. PMID 23235589
7. Ferguson C, Gidwani S, Best evidence topic reports. Delivery of bronchodilators in acute asthma in children. Emerg Med J. 2006 Jun;23(6):471-2. PMID 16714515
8. Lavorini F, Fontana GA, Targeting drugs to the airways: The role of spacer devices. Expert Opin Drug Deliv. 2009 Jan;6(1):91-102. PMID 19236210
9. Muley P, Shah M, Muley A, Safety of inhaled fluticasone propionate therapy for pediatric asthma - a systematic review. Curr Drug Saf. 2013 Jul;8(3):186-94. PMID 23859431
10. Price D, Bosnic-Anticevich S, Briggs A, et al., Inhaler competence in asthma: common errors, barriers to use and recommended solutions. Respir Med. 2013 Jan;107(1):37-46. PMID 23098685
11. Rodriguez C, Sossa M, Lozano JM, Commercial versus home-made spacers in delivering bronchodilator therapy for acute therapy in children. Cochrane Database Syst Rev. 2008(2):Cd005536. PMID 18425921
12. Alotaibi S, Hassan WM, Alhashimi H, Concurrent use of metered dose inhalers without spacer and dry powder inhalers by asthmatic children adversely affect proper inhalation technique. Internet J Pediatr Neonatol. 2011 Jun 14;13(1) PMID 21760757
13. Berger WE, Bensch GW, Weinstein SF, et al., Bronchodilation with mometasone furoate/formoterol fumarate administered by metered-dose inhaler with and without a spacer in children with persistent asthma. Pediatr Pulmonol. 2014 May;49(5):441-50. PMID 24019197
14. Boss H, Minic P, Nave R, Similar Results in Children with Asthma for Steady State Pharmacokinetic Parameters of Ciclesonide Inhaled with or without Spacer. Clin Med Insights Pediatr. 2010;4:1-10. PMID 23761990

**Topic 2: Role of Spacers in Asthma**


15. Ciaccio CE, Portnoy JM, Spacers and valved holding chambers in asthma drug delivery: how many breaths are needed to achieve adequate lung deposition? Curr Allergy Asthma Rep. 2011 Dec;11(6):445-6. PMID 21901303
16. Di Berardino F, Forti S, Piatti G, et al., A comparative study of two different metered-dose inhaler-valved holding chambers in the administration of salbutamol. Chest. 2010 Feb;137(2):502-3. PMID 20133310
17. Engelstatter R, Szlavik M, Gerber C, et al., Once-daily ciclesonide via metered-dose inhaler: Similar efficacy and safety with or without a spacer. Respir Med. 2009 Nov;103(11):1643-50. PMID 19596188
18. Kolasani BP, Lanke VM, Diyya S, Influence of delivery devices on efficacy of inhaled fluticasone propionate: a comparative study in stable asthma patients. J Clin Diagn Res. 2013 Sep;7(9):1908-12. PMID 24179895
19. Mansfield LE, Maynes R, A valved holding chamber does not decrease the bronchodilator activity of budesonide-formoterol combination metered dose inhaler. J Asthma. 2013 Feb;50(1):71-4. PMID 23176189
20. Mosnaim GS, Li H, Damitz M, et al., Evaluation of the Fight Asthma Now (FAN) program to improve asthma knowledge in urban youth and teenagers. Ann Allergy Asthma Immunol. 2011 Oct;107(4):310-6. PMID 21962090
21. Nair A, McKinlay L, Williamson P, et al., Comparative lung bioavailability of fluticasone/salmeterol via a breath-actuated spacer and conventional plastic spacers. Eur J Clin Pharmacol. 2011 Apr;67(4):355-63. PMID 21240480
22. Oliveira RF, Teixeira SF, Silva LF, et al., Development of new spacer device geometry: a CFD study (part I). Comput Methods Biomech Biomed Engin. 2012;15(8):825-33. PMID 21491261
23. Reznik M, Jaramillo Y, Wylie-Rosett J, Demonstrating and assessing metered-dose inhaler-spacer technique: pediatric care providers' self-reported practices and perceived barriers. Clin Pediatr (Phila). 2014 Mar;53(3):270-6. PMID 24336438
24. Reznik M, Silver EJ, Cao Y, Evaluation of MDI-spacer utilization and technique in caregivers of urban minority children with persistent asthma. J Asthma. 2014 Mar;51(2):149-54. PMID 24131031
25. Rodriguez-Martinez CE, Sossa-Briceno MP, Castro-Rodriguez JA, Comparison of the bronchodilating effects of albuterol delivered by valved vs. non-valved spacers in pediatric asthma. Pediatr Allergy Immunol. 2012 Nov;23(7):629-35. PMID 23005919
26. Schultz A, Sly PD, Zhang G, et al., Incentive device improves spacer technique but not clinical outcome in preschool children with asthma. J Paediatr Child Health. 2012 Jan;48(1):52-6. PMID 22040259
27. Wolthers OD, Sergio F, Systemic activity of inhaled beclomethasone dipropionate: a double-blind comparison of volume spacers. Acta Paediatr. 2012 Feb;101(2):159-63. PMID 21790779

# PCORnet: First Interventional Study
# Research Prioritization Topic Brief

## Patient Outcomes Research to Advance Learning (PORTAL)
## Clinical Data Research Network

April 28-29, 2014



Questions or comments may be sent to Jason Rotter at PCORI at jrotter@pcori.org or by mail to Suite 900, 1828 L Street, NW, Washington, DC 20036.

**Topic 3: Establishing the Optimal Maintenance Aspirin Dose for Secondary Prevention in Patients with Coronary Artery Disease**

| Criteria | Brief Description |
|---|---|
| **Introduction** | |
| Overview/definition of topic | Although aspirin is an effective therapy for the secondary prevention of coronary artery disease (CAD) prescribed to millions of patients, the optimal maintenance dosage of aspirin remains under debate. The latest U.S. clinical guidelines for the treatment of myocardial infarction (MI) state that "aspirin 81 mg is the preferred maintenance dose," but qualifies this assertion as Class of Evidence (IIa), Level of Evidence (B), indicating some conflicting evidence exists.[1] In spite of this guideline, use of high-dose (325mg) aspirin in the U.S. remains common (53.6% in a recent study[2]) and variation in aspirin dose is primarily due to practice patterns rather than clinical factors. [3]<br><br>It is unclear whether high-dose aspirin offers substantial benefits over low-dose aspirin. Observational evidence based on large systematic reviews of aspirin trials reported that low-dose aspirin appears to be as effective in preventing recurrent cardiovascular events as higher-dose aspirin, but with rates of gastrointestinal (GI) bleeding significantly higher for higher-dose aspirin.[4,5] Only one large randomized controlled trial (RCT) has performed a head-to-head comparison of low-dose versus high-dose aspirin,[6] which reported no significant difference between higher-dose aspirin and lower-dose aspirin with respect to a primary outcome of cardiovascular death, MI or stroke; however, this study was limited to examining 30-day outcomes for a restricted population—namely patients who had percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS). Thus, an evidence gap exists regarding the optimal *long-term* dose of aspirin that is safe and effective for the *general population* of CAD patients. |

**Topic 3: Establishing the Optimal Maintenance Aspirin Dose for Secondary Prevention in Patients with Coronary Artery Disease**

| | |
|---|---|
| Overview/definition of topic (continued) | **A definitive RCT answering whether low-dose aspirin is the optimal long-term maintenance dose of aspirin has the potential to transform clinical practice for millions of Americans with CAD. We propose a pragmatic RCT in which patients with a history of MI, ACS, PCI, or bypass surgery who are currently taking full-dose (325mg) daily aspirin be randomized to low-dose (81 mg) versus 325 mg daily aspirin.** We hypothesize that low-dose aspirin is *non-inferior* to full-dose aspirin using a combined efficacy endpoint of hospitalization for recurrent MI or ACS, repeat PCI or bypass surgery, and all-cause death (excluding death associated with hospitalization for GI bleeding). We hypothesize that low-dose aspirin is *superior* to full-dose aspirin with respect to a primary safety outcome of hospitalization for GI bleeding. We propose excluding patients prescribed additional anticoagulants or anti-platelet medications other than aspirin.<br><br>**This unanswered clinical question is an ideal topic for PCORnet—**reducing the dose of aspirin is a simple intervention; patients with CAD can be readily identified by electronic health record (EHR) data and enrolled over a sustained period of time; the cost of aspirin is negligible; outcomes such as recurrent CAD events and major bleeding events are readily ascertained using diagnosis codes; a multi-network approach is needed to develop a large sample cohort. **The findings from the proposed study are likely to provide definitive evidence to change current clinical guidelines, improving the care of 15.4 million Americans with CAD.** |
| Relevance to patient-centered outcomes | Demonstrating that low-dose aspirin is as effective as full-dose aspirin encompasses several important patient-centered outcomes. Cardiac events such as MI and ACS are serious conditions that are life-threatening, and can often lead to chronic cardiac conditions such as angina or heart failure that reduce quality of life and functional capacity. Revascularization procedures required after recurrent cardiac events also carry non-trivial risks of MI, stroke, bleeding and death; avoiding these procedural complications is important to patients.<br><br>Regarding the safety of aspirin, GI bleeding is a serious side effect that is potentially fatal, and often requires procedures such as endoscopy or blood transfusions that carry their own attendant risks. |
| **Patient-centeredness** | |

**Topic 3: Establishing the Optimal Maintenance Aspirin Dose for Secondary Prevention in Patients with Coronary Artery Disease**

| | |
|---|---|
| Is the proposed research focused on questions and outcomes of specific interest to patients, their caregivers, and clinicians? | Patients desire effective treatment without undue risk from complications of therapy— both efficacy and safety are investigated in our proposed study. Currently half of patients in the U.S. receive full-dose aspirin for secondary prevention of CAD,[2] even though low-dose aspirin is proposed to have equivalent efficacy with a lower risk of major bleeding. Reducing the risk of serious GI bleeding while demonstrating equivalent efficacy for preventing subsequent heart attacks and revascularization procedures are important outcomes that patients care about. |
| | |
| **Burden on Society** | |
| Recent prevalence in populations and subpopulations | Cardiovascular disease is the #1 cause of death in the U.S., and CAD is implicated in 1 out of every 6 deaths in the U.S. in 2010.[7] The American Heart Association reports that *15.4 million adults suffer from CAD,* or 6.4% of the U.S. adult population, and CAD poses a significant disease burden across all race-sex groups: white males (8.2%), white females (4.6%), black males (6.8%), black females (7.1%), Mexican-American males (6.7%) and Mexican-American females (5.3%).[7]<br><br>Given the high prevalence of CAD, the potential for reducing bleeding events using low-dose aspirin is substantial. Based on a large meta-analysis of high risk patients, low-dose aspirin reduces major bleeding events by approximately 0.7 absolute percentage points compared with full-dose aspirin.[5] Assuming that half of CAD patients currently receive full dose aspirin, this simple intervention can prevent 53,900 major bleeding events (=15.4 million x 0.7% x 50%). |
| Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services | Patients suffer greatly from CAD events. Approximately 34% of patients who develop an ischemic coronary event will eventually die from it.[7] Subsequent CAD events increase the risk of developing heart failure, a condition that substantially decreases functional capacity and quality of life, and is the leading reason for hospitalization in adults.[8] Treatment of CAD represents a tremendous expenditure of health care services, with 1.3 million hospitalizations in 2010 and over 11.9 million ambulatory care visits.[7]<br><br>Bleeding events from aspirin therapy also have a substantial impact on patients. Bleeding can be fatal or life-threatening and occurs not infrequently for high-dose aspirin (1.6% for daily aspirin >200mg).[5] Assessment and treatment of bleeding consume substantial health care services, including hospitalization, blood transfusions, or procedures such as GI endoscopy. |
| **Assessment of Current Options** | |

**Topic 3: Establishing the Optimal Maintenance Aspirin Dose for Secondary Prevention in Patients with Coronary Artery Disease**

| | |
|---|---|
| Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options? | There is convincing evidence that aspirin reduces risk of cardiovascular events in high risk patients. A large meta-analysis of 144,051 patients from 195 RCTs demonstrated that anti-platelet therapy (predominately aspirin) significantly lowered risk of serious vascular events (MI, stroke, vascular death);[4] when restricted to a subset of 65 RCTs incorporating varying doses of aspirin, no difference in efficacy between low-dose aspirin (75-150 mg/day) and higher dose aspirin (160-1500mg/day) was found.[4]<br><br>Regarding bleeding rates by aspirin dose, a meta-analysis of 192,036 high-risk CVD patients enrolled in 31 RCTs reported that the total bleeding rate for low-dose aspirin (<100 mg) was significantly lower compared with high-dose aspirin (>200mg): 3.7% v 8.5%, p<0.0001.[5] Rates of major bleeding were also lower with low-dose aspirin compared with high-dose aspirin: 1.6% v 2.3%, p<0.0001.[5]<br><br>However, a recent trial has cast some confusion on whether low-dose aspirin has equivalent efficacy and superior safety compared with high-dose aspirin. Published in 2010, the CURRENT-OASIS 7 trial randomized 25,086 patients with ACS referred for PCI, comparing higher-dose aspirin (300-325 mg daily) vs lower-dose aspirin (75-100 mg daily) as well as double-dose clopidogrel vs standard dose clopidogrel in a 2x2 factorial design.[6] There was no difference between higher-dose and lower-dose aspirin with respect to the primary outcome of cardiovascular death, myocardial infarction, or stroke at 30 days (4.2% vs. 4.4%; p=0.61)[6]; however, rates of recurrent ischemia (a secondary outcome) were significantly lower for patients in the high-dose aspirin arm (0.3% v 0.5%, p=0.02) which *brings into question whether efficacy was truly equivalent*. Furthermore, rates of major bleeding were similar for high-dose and low-dose aspirin arms (2.3% vs. 2.3%, p=0.90), *a finding that conflicts with observational data*.[5]<br><br>**Providing definitive evidence as to whether low-dose aspirin is safer, but as effective, as high-dose aspirin for secondary prevention of CAD represents a significant opportunity for PCORI to answer an important yet unresolved clinical question.** |
| What could new research contribute to achieving better patient-centered outcomes? | New research aimed at determining the optimal dose aspirin for secondary prevention of CAD has the potential to minimize bleeding complications that significantly impact mortality, morbidity and quality of life of patients. At the same time, our study would ensure that public health benefits of aspirin therapy for reducing recurrent CAD events and procedures remain unchanged. |

**Topic 3: Establishing the Optimal Maintenance Aspirin Dose for Secondary Prevention in Patients with Coronary Artery Disease**

| | |
|---|---|
| Have recent innovations made research on this topic especially compelling? | Use of full dose aspirin will become even more problematic in the near future because newer antiplatelet drugs are suspected to be less effective in combination with full dose aspirin. For example, the recent PLATO trial found that the novel antiplatelet medication ticagrelor improved outcomes over clopidogrel for patients with ACS worldwide– **except for subjects enrolled in the U.S.**— which is believed to be due to an interaction with higher doses of aspirin.[2,9] As a result, the FDA added a warning to the ticagrelor label stating that the medication only be used in combination with low-dose aspirin (75-100mg). |
| How widely does care now vary? | The substantial world-wide variability of full-dose aspirin use is exemplified by the recent PLATO trial. [2,9] **In the U.S. 53.6% of patients receive high-dose aspirin after ACS, while only 1.7% of patients did so in the rest of the world.[2,9]** There is significant site-to-site variation in the use of low-dose aspirin. In a 23,336 patient trial of dual anti-platelet therapy, only 28.0% of U.S. subjects were prescribed low-dose aspirin after PCI. Patient characteristics only explained 1.6% of total variance in aspirin dose, while study site accounted for 45.9% of the unexplained variability.[3] **In summary, the U.S. has a strikingly high use of high-dose aspirin compared with the rest of the work, with apparently no strong basis other than local practice patterns.** |
| What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)? | The recent CURRENT-OASIS 7[6] and PLATO[2] trials illustrate the ongoing interest in understanding optimal aspirin dosing for patients with CAD, but have focused exclusively on patients requiring dual-antiplatelet therapy after PCI in ACS settings. An evidence gap remains on the optimal long-term dose of aspirin outside of the post-acute PCI setting. Our review of clinicaltrials.gov indicates that no such RCT is currently examining different aspirin doses for secondary prevention of CAD. |
| **Potential for New Information to Improve Care and Patient-Centered Outcomes** | |
| How likely is it that new CER on this topic would provide better information to guide clinical decision making? | The latest U.S. ACCF/AHA clinical guidelines for the treatment of MI recommend *"aspirin 81 mg is the preferred maintenance dose"* at a Class of Evidence (IIa) and Level of Evidence (B), which indicates that it is reasonable course of treatment, but some conflicting evidence exists. The European clinical guidelines for the treatment of MI specifically state that *"the dosage of aspirin is debated."*[10] **A large, highly-publicized clinical trial would provide the necessary evidence to definitively alter these influential guidelines to effect change in clinical care.** |
| What are the facilitators and barriers that would affect the implementation of new findings in practice? | Low-dose aspirin for secondary prevention of CAD is already supported by U.S. clinical guidelines, which facilitates implementation. The marginally lower cost of low-dose aspirin is also a factor favoring implementation. There are no regulatory (FDA) barriers to adoption of low-dose aspirin for this indication. |

**Topic 3: Establishing the Optimal Maintenance Aspirin Dose for Secondary Prevention in Patients with Coronary Artery Disease**

| | |
|---|---|
| How likely is it that the results of new research on this topic would be implemented in practice right away? | It is very likely that a study demonstrating the non-inferiority of low-dose aspirin and its superiority in reducing GI bleeding will be implemented quickly into clinical practice for two reasons: 1) a large randomized trial would raise the Class and Level of Evidence for low-dose aspirin in the U.S. clinical guidelines to "Class I, Level A"; 2) as a result, low-dose aspirin likely would be adopted as a national quality measure, ensuring a strong impetus for implementation. |
| Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies? | Aspirin use has been the mainstay of CAD therapy for decades, and unlikely to be completely replaced by other anti-platelet medications. To our knowledge there are no active trials comparing the efficacy and safety of different aspirin dosages in the general CAD population.<br><br>There is on-going research on personalizing the dose of aspirin, as it is hypothesized that particular subgroups of patients may have increased "resistance" to aspirin and higher risk of cardiovascular events.[11,12] Genomic and proteomic markers may play an increasingly important role for aspirin dose selection in the future.[13,14] However, identification and validation of specific markers of aspirin resistance will take several years. In the meantime, **a PCORnet RCT can establish either low- or high-dose aspirin as the preferred maintenance dose,** and future studies of personalized medicine can increase (or decrease) the dose from this baseline. |
| **Feasibility of the clinical trial within health systems** | |
| Does this trial meet the requisite technical, governance and regulatory constraints described below*? | The proposed RCT minimizes the technical infrastructure for data capture. Required data elements include fields capturing dose of a single medication, reason for study inclusion (prior MI, ACS, angina, or revascularization), and outcomes (all-cause death, hospitalization for MI, revascularization, or GI bleeding) which are readily available from clinical and claims data. All these data elements are binary indicators (yes/no) that do not required for transformations, mappings, or complex data extraction procedures.<br><br>The topic of the proposed RCT simplifies regulatory and governance hurdles. Clinical responsibility for preventing recurrent CAD events typically resides within a single specialty (cardiology). The chiefs of cardiology departments at our CDRN sites already assemble regularly for quality and operational initiatives, and we anticipate our study would only have to be presented before a small body of cardiology decision-makers for approval. Our study's focus on one of the most widely used medications in the world is also an advantage, as individual CDRN sites would be more comfortable agreeing to cede IRB and consent processes to a central site for such commonly prescribed drug. |
| Is the trial characterized by operational simplicity? | **Our study's intervention is the essence of operational simplicity: changing the dose of a single medication.** Patients simply substitute a smaller dose of aspirin instead of a full dose. Administrative burden is minimal for providers – other than informed consent, we expect providers to simply document the dose of aspirin in the EHR. |

**Topic 3: Establishing the Optimal Maintenance Aspirin Dose for Secondary Prevention in Patients with Coronary Artery Disease**

| | |
|---|---|
| Does the trial make use of EHR to identify patients and measure outcomes? | We propose that the trial use EHR to identify subjects with prior CAD—namely prior MI, ACS, PCI or bypass surgery. Patients with these characteristics are readily identifiable from clinical diagnosis codes and procedure codes.<br><br>Outcomes are readily identified from the EHR. Patients with recurrent MI or coronary revascularization are easily identified from discharge diagnoses from facility claims. Serious episodes of GI bleeding also require hospitalization and are identifiable using discharge diagnosis codes. |

References


1. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* Jan 29 2013;127(4):e362-425.
2. Mahaffey KW, Wojdyla DM, Carroll K, et al. Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation.* Aug 2 2011;124(5):544-554.
3. Matteau A, Yeh RW, Kereiakes D, et al. Frequency of the Use of Low- Versus High-Dose Aspirin in Dual Antiplatelet Therapy After Percutaneous Coronary Intervention (from the Dual Antiplatelet Therapy Study). *The American journal of cardiology.* Apr 1 2014;113(7):1146-1152.
4. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ (Clinical research ed.).* Jan 12 2002;324(7329):71-86.
5. Serebruany VL, Steinhubl SR, Berger PB, et al. Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomized controlled trials. *The American journal of cardiology.* May 15 2005;95(10):1218-1222.
6. Mehta SR, Bassand JP, Chrolavicius S, et al. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. *The New England journal of medicine.* Sep 2 2010;363(10):930-942.
7. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation.* Jan 21 2014;129(3):e28-e292.
8. Hall MJ, DeFrances CJ, Williams SN, Golosinskiy A, Schwartzman A. National Hospital Discharge Survey: 2007 Summary. Available at http://www.cdc.gov/nchs/data/nhsr/nhsr029.pdf. Accessed April 8, 2014. *National Health Statistics Reports.* 2010;29(October 26, 2010).
9. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *The New England journal of medicine.* Sep 10 2009;361(11):1045-1057.
10. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *European heart journal.* Oct 2012;33(20):2569-2619.

**Topic 3: Establishing the Optimal Maintenance Aspirin Dose for Secondary Prevention in Patients with Coronary Artery Disease**


**11.** Grinstein J, Cannon CP. Aspirin resistance: current status and role of tailored therapy. *Clinical cardiology.* Nov 2012;35(11):673-681.

**12.** Krasopoulos G, Brister SJ, Beattie WS, Buchanan MR. Aspirin "resistance" and risk of cardiovascular morbidity: systematic review and meta-analysis. *BMJ (Clinical research ed.).* 2008-01-24 23:02:35 2008;336(7637):195-198.

**13.** Ahmad T, Voora D, Becker RC. The pharmacogenetics of antiplatelet agents: towards personalized therapy? *Nature reviews. Cardiology.* Oct 2011;8(10):560-571.

**14.** Voora D, Cyr D, Lucas J, et al. Aspirin exposure reveals novel genes associated with platelet function and cardiovascular events. *Journal of the American College of Cardiology.* Oct 1 2013;62(14):1267-1276.

# PCORnet: First Interventional Study

# Research Prioritization Topic Brief

**Andrew A. Nierenberg, MD; Thilo Deckersbach, PhD; Louisa Sylvia, PhD**

**[PPRN]**

April 28-29, 2014



Questions or comments may be sent to Jason Rotter at PCORI at jrotter@pcori.org or by mail to Suite 900, 1828 L Street, NW, Washington, DC 20036.

**Topic 4: Mindfulness-based Weight Reduction Using a Simple Web-based Training**

| Criteria | Brief Description |
|---|---|
| **Introduction** | |
| Overview/definition of topic | We propose to investigate the comparative effectiveness of a brief web-based mindfulness dietary intervention for overweight or obese individuals who would like to lose weight. Overweight/obese individuals will be randomized to either (1) mindfulness dietary intervention or (2) dietary intervention without mindfulness. Interested and eligible obese/overweight participants (as defined by the PCORI Task Force on Obesity, Co-chaired by Dr. Sylvia) will be recruited via CDRNs across PCORnet.<br><br>The mindfulness intervention will begin with an on-line video outlining the basics to nutrition (i.e., balanced diet) and a mindfulness skill that patients can learn within a few minutes (a breathing mindfulness exercise). Patients will also have access to short video clips demonstrating how mindfulness can be applied in daily life eating situations (e.g. choosing food, eating, eating pace, mindfulness about flavors, using mindfulness instead of eating when stressed). The control group will begin with the same video, but without introducing the mindfulness skill. This group will also have access to short video clips about nutritional education (e.g., serving size, low-fat substitutions, importance of fiber, reducing intake of sugar sweetened beverages). Patients in both groups will be sent email reminders to view the videos and short "surveys" to give feedback on the videos as well as to score treatment integrity.<br><br>The primary outcome will be weight, a routinely collected electronic health data point. The secondary outcomes will be Body Mass Index (BMI). |
| Relevance to patient-centered outcomes | A recent Gallup Poll of Americans showed that 56% of Americans want to lose weight.[1] The PCORNet Obesity Task Force (Dr. Sylvia, Co-Chair) was formed to address this important public health issue and is a key area to develop effective interventions. Weight loss is a central concern of patients regardless of other comorbid conditions or treatments. |
| **Patient-centeredness** | |

**Topic 4: Mindfulness-based Weight Reduction Using a Simple Web-based Training**

| | |
|---|---|
| Is the proposed research focused on questions and outcomes of specific interest to patients, their caregivers, and clinicians? | The main outcome for this study will be weight. Weight is routinely collected during medical visits. Weight is monitored by clinicians because of its clear indication of obesity, a risk factor for cardiovascular disease. As stated above, more than half of the population would like to reduce their weight, highlighting patient centeredness of this proposal. Body Mass Index (BMI) will be a secondary outcome because height is less routinely collected (although it just needs to be recorded once) and BMI is subject to measurement error. For example, in a review of 500 randomly selected cases, 67% of these provided information about weight, and 41% on both height and weight. [2] |
| **Burden on Society** | |
| Recent prevalence in populations and subpopulations | More than one-third of U.S. adults (34.9%) are obese.[3] Although recent data highlights a significant decrease in obesity among 2- to 5-year-old children (from 13.9% to 8.4%; P=.03), there was a significant *increase* in obesity among women aged 60 years and older (from 31.5% to 38.1%; P=.006). Moreover, there was a dramatic increase in obesity in the United States from 1990 through 2010, and of note, no U.S. states met the nation's Healthy People 2010 goal to lower obesity prevalence to 15%. Instead, there were 12 states with an obesity prevalence of 30% whereas 10 years earlier in 2000, there were no U.S. states that had an obesity prevalence of 30% or more. [4] According to the Centers for Disease Control and Prevention, non-Hispanic blacks have the highest age-adjusted rates of obesity (47.8%) followed by Hispanics (42.5%), non-Hispanic whites (32.6%), and non-Hispanic Asians (10.8%). Obesity is higher among middle age adults, 40-59 years old (39.5%) than among younger adults, age 20-39 (30.3%) or adults over 60 or above (35.4%) adults. |

**Topic 4: Mindfulness-based Weight Reduction Using a Simple Web-based Training**

| | |
|---|---|
| Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services | Obesity increases the risk of death. In a nationally representative cohort of civilian, non-institutionalized U.S. adults aged up to 74 years at baseline, one study found that for women aged 45 to 54, 55 to 64, and 65 to 74 years, the mortality relative risks for obesity were 2.0, 1.6, and 0.9, respectively. The corresponding relative risks for men were 1.4, 1.2, and 1.1. [5] Obesity also negatively impacts patients' productivity and quality of life. A recent study evaluating work absence and productivity among individuals of varying body mass index with or at risk for diabetes mellitus found that obese individuals had the greatest impairment at work (11%-15% of work time), greatest impairment of daily activities (20 %-34% of time), and greatest overall impairment (11%-15% of time). Obesity was also an independent predictor of overall work impairment and life disruption ($p < .001$). [6]<br><br>Based on data from the U.S. Medical Expenditure Panel Survey (MEPS), obesity was responsible for about 6 percent of medical costs in 1998, or about $42 billion (in 2008 dollars); however, by 2006, obesity was responsible for closer to 10 percent of medical costs, or nearly $86 billion a year. [7-8] In 2006, spending on obesity-related conditions accounted for an estimated 8.5 percent of Medicare spending, 11.8 percent of Medicaid spending, and 12.9 percent of private-payer spending. It is estimated that by 2030, if the obesity trends continue unchecked, obesity-related medical costs alone could rise by $48 to $66 billion per year in the U.S. [8] |

**Topic 4: Mindfulness-based Weight Reduction Using a Simple Web-based Training**

| **Assessment of Current Options** | |
|---|---|
| Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options? | The causes of obesity are complex and multifactorial and include genetic, behavioral, environmental, physiological, social, and cultural determinants that lead to energy imbalance and promote excessive fat accumulation. [9] The World Health Organization Consultation on Obesity has concluded that behavioral and environmental factors are predominantly responsible for the excess energy intake (and, to a lesser extent, reduced energy expenditure) that has resulted in the dramatic rise in obesity over the past few decades. [10]<br><br>There are three management options for weight: (1) medications/supplements; (2) surgery; and (3) lifestyle interventions. There is only one medication, orlistat, which currently has U.S. Food and Drug Administration approval for the long-term treatment of obesity in the United States. There are very few randomized clinical trials (RCTs) of orlistat use. [11] At least one new weight loss medication (rimonabant) was under development but has not been approved in the US, and another weight loss medication—Meridia (sibutramine)—was recently withdrawn from the U.S. market after the drug was found to be associated with increased risk of heart attack and stroke. Use of over-the-counter dietary supplements is common in the United States, despite the lack of FDA approval and or randomized clinical trials of these supplements for weight loss Nevertheless, a systematic literature review of the effectiveness of these dietary weight loss supplements found the evidence for their use unconvincing and recommended they not be used. [12]<br><br>Given the lack of efficacy of weight loss medications and their often high side effect burden and the cost/barriers to weight loss surgeries, the National Institute of Health made a call to action to improve lifestyle interventions for weight loss. [13] Lifestyles interventions for obesity can effect at making meaningful changes in weight (5-10%), but often tend to be long (e.g., 6 months or longer), costly, and burdensome for participants. [14] Thus, effective web-based interventions for obesity seem sorely needed. Preliminary data of internet-based lifestyle interventions for obesity is promising, but very limited by lack of control groups. [15] |

**Topic 4: Mindfulness-based Weight Reduction Using a Simple Web-based Training**

| | |
|---|---|
| What could new research contribute to achieving better patient-centered outcomes? | Our proposed brief mindfulness-based weight loss intervention improves upon previous lifestyle interventions for obesity as it will be easy to disseminate and yield low participant burden by being internet-based. More specifically, previous dietary interventions have also tend to be overly focused on changing the dietary composition of food/meals, or try to teach overweight/obese individuals healthier eating habits, combined with reducing the caloric intake of food and exercise. [16] This approach fails to address fundamental aspects of human behavior:<br>(1) Changing the composition of food reducing caloric intake can be distressing/uncomfortable (e.g. individuals have to tolerate hunger sensations)<br>(2) Eating high caloric foods is often induced by stress as a way to decrease stress<br>(3) "Old" eating habits and food preferences are not erased, but "new" habits/food preferences develop competing with the "old" habit.<br><br>The practice of mindfulness has been found produce beneficial effects for functional somatic, and stress-related symptoms and, therefore, has been increasingly incorporated into stress-reduction and psychotherapy programs. [17-18] Mindfulness refers to paying non-judgmental attention to experiences in the present moment. [19]<br>Specifically, mindfulness provides individuals with a greater capacity to tolerate uncomfortable sensations, feelings and thoughts (e.g. hunger); provides a different way to handle stress other than eating and increases awareness towards unfavorable habits (e.g. food choices) and promotes and strengthens new habits. Therefore, the addition of mindfulness to dietary interventions for weight-loss may augment individuals' ability to lose wait and, more importantly, sustain weight loss. |

**Topic 4: Mindfulness-based Weight Reduction Using a Simple Web-based Training**

| | |
|---|---|
| Have recent innovations made research on this topic especially compelling? | Recent findings suggest that a weight-loss intervention that maximizes meal-to-meal hunger suppression and favor techniques that systematically increase individuals' food preferences towards hunger-suppressing (low-calorie) foods and decrease their food preferences for refined-carbohydrate, low-fiber (high calorie) foods have the best chance of promoting and sustaining weight loss [20]<br><br>Mindfulness-based interventions (MBIs) targeting eating behaviors have gained significant popularity in recent years. O'Reilly and colleagues conducted a literature review to determine the effectiveness of MBIs for treating obesity-related eating behaviors. A total of N=21 smaller scale studies were identified. 86% of the reviewed studies reported improvements in the targeted eating behaviors. [21]<br><br>The Gap: It is unclear whether mindfulness indeed augments existing dietary interventions. |
| How widely does care now vary? | There is currently wide variety in the care of obesity. This variety is likely due to several reasons, such as, lack of standardized assessment, lack of knowledge, time, and prevalence of obesity in providers. For example, the care of obesity is often not approached in a standardized way as there is no gold standard of assessment for nutrition and exercise. [22] Many providers also report not knowing the best ways to counsel patients on weight loss as well as being concerned about upsetting patients about assessing/managing weight given the stigma of obesity. [23] Providers who are obese/overweight themselves have a particularly difficult time managing the weight of their patients and report having considerable time constraints (i.e., believe that they do not have the time to weight loss counseling). For example, Harvard Medical School launched an "Active Patients, Active Doctors" campaign in 2010 to encourage providers to exercise as this increased the discussion of healthy living with patients. Thus, an evidence-based, standardized brief weight loss intervention that is easily disseminated to patients directly, as well as through their providers, is sorely needed to provide a baseline standard of care for overweight and obese individuals. |

**Topic 4: Mindfulness-based Weight Reduction Using a Simple Web-based Training**

| | |
|---|---|
| What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)? | Mindfulness-based interventions (MBIs) targeting eating behaviors have gained rapid popularity in recent years. In a systematic review on mindfulness-based interventions for obesity, 85% of the studies were conducted in the past 10 years, documenting that mindfulness is a topic of high interest from a research perspective. A search protocol was conducted using the online databases Google Scholar, PubMed, PsycINFO and Ovid Healthstar. A total of N=21 small scale mindfulness-related weight loss studies have been conducted so far. Interventions including combined mindfulness and cognitive behavioral therapies, mindfulness-based stress reduction, acceptance-based therapies, mindful eating programs, and combinations of mindfulness exercises. Targeted eating behavior outcomes included dietary intake, binge eating, emotional eating, and external eating. Eighteen (86%) of the reviewed studies reported improvements in the targeted eating behaviors. Overall, the results of this first review on the topic support the efficacy of MBIs for changing obesity-related eating behaviors, specifically binge eating, emotional eating and external eating. |
| **Potential for New Information to Improve Care and Patient-Centered Outcomes** | |
| How likely is it that new CER on this topic would provide better information to guide clinical decision making? | Provided mindfulness-based dietary interventions are more effective than regular interventions, mindfulness can be advertised to clinicians as a low-cost add-on to recommended dietary interventions without any additional cost. Therefore, the main obstacle after demonstrating effectiveness on a large scale is dissemination and promotion of the web-based instructional videos. |
| What are the facilitators and barriers that would affect the implementation of new findings in practice? | The main barrier for making mindfulness components more widely available to the public is the emphasis that mindfulness should be taught by licensed mindfulness teachers with several years of experience. Research shows that instruction based mindfulness-videos are as effective than teacher based instructions. Therefore, our mindfulness web-based videos overcome the barrier of attending in-person meetings or groups for mindfulness. An on-line video training also respects patients' privacy and minimizes the burden of shame that can prevent patients from seeking help. |

**Topic 4: Mindfulness-based Weight Reduction Using a Simple Web-based Training**

| | |
|---|---|
| How likely is it that the results of new research on this topic would be implemented in practice right away? | This intervention is developed with the intent to maximize its dissemination. By using video clips to administer the intervention, the treatment is standardized and affordable for both patients and their providers. The video clips can also be easily translated to different languages to further maximize the scope of implementation. Thus, if effective, the intervention can be marketed by PCORnet and is readily available for download via the web because it is entirely web-based. Therefore, the main aspect involves promotion, marketing and patient and clinician engagement |
| Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies? | The addition of mindfulness components to existing psychotherapy interventions has developed over the past decade. This would be the first large-scale program that evaluates the effectiveness of adding mindfulness to dietary interventions. Should mindfulness make a meaningful difference, it will become part of the gold standard of weight loss counseling. The mindfulness components will be web-based and will be available to any interested individual for download (video and audio files). The same is true for the dietary elements of the program (e.g. short videos on types of foods, portion sizes, etc.). |
| **Feasibility of the clinical trial within health systems** | |

**Topic 4: Mindfulness-based Weight Reduction Using a Simple Web-based Training**

| | |
|---|---|
| Does this trial meet the requisite technical, governance and regulatory constraints described below*? | This simple pragmatic trial meets the requisite constraints:<br>• We should be able to capture weight as a required **data element to identify and** follow up patients in standard fashion across systems.<br>• Capturing weight as the data element eliminates or substantially minimize the need for transformations, mappings, or complex data extraction procedures.<br>• We should be able to use PCORI **networking software and standardized querying** to facilitate subject identification.<br><br>**Regulatory and governance constraints:**<br>• Obesity is common as a topic of interest across the CDRNS.<br>• We should be able to easily obtain or facilitate consent for this low-risk intervention and either coordinate or defer IRB approval. |
| Is the trial characterized by operational simplicity? | Yes. Eligible patients will be identified via EHR and contacted via the CDRNs. Interested participants will enroll in the CDRNs and be randomized to either intervention. Weight tracking will be done through EHR via the CDRN. As requested, we will also include key decision makers within each participating CDRN to give feedback on the final study design and intervention and ongoing implementation of the study. For example, representatives on the PCORNet Obesity Task Force could be asked to join the study team or nominate individuals with their CDRN. |
| Does the trial make use of EHR to identify patients and measure outcomes? | EHR will be used to identify eligible participants in the participating CDRNs (e.g. overweight/obese) and contacted through the CDRN. Outcomes (i.e., weight, height) are routinely measured and recorded in the EHR. |

## References

1. Moore D. Close to 6 in 10 Americans Want to Lose Weight. Gallup, 2006.
2. Campbell SE, Avenell A and Walker AE. Assessment of nutritional status in hospital in-patients. *QJM*. 2002; 95: 83-7.
3. Ogden CL, Carroll MD, Kit BK and Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA*. 2014; 311: 806-14.
4. Prevention CfDCa. Adult Obesity Facts. 2014.
5. Davis MA, Neuhaus JM, Moritz DJ, Lein D, Barclay JD and Murphy SP. Health behaviors and survival among middle-aged and older men and women in the NHANES I Epidemiologic Follow-up Study. *Prev Med*. 1994; 23: 369-76.
6. Rodbard HW, Fox KM and Grandy S. Impact of obesity on work productivity and role disability in individuals with and at risk for diabetes mellitus. *Am J Health Promot*. 2009; 23: 353-60.
7. Finkelstein EA, Trogdon JG, Cohen JW and Dietz W. Annual medical spending attributable to obesity: payer-and service-specific estimates. *Health Aff (Millwood)*. 2009; 28: w822-31.
8. Wang YC, McPherson K, Marsh T, Gortmaker SL and Brown M. Health and economic burden of the projected obesity trends in the USA and the UK. *Lancet*. 2011; 378: 815-25.
9. Jenkins DJ, Wolever TM, Taylor RH, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. *Am J Clin Nutr*. 1981; 34: 362-6.
10. Brownell KD. *The Learn Program for Weight Management. 10th ed.* . Dallas, TX: American Health Publishing, 2004.
11. Felix HC and West DS. Effectiveness of weight loss interventions for obese older adults. *Am J Health Promot*. 2013; 27: 191-9.
12. Pittler MH and Ernst E. Dietary supplements for body-weight reduction: a systematic review. *Am J Clin Nutr*. 2004; 79: 529-36.
13. Allison DB, Newcomer JW, Dunn AL, et al. Obesity among those with mental disorders: a National Institute of Mental Health meeting report. *Am J Prev Med*. 2009; 36: 341-50.
14. Kirk SF, Penney TL, McHugh TL and Sharma AM. Effective weight management practice: a review of the lifestyle intervention evidence. *Int J Obes (Lond)*. 2012; 36: 178-85.
15. Manzoni GM, Pagnini F, Corti S, Molinari E and Castelnuovo G. Internet-based behavioral interventions for obesity: an updated systematic review. *Clin Pract Epidemiol Ment Health*. 2011; 7: 19-28.
16. Deckersbach T, Holzel BK, Eisner LR, et al. Mindfulness-based cognitive therapy for nonremitted patients with bipolar disorder. *CNS Neurosci Ther*. 2012; 18: 133-41.
17. Baer R. Mindfulness training as a clinical intervention: A conceptual and empirical review. . *Clinical Psychology: Science & Practice*. 2003; 10: 125-43.
18. Grossman P, Niemann L, Schmidt S and Walach H. Mindfulness-based stress reduction and health benefits. A meta-analysis. *J Psychosom Res*. 2004; 57: 35-43.
19. Kabat-Zinn J. *Full Catastrophe Living*. New York: Bantam Dell, 1990.
20. Salinardi TC, Batra P, Robert SB, et al. A lifestyle intervention reduces body weight and improves cardiometabolic risk factors in worksites. Am J Clin Nutr. In Press. *Am J Clin Nutr*. 2013; 97: 667-76.

**Topic 4: Mindfulness-based Weight Reduction Using a Simple Web-based Training**


21. O'Reilly GA, Cook L, Spruijt-Metz D and Black DS. Mindfulness-based interventions for obesity-related eating behaviours: a literature review. *Obes Rev*. 2014.
22. Waitzberg DL and Correia MI. Nutritional assessment in the hospitalized patient. *Curr Opin Clin Nutr Metab Care*. 2003; 6: 531-8.
23. Schwarzkopf ND. A descriptive study of childhood obesity monitoring practices used by Montana pediatric providers. Montana State University-Bozeman, College of Nursing, 2008.

# PCORnet: First Interventional Study Research Prioritization Topic Brief

**Kathleen McTigue, MD MS MPH**
**PaTH Clinical Data Research Network**

April 28-29, 2014



Questions or comments may be sent to Jason Rotter at PCORI at jrotter@pcori.org or by mail to Suite 900, 1828 L Street, NW, Washington, DC 20036.

**Topics 5: Comparative Effectiveness of Interventions to Maximize and Maintain Weight Loss after Bariatric Surgery**

| Criteria | Brief Description |
|---|---|
| **Introduction** | |
| Overview/definition of topic | The optimal behavioral support needed to help patients maximize and maintain weight loss after bariatric surgery is unknown. We propose a pragmatic clinical trial design to assess comparative effectiveness of 3 web-based behavioral interventions that have been developed and implemented for individuals who are obese, but have not been implemented or tested in the post-bariatric surgery population. The 3 proposed study conditions are remotely delivered, so will have minimal on impact on routine clinical care. The main study outcome will be percent weight change. |
| Relevance to patient-centered outcomes | After the significant personal and economic investment in bariatric surgery, the importance of optimizing weight loss success and maintenance following bariatric surgery cannot be underestimated from the patient's perspective. Those individuals choosing a surgical option for weight loss are in need of a range of accessible options to help guide their post-operative lifestyle adjustments and to address other concerns or problems that may arise. Often their issues and need for specific dietary guidance are different from patients seeking lifestyle interventions without having had bariatric surgery, so personalized advice is likely to be particularly useful. Reduced or discontinued medications[1] are likely to result in improved convenience and satisfaction for patients.[2,3]<br><br>The change in parameters related to the control of weight-related cardiovascular risk factors likely to be of particular interest to the providers who are working with patients to manage these risk factors. Limiting these evaluations to the subset of patients with the relevant co-morbidity at baseline will help minimize missing data. For example blood pressure will be assessed for patients with hypertension prior to surgery, HbA1c for patients with diabetes prior to surgery and lipid levels for patients with dyslipidemia prior to surgery. It is possible that the behavioral interventions may lead to more nutritional deficiencies, if they successfully promote weight maintenance. Therefore, determining the frequency at which laboratory tests assessing for nutritional deficiencies are (a) monitored and (b) abnormal will enable assessment of whether recommendations for nutritional monitoring should be adjusted when patients are provided with evidence-based remote behavioral lifestyle support following bariatric surgery. |

**Topics 5: Comparative Effectiveness of Interventions to Maximize and Maintain Weight Loss after Bariatric Surgery**

| **Patient-centeredness** | |
|---|---|
| Is the proposed research focused on questions and outcomes of specific interest to patients, their caregivers, and clinicians? | While minimal published data address patient perspectives on post-surgical lifestyle intervention, the available data indicate that a large proportion of participants would prefer better behavioral support following surgery.[4] For many individuals who undergo bariatric surgery, it is a weight loss option "of last resort" after multiple failed weight loss efforts,[5] and one which most individuals undertake primarily to improve their health.[6-8] These findings emphasize the importance of optimizing weight loss success. In addition, bariatric surgery is an experience that often transforms patients' lives in various ways, including increased capacity for activity, more energy, mobility and confidence,[9] and so represents a unique opportunity to succeed in behavior change. In addition, patients planning to undergo bariatric surgery appear to value weight loss highly, with 73% in one sample reporting that they were willing to risk death to achieve a weight loss of 20% of their weight.[8] Healthier eating and physical activity patterns are important for optimizing the success of weight loss following bariatric surgery.[10-13] Yet (since failure of behavioral weight loss is typically a prerequisite for bariatric surgery) bariatric surgery patients have demonstrated that they have particular difficulty with behavior change, and adherence with most diet and physical activity behaviors following surgery is quite low.[14-16] Assistance with behavior change in the critical post-surgical period is thus important to help patients achieve their goal of succeeding with long-term weight management.<br><br>The literature suggests that primary care providers (PCPs) would appreciate assistance with managing care for patients who have had bariatric surgery. For example, although approximately 85% of primary care providers (PCPs) in one sample treated patients who had undergone bariatric surgery, 35% felt unprepared to provide good quality long-term medical care to these patients, 40% did not feel competent in prescribing weight loss programs for severely obese individuals, and only 4% reported having read the NIH "Consensus Statement on Gastrointestinal Surgery for Severe Obesity."[17]<br><br>Experts on surgical weight loss have recognized the need to encourage post-surgical physical activity and to address behavioral and psychological care in weight loss surgery patients.[18] While standards for behavioral intervention are not yet well established, it is likely that interventions that may improve long-term surgical outcome data would be welcomed by providers of surgical care. For example data from other surgical fields suggest that the likelihood of surgical success is a critical factor that patients consider in deciding to undergo surgery.[19,20] Therefore, addressing factors to improve longer-term surgical success, may increase interest and access to bariatric surgery for potential medically-indicated candidates. |

**Topics 5: Comparative Effectiveness of Interventions to Maximize and Maintain Weight Loss after Bariatric Surgery**

| **Burden on Society** | |
|---|---|
| Recent prevalence in populations and subpopulations | Severe obesity has increased more rapidly than less extreme levels of excess body weight in the US,[21] and 15% of US adults had a BMI≥35 kg/m$^2$, while 6% had BMI≥40 kg/m$^2$in 2009-2010.[22] Clearly, a large number of US individuals are potentially eligible for bariatric surgery. Accordingly, weight loss surgery increased dramatically in the US between 1998-2003, then plateaued or declined slightly over the next five years,[23-25] with data published in 2010 suggesting that rates have stabilized at approximately 113,000 cases per year and that bariatric surgery costs the health economy at least $1.5 billion annually.[24] |
| Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services | Severe obesity entails a significant health burden for affected individuals and for the US health care system. It is linked with high risk for numerous health problems, including mortality, CHD, diabetes, hypertension, and impaired quality of life[17,26,27] Compared with normal BMI, a BMI of 30-35 is associated with about 25% higher health care expenditures, a BMI of 35-40 is associated with about 50% higher health care expenditures and a BMI of over 40 is associated with approximately doubled health care costs.[28] Marked racial/ethnic variation in extreme obesity is consistently reported, with severe obesity being more common in certain minority racial/ethnic backgrounds.[29,30]<br><br>Bariatric surgery can lead to dramatic weight loss and improvements in weight-related health problems such as hypertension, dyslipidemia and type 2 diabetes – including frequent resolution of diabetes and other cardiovascular risk factors.[31-33] However, weight regain is not uncommon following weight loss surgery. In one surgical cohort, approximately 50% of patients experienced weight regain within 24 months.[34] In another cohort, there was significant weight gain from the lowest BMI at approximately 2 years of follow-up to the BMI at 5 and 10 years of follow-up.[35] Weight regain and surgical failure, defined by BMI, are more common in individuals with the highest initial BMI.[34,35] For example, in one study, 18% of all patients and 43% of those whose starting BMI was >50 (37% of the cohort) experienced bariatric surgery "failure" (BMI > 35 kg/m$^2$) at 5 years of follow-up.[35] With weight regain, the health benefits associated with bariatric surgery tend to be diminished. For example, one study found that although diabetes initially resolved or improved in all patients in a bariatric cohort, it recurred or worsened in 24% after an average of 5 years of follow-up, and weight loss failure was associated with such recurrence or worsening of diabetes status.[36] Weight regain following bariatric surgery is also associated with worsening health-related quality of life.[24] |

**Topics 5: Comparative Effectiveness of Interventions to Maximize and Maintain Weight Loss after Bariatric Surgery**

| **Assessment of Current Options** | |
|---|---|
| Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options? | A recent systematic review and meta-analysis concluded that behavioral management had a positive effect following weight loss surgery; among the 5 RCTs examined, behavioral lifestyle interventions led to nearly 2% more weight loss compared with usual care.[37] In 13 of 15 studies, patients who received postoperative interventions experienced larger weight losses as compared to those who received usual postoperative care.[37]<br><br>Potential harms of lifestyle intervention following bariatric surgery has not been a focus on research, despite the fact that the encouragement of post-surgical physical activity as well as behavioral and psychological care is recommended for weight loss surgery patients, suggesting a need for formal safety assessment.[18] A large literature on lifestyle intervention in the general population has established that lifestyle interventions are typically safe.[38] |
| What could new research contribute to achieving better patient-centered outcomes? | A need for better post-surgical behavioral care is recognized by patients and providers, and interventions exist that could be adapted to the surgical weight loss setting. However, current knowledge is limited by the small number of randomized trials of behavioral interventions following surgery, and the fact that existing studies have typically had small sample sizes, heterogeneous samples, and a frequent lack of gender diversity.[37,39] New research could identify which intervention approaches are most promising for supporting sustainable healthy lifestyles among patients following bariatric surgery, and for incurring high health care costs. In addition, it could help to identify if the type of surgery or factors related to the intervention (e.g., delivery mode, timing or duration of intervention, adherence with behavioral recommendations), concurrent treatment of mental health problems, and other patient and health system factors that influence outcomes. |

**Topics 5: Comparative Effectiveness of Interventions to Maximize and Maintain Weight Loss after Bariatric Surgery**

| | |
|---|---|
| Have recent innovations made research on this topic especially compelling? | Outside of the bariatric surgery setting, a large literature has established methods for promoting weight loss that are relevant to clinical care,[20,39,40] and such approaches have been applied in severely obese samples.[11] In addition, a growing literature has established that behavioral approaches can assist in the maintenance of weight loss.[41-49]<br><br>Experts on weight loss surgery have emphasized the importance of multidisciplinary care for weight loss surgery patients.[18,37,50] In addition, a recent expert panel on weight loss surgery identified the need for research on the effectiveness of general medical, surgical, nutrition and psychological aspects of multidisciplinary treatment. It also recognizes the need to encourage post-surgical physical activity and to address behavioral and psychological care in weight loss surgery patients.[18]<br><br>Published data suggest that counseling for physical activity and/or nutrition following bariatric surgery can lead to improvements in weight outcomes.[20,37,39] One recent systematic review and meta-analysis concluded that behavioral management had a positive effect following weight loss surgery; among the 5 RCTs examined, behavioral lifestyle interventions led to nearly 2% more weight loss compared with usual care.[37] Furthermore, compared with peri-operative treatment, post-operative behavioral intervention may result in better program adherence,[51] which is likely to lead to improved outcomes. |
| How widely does care now vary? | Although follow-up by a multidisciplinary team is recommend for bariatric surgery patients to assist in the maintenance of weight loss, one study of weight regain following bariatric surgery, 60% never underwent nutritional follow-up treatment.[34] Patients who undergo bariatric surgery are recommended to return to the bariatric surgery program for follow-up within 2 weeks of surgery, 6 months postoperatively and annually thereafter.[37,52,53] Patients also are encouraged to participate in postoperative support groups. More frequent postoperative follow-up and/or attendance at support groups is associated with greater weight loss.[54-57] However, only 40% of patients return for each of their first four annual follow-up visits, and support groups attendance is low and decreases over time.[58,59] |

**Topics 5: Comparative Effectiveness of Interventions to Maximize and Maintain Weight Loss after Bariatric Surgery**

| | |
|---|---|
| What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)? | A Medline searche illustrate the increasing interest in this topic. Use of the search terms "behavior therapy" or "lifestyle intervention" or "behavioral weight loss" combined "bariatric surgery" (restricted to articles that focus on bariatric surgery) provides a conservative estimate of publications. In the past 5 years (2009-2013), 29 indexed articles fit the Medline search criteria, while across the prior *decade* (1999-2008), only 7 such articles were published (with none prior to 2005). Yet, few funded research projects appear to be ongoing. For example, review of the study names for the top 100 results of an NIH Reporter "Matchmaker" search using the terms "bariatric surgery" and "behavioral intervention" revealed only 5 ongoing studies that clearly address lifestyle change in the setting of bariatric surgery. A high level of interest is also evidenced by positive recent editorials in the surgical literature, which address behavioral treatment following weight loss surgery, accompanying the publication of two small intervention studies.[60,61] Although technology-based lifestyle interventions have not been studied in randomized bariatric surgery trials, a recent observational study of an internet-based behavioral program provided to bariatric surgery patients over six months found that more frequent use of website features (weight logging, food diary usage, and goal setting) was associated with improvements in weight loss following surgery.[62] Importantly, there is evidence that bariatric surgery patients are more receptive to participating in a behavioral intervention after surgery than before surgery.[51] |
| **Potential for New Information to Improve Care and Patient-Centered Outcomes** | |
| How likely is it that new CER on this topic would provide better information to guide clinical decision making? | Failure of surgical treatment is a significant concern for both patients and providers. Factors related and contributing to extremes of outcomes following bariatric surgery are relatively unknown and knowledge about them would significantly impact the risk and benefit ratio that would help to guide and inform clinical decision making. |

**Topics 5: Comparative Effectiveness of Interventions to Maximize and Maintain Weight Loss after Bariatric Surgery**

| | |
|---|---|
| What are the facilitators and barriers that would affect the implementation of new findings in practice? | Barriers and facilitators are best understood in the context of typical patterns of post-surgical care. Attendance at pre-surgical visits is typically high, likely reflecting patients' high level of motivation to obtain clearance for surgery. However, despite guidelines recommending close, ongoing, multidisciplinary care after surgery,[63] adherence to follow-up care decreases after surgery,[34] particularly as time passes.[64] Patients often attribute decreased adherence to financial or time limitations, and this is further impacted by the fact that many patients travel distances greater than an hour to have surgery at a reputable center.<br><br>Thus, facilitators of the implementation of new findings in practice include the ease of use of remote counseling tools and the ability for patients with complicated schedules or live far from the health center to easily access evidence-based counseling resources. In addition, the use of routine clinical referral and consultant feedback procedures to incorporate the interventions into post-surgical care will ensure that the intervention integrates smoothly with normal clinical flow. The primary barrier is access to technology, which is consistently improving. For example, approximately 70% of US adults now have home broadband access; another 10% lack home broadband access, but have a smartphone.[65] Recently, broadband adoption grew the most in populations that have historically shown below-average internet use, including senior citizens, low-income Americans, and rural adults.[66] Although "digital divide" concerns remain, as internet access has expanded dramatically in recent years, so has minority web use, with 64%of African American and 53%-62% of Hispanic[67] homes reporting home internet access.[67] |
| How likely is it that the results of new research on this topic would be implemented in practice right away? | As outlined above, the need for better post-surgical behavioral support has been recognized by weight loss surgery patients, leaders in the bariatric surgery community, and primary care providers, which is critical for implementation. Use of a reputable implementation model such as PRISM or RE-AIM will also help ensure successful implementation[24,68] as will the aim to design implementation strategies that coordinate smoothly with existing processes of care. The interventions being proposed by $P^2$aTH will also be easy to implement and will not disrupt routine clinical practice, which is a requirement for successful long-term implementation. |
| Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies? | The proposed studies should produce durable information. Bariatric procedures are well-established with regular follow up intervals, and weight regain concerns arise across the entire range of procedures. Thus, changes in surgical approaches are unlikely to change the core issue in a rapid manner. Similarly, tenets of effective lifestyle interventions have been established and are relatively stable – but are challenging to incorporate into the clinical setting, and little attention has focused on adapting such approaches for the bariatric population. |

**Topics 5: Comparative Effectiveness of Interventions to Maximize and Maintain Weight Loss after Bariatric Surgery**

| **Feasibility of the clinical trial within health systems** | |
|---|---|
| Does this trial meet the requisite technical, governance and regulatory constraints described below*? | The trial meets the technical infrastructure characteristics, regulatory and governance restraints.<br><br>In order to be technically feasible, study subjects and required data elements need to be easily identified and standardized across health systems. We will use PCORI networking software and standardized querying to help identify potential participants. Subject identification will occur either by: 1) identifying patients who have undergone bariatric surgery through hospital procedure codes or 2) through bariatric surgery clinics. Required data elements will be defined and collected in a standard fashion across health systems (e.g., baseline weight, height, demographic data, type of bariatric surgery, medical co-morbidities). Body weight and height are standard data elements in the majority of EHR systems, and can be captured to assist in recruitment and in assessing the interventions' adoption and reach. Furthermore, in patients who have had bariatric surgery, self-reported weights have been found to be close to measured values.[69] Outcome measures will similarly be easy to ascertain through EHR data (weight, blood pressure, lab results, medications, follow-up visits). The interventions proposed have minimal impact on routine clinical care. Patients who consent to participate in the study will be randomized to participate in an intervention arm or the comparator (usual care). The interventions being proposed by P$^2$aTH are either web-based or telephone-based, so there will be minimal impact on clinical resources.<br><br>As described above, the data elements necessary for this study can be collected in a standard fashion across systems using EHR. The data elements needed for this study include those planned to be standardized as part of the P$^2$aTH network; we believe that these common elements will also be standardized across PCORnet. These data elements can be queried from individual CDRNs using PopMedNet, as recommended by PCORI.<br><br>This topic was put forth by P$^2$aTHinvestigators from all four P$^2$aTH institutions and agreed upon by the P$^2$aTH steering committee due to its ability to have significant impact on bariatric surgery outcomes. The P$^2$aTH network has proposed a central IRB process for research studies to be conducted within P$^2$aTH to facilitate obtaining and facilitating consent. |
| Is the trial characterized by operational simplicity? | The trial will be characterized by operational simplicity, with common data elements and minimal impact on routine clinical care. Providers will use routine referral procedures to help patients' access the study's resources. The interventions being proposed by P$^2$aTH are either web-based or telephone-based, so there will be minimal impact on clinical resources. Provider feedback will be provided through normal clinical channels, so that it is available for consideration/comment at the time of the regularly scheduled patient follow-up visit. Any need for communication between study staff and the health care team (e.g., in the event of a participant health concern) will occur using normal clinical communication practices such as EHR messaging (tailored to the norms of the referring clinical site). |

**Topics 5: Comparative Effectiveness of Interventions to Maximize and Maintain Weight Loss after Bariatric Surgery**

| | |
|---|---|
| Does the trial make use of EHR to identify patients and measure outcomes? | The trial will use the EHR to identify potential participants through reports based on patient lists of surgical providers, procedure codes, and the combination of discharge diagnoses and associated dates.<br><br>EHR-based outcomes will be abstracted from the EHR, leveraging this important resource and minimizing participant burden. Intervention reach variables will include data to identify and describe the number of potentially eligible patients (e.g., total number of bariatric surgery patients in the health system during the time-frame of interest). Additional measures will include baseline values of height (from vital signs) and weight-related comorbidities (from problem lists and/or discharge diagnoses) which will be used to characterize the enrolled sample. Body weight trajectories for the 2 years prior to surgery and during/after surgery will be abstracted from vital signs. EHR data will also allow us to objectively track blood pressure, weight, and health service utilization across the timeframe of the study. When available, laboratory, vital signs, and demographic data will be abstracted at baseline (within 1 year prior to surgery date) and at the end of the intervention (again with a 1-year window) to estimate change in cardiovascular risk (Framingham risk score has been shown to be responsive to weight loss interventions in prior studies, and is calculated from age, sex, total and HDL cholesterol, and blood pressure). |

## References


1. Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. *The New England journal of medicine.* Apr 26 2012;366(17):1567-1576.
2. Benson J, Britten N. Patients' decisions about whether or not to take antihypertensive drugs: qualitative study. *BMJ.* Oct 19 2002;325(7369):873.
3. Briesacher BA, Gurwitz JH, Soumerai SB. Patients at-risk for cost-related medication nonadherence: a review of the literature. *Journal of general internal medicine.* Jun 2007;22(6):864-871.
4. Brandenburg D, Kotlowski R. Practice makes perfect? Patient response to a prebariatric surgery behavior modification program. *Obesity surgery.* Jan 2005;15(1):125-132.
5. Wysoker A. The lived experience of choosing bariatric surgery to lose weight. *Journal Am Psychiatr Nurses Assoc.* 2005;11(1):26-34.

**6.** Munoz DJ, Lal M, Chen EY, et al. Why patients seek bariatric surgery: a qualitative and quantitative analysis of patient motivation. *Obesity surgery.* Nov 2007;17(11):1487-1491.

**7.** Libeton M, Dixon JB, Laurie C, O'Brien PE. Patient motivation for bariatric surgery: characteristics and impact on outcomes. *Obesity surgery.* Mar 2004;14(3):392-398.

**8.** Wee CC, Jones DB, Davis RB, Bourland AC, Hamel MB. Understanding patients' value of weight loss and expectations for bariatric surgery. *Obesity surgery.* Apr 2006;16(4):496-500.

**9.** Bocchieri LE, Meana M, Fisher BL. Perceived psychosocial outcomes of gastric bypass surgery: a qualitative study. *Obesity surgery.* Dec 2002;12(6):781-788.

**10.** Welch G, Wesolowski C, Piepul B, Kuhn J, Romanelli J, Garb J. Physical activity predicts weight loss following gastric bypass surgery: findings from a support group survey. *Obesity surgery.* May 2008;18(5):517-524.

**11.** Evans RK, Bond DS, Wolfe LG, et al. Participation in 150 min/wk of moderate or higher intensity physical activity yields greater weight loss after gastric bypass surgery. *Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery.* Sep-Oct 2007;3(5):526-530.

**12.** Colles SL, Dixon JB, O'Brien PE. Grazing and loss of control related to eating: two high-risk factors following bariatric surgery. *Obesity (Silver Spring).* Mar 2008;16(3):615-622.

**13.** Silver HJ, Torquati A, Jensen GL, Richards WO. Weight, dietary and physical activity behaviors two years after gastric bypass. *Obesity surgery.* Jul 2006;16(7):859-864.

**14.** Thomas JG, Bond DS, Ryder BA, et al. Ecological momentary assessment of recommended postoperative eating and activity behaviors. *Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery.* Mar-Apr 2011;7(2):206-212.

**15.** Toussi R, Fujioka K, Coleman KJ. Pre- and postsurgery behavioral compliance, patient health, and postbariatric surgical weight loss. *Obesity (Silver Spring).* May 2009;17(5):996-1002.

**16.** Elkins G, Whitfield P, Marcus J, Symmonds R, Rodriguez J, Cook T. Noncompliance with behavioral recommendations following bariatric surgery. *Obesity surgery.* Apr 2005;15(4):546-551.

**17.** Balduf LM, Farrell TM. Attitudes, beliefs, and referral patterns of PCPs to bariatric surgeons. *J Surg Res.* Jan 2008;144(1):49-58.

**18.** Blackburn GL, Hutter MM, Harvey AM, et al. Expert panel on weight loss surgery: executive report update. *Obesity (Silver Spring).* May 2009;17(5):842-862.

**19.** Modi CS, Veillette CJ, Gandhi R, Perruccio AV, Rampersaud YR. Factors That Influence the Choice to Undergo Surgery for Shoulder and Elbow Conditions. *Clin Orthop Relat Res.* Nov 2 2013.

**20.** Faria SL, de Oliveira Kelly E, Lins RD, Faria OP. Nutritional management of weight regain after bariatric surgery. *Obesity surgery.* Feb 2010;20(2):135-139.

**21.** Sturm R. Increases in clinically severe obesity in the United States, 1986-2000. *Archives of internal medicine.* Oct 13 2003;163(18):2146-2148.

**22.** Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. *JAMA : the journal of the American Medical Association.* Feb 1 2012;307(5):491-497.

**23.** Kohn GP, Galanko JA, Overby DW, Farrell TM. Recent trends in bariatric surgery case volume in the United States. *Surgery.* Aug 2009;146(2):375-380.

**24.** Karlsson J, Taft C, Ryden A, Sjostrom L, Sullivan M. Ten-year trends in health-related quality of life after surgical and conventional treatment for severe obesity: the SOS intervention study. *Int J Obes (Lond).* Aug 2007;31(8):1248-1261.

**25.** Nguyen NT, Masoomi H, Magno CP, Nguyen XM, Laugenour K, Lane J. Trends in use of bariatric surgery, 2003-2008. *J Am Coll Surg.* Aug 2011;213(2):261-266.

**26.** Arterburn DE, McDonell MB, Hedrick SC, Diehr P, Fihn SD. Association of body weight with condition-specific quality of life in male veterans. *Am J Med* 2004;117:738-746.

**27.** McTigue K, Larson JC, Valoski A, et al. Mortality and cardiac and vascular outcomes in extremely obese women. *JAMA.* Jul 5 2006;296(1):79-86.

**28.** Andreyeva T, Sturm R, Ringel JS. Moderate and severe obesity have large differences in health care costs. *Obesity research.* Dec 2004;12(12):1936-1943.

**29.** Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999-2004. *Jama.* Apr 5 2006;295(13):1549-1555.

**30.** Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. *Jama.* Jan 20 2010;303(3):235-241.

**31.** Buchwald H, Estok R, Fahrbach K, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *The American journal of medicine.* Mar 2009;122(3):248-256 e245.

**32.** Maggard MA, Shugarman LR, Suttorp M, et al. Meta-analysis: surgical treatment of obesity. *Ann Intern Med.* Apr 5 2005;142(7):547-559.

**33.** Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. *JAMA.* Oct 13 2004;292(14):1724-1737.

**34.** Magro DO, Geloneze B, Delfini R, Pareja BC, Callejas F, Pareja JC. Long-term weight regain after gastric bypass: a 5-year prospective study. *Obes Surg.* Jun 2008;18(6):648-651.

**35.** Christou NV, Look D, Maclean LD. Weight gain after short- and long-limb gastric bypass in patients followed for longer than 10 years. *Annals of surgery.* Nov 2006;244(5):734-740.

**36.** DiGiorgi M, Rosen DJ, Choi JJ, et al. Re-emergence of diabetes after gastric bypass in patients with mid- to long-term follow-up. *Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery.* May-Jun 2010;6(3):249-253.

**37.** Rudolph A, Hilbert A. Post-operative behavioural management in bariatric surgery: a systematic review and meta-analysis of randomized controlled trials. *Obes Rev.* Apr 2013;14(4):292-302.

**38.** Moyer VA. Screening for and management of obesity in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* Sep 4 2012;157(5):373-378.

**39.** Kalarchian MA, Marcus MD, Courcoulas AP, Cheng Y, Levine MD, Josbeno D. Optimizing long-term weight control after bariatric surgery: a pilot study. *Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery.* Nov-Dec 2012;8(6):710-715.

**40.** NHLBI Obesity Education Initiative. *Clinical guidelines on the identification, evaluation and treatment of overweight and obesity in adults: the Evidence Report.* Bethesda, MD: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute;1998. NIH Publication No. 98-4083.

**41.** Weiss EC, Galuska DA, Kettel Khan L, Gillespie C, Serdula MK. Weight regain in U.S. adults who experienced substantial weight loss, 1999-2002. *Am J Prev Med.* Jul 2007;33(1):34-40.

**42.** Tate DF, Jeffery RW, Sherwood NE, Wing RR. Long-term weight losses associated with prescription of higher physical activity goals. Are higher levels of physical activity protective against weight regain? *Am J Clin Nutr.* Apr 2007;85(4):954-959.

**43.** Turk MW, Yang K, Hravnak M, Sereika SM, Ewing LJ, L.E. B. Randomized clinical trials of weight loss maintenance. *Journal of Cardiovascular Nursing.* 2008;24(1):58-80.

**44.** Donnelly JE, Blair SN, Jakicic JM, Manore MM, Rankin JW, Smith BK. American College of Sports Medicine Position Stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. *Med Sci Sports Exerc.* Feb 2009;41(2):459-471.

**45.** Lecheminant JD, Gibson CA, Sullivan DK, et al. Comparison of a low carbohydrate and low fat diet for weight maintenance in overweight or obese adults enrolled in a clinical weight management program. *Nutr J.* 2007;6:36.

**46.** Due A, Larsen TM, Mu H, Hermansen K, Stender S, Astrup A. Comparison of 3 ad libitum diets for weight-loss maintenance, risk of cardiovascular disease, and diabetes: a 6-mo randomized, controlled trial. *Am J Clin Nutr.* Nov 2008;88(5):1232-1241.

**47.** Delbridge EA, Prendergast LA, Pritchard JE, Proietto J. One-year weight maintenance after significant weight loss in healthy overweight and obese subjects: does diet composition matter? *Am J Clin Nutr.* Nov 2009;90(5):1203-1214.

**48.** Butryn ML, Phelan S, Hill JO, Wing RR. Consistent self-monitoring of weight: a key component of successful weight loss maintenance. *Obesity (Silver Spring).* Dec 2007;15(12):3091-3096.

**49.** Befort CA, Stewart EE, Smith BK, Gibson CA, Sullivan DK, Donnelly JE. Weight maintenance, behaviors and barriers among previous participants of a university-based weight control program. *Int J Obes (Lond).* Mar 2008;32(3):519-526.

**50.** McMahon MM, Sarr MG, Clark MM, et al. Clinical management after bariatric surgery: value of a multidisciplinary approach. *Mayo Clin Proc.* Oct 2006;81(10 Suppl):S34-45.

**51.** Leahey TM, Bond DS, Irwin SR, Crowther JH, Wing RR. When is the best time to deliver behavioral intervention to bariatric surgery patients: before or after surgery? *Surg Obes Relat Dis.* Jan-Feb 2009;5(1):99-102.

**52.** Mechanick JI, Kushner RF, Sugerman HJ, et al. American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery Medical guidelines for clinical practice for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient. *Endocr Pract.* Jul-Aug 2008;14 Suppl 1:1-83.

**53.** Fujioka K. Follow-up of nutritional and metabolic problems after bariatric surgery. *Diabetes Care.* Feb 2005;28(2):481-484.

**54.** Compher CW, Hanlon A, Kang Y, Elkin L, Williams NN. Attendance at clinical visits predicts weight loss after gastric bypass surgery. *Obes Surg.* 2012;22:927-934.

**55.** Pontiroli AE, Fossati A, Vedani P, et al. Post-surgery adherence to scheduled visits and compliance, more than personality disorders, predict outcome of bariatric restrictive surgery in morbidly obese patients. *Obes Surg.* Nov 2007;17(11):1492-1497.

**56.** Livhits M, Mercado C, Yermilov I, et al. Behavioral factors associated with successful weight loss after gastric bypass. *Am Surg.* Oct 2010;76(10):1139-1142.

**57.** Kaiser KA, Franks SF, Smith AB. Positive relationship between support group attendance and one-year postoperative weight loss in gastric banding patients. *Surg Obes Relat Dis.* Jan-Feb 2011;7(1):89-93.

**58.** Gould JC, Beverstein G, Reinhardt S, Garren MJ. Impact of routine and long-term follow-up on weight loss after laparoscopic gastric bypass. *Surg Obes Relat Dis.* Nov-Dec 2007;3(6):627-630; discussion 630.

**59.** Orth WS, Madan AK, Taddeucci RJ, Coday M, Tichansky DS. Support group meeting attendance is associated with better weight loss. *Obes Surg.* Apr 2008;18(4):391-394.

**60.** Creel DB. Comment on: when is the best time to deliver behavioral intervention to bariatric surgery patients: before or after surgery? *Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery.* Jan-Feb 2009;5(1):102-103.

**61.** Heinberg LJ. Comment on: Optimizing long-term weight control after bariatric surgery: a pilot study. *Surgery for obesity and related diseases : official journal of the American Society for Bariatric Surgery.* Nov-Dec 2012;8(6):715-716.

**62.** Wilson E, B. S, Joyce C, Papasavas P, Sarwer D. A 6-Month observational study of the REALIZE mySUCCESS program's impact on weigth loss and compliance in REALIZE adjustable gastric band patients. *Personal Communication.* 2011.

**63.** Mechanick JI, Kushner RF, Sugerman HJ, et al. American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery medical guidelines for clinical practice for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient. *Obesity (Silver Spring).* Apr 2009;17 Suppl 1:S1-70, v.

**64.** Poole NA, Al Atar A, Kuhanendran D, et al. Compliance with surgical after-care following bariatric surgery for morbid obesity: a retrospective study. *Obes Surg.* Feb 2005;15(2):261-265.

**65.** Zickuhr K, Smith A. Home Broadband 2013. *Pew Research Center's Internet & American Life Project*2013.

**66.** Home Broadband Adoption 2013. http://www.pewinternet.org/Trend-Data-(Adults)/Home-Broadband-Adoption.aspx. Accessed October 4, 2013.

**67.** Wire N. What you think you know vs. what you need to know about U.S. Hispanics and Media. 2011. http://blog.nielsen.com/nielsenwire/media_entertainment/what-you-think-you-know-vs-what-you-need-to-know-about-u-s-hispanics-and-media/. Accessed 10/4/2013.

**68.** Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. *Am J Public Health.* Sep 1999;89(9):1322-1327.

**69.** Christian NJ, King WC, Yanovski SZ, Courcoulas AP, Belle SH. Validity of self-reported weights following bariatric surgery. *JAMA.* Dec 11 2013;310(22):2454-2456.

# PCORnet: First Interventional Study Research Prioritization Topic Brief

**Jodi Segal, MD, MPH, Johns Hopkins University (P2ATH CDRN)**
**Russell Rothman, MD, MPP, Vanderbilt University (Mid-South CDRN)**

**April 28-29, 2014**



Questions or comments may be sent to Jason Rotter at PCORI at jrotter@pcori.org or by mail to Suite 900, 1828 L Street, NW, Washington, DC 20036.

## Topic 6: Optimal Second-Line Agents for Treatment of Type 2 Diabetes Mellitus

| Criteria | Brief Description |
|---|---|
| **Introduction** | |
| Current evidence and guidelines support the use of metformin as first line oral therapy for treatment of blood glucose in patients with type 2 diabetes. However, the optimal second drug to add for patients with suboptimal glucose control remains unknown. Guidelines suggest that any of 5 different treatment options (oral sulfonylurea vs DPP-IV inhibitor vs TZD vs GLP-1 agonist vs insulin) are appropriate, and are currently part of usual care.<br>We will propose a pragmatic, randomized clinical trial within the PCORnet. This trial seeks to learn what is the optimal second-line agent for the treatment of patients with type 2 DM with a focus on outcomes important to patients including avoidance of hyperglycemia and hypoglycemia, quality of life, tolerability of the medication, and glycated hemoglobin (A1C). Patients with type 2 DM who are currently on monotherapy with metformin with an 7%<A1C<10%, who do not have an absolute contraindication to one or more of the study medications, will be randomized to one of 5 treatment options: 1) sulfonylurea 2)oral DPP-IV inhibitor, 3) oral TZD, 4) GLP-1 analogue, or 5) long acting insulin. Outcomes will include A1C, blood pressure, lipids, BMI, CV events, mortality, use of clinical serves (clinic visits, hospitalizations, ED visits), medication adherence, and patient reported outcomes (hypogylemic events, quality of life, treatment satisfaction). | |

**Topic 6: Optimal Second-Line Agents for Treatment of Type 2 Diabetes Mellitus**

| | |
|---|---|
| Overview/definition of topic | • Metformin is well accepted as the first line therapy in type 2 diabetes mellitus (DM), as supported by several clinical practice guidelines.[1-3] However, the optimal choice of second agent remains unclear. Often the choice of the second agent is made based on contraindications or relative contraindications. If these are not relevant in the care of a given patient, clinicians use other factors to choose the second therapy including cost to the patient, expected side effects, tolerability, and effectiveness; and patient preference. However, there is little *effectiveness* data to guide this decision about the second agent, and exceptionally little data about treatment effect heterogeneity.<br>  • Presently underway since 2013 is a large trial called GRADE (Glycemia Reduction Approaches in Diabetes –accessible at http://care.diabetesjournals.org/content/36/8/2254.full<br>  • The brief description on the clinicaltrials.gov site states that GRADE is a *pragmatic trial*. This trial, which is sponsored by NIH as well as pharmaceutical manufacturers, seeks to enroll 5000 individuals with type 2 DM to test the addition of a second agent to metformin. The GRADE trial has the stated purpose of "comparing the commonly used diabetes medications, when combined with metformin, on glycemia-lowering effectiveness and patient-centered outcomes." GRADE is a four arm trial that adds one of four medications, open-label, to the regimen of patients taking metformin and with inadequate glycemic control. The four medications are glimepiride, sitagliptin, liraglutide, and insulin glargine. The primary outcome is time to achieving a Hba1c measurement of less than 7.0%. The trial has extensive inclusion and exclusion criteria, beyond those required for safety.<br>• In many ways, GRADE deviates substantially from a pragmatic trial. Using the PRECIS framework to evaluate the design of GRADE, one concludes that many of the choices of the investigators suggest that this was designed as closer to an explanatory trial than a pragmatic trial. The GRADE trial has extensive inclusion and exclusion criteria which would not be applied in usual clinical practice. GRADE requires an 8 week run-in period which selects for particularly compliant participants which also deviates from usual care. Patients are followed on a treatment protocol to assess need for medication changes. The choice of outcomes is a surrogate for clinically relevant outcomes (Hba1c) – this is not a patient-relevant outcome. In addition, the GRADE trial relies heavily on face-to-face contact for patient recruitment, enrollment, and data collection, similar to traditional clinical trials. |

**Topic 6: Optimal Second-Line Agents for Treatment of Type 2 Diabetes Mellitus**

| | |
|---|---|
| Relevance to patient-centered outcomes | • By necessity, most trials of diabetes medications have used the surrogate endpoint of hba1c or fasting glucose or post-prandial glucose as indicators of efficacy. These endpoints have been sufficient for the approval of new diabetes medications, given the long interval from diagnosis until clinical complications of diabetes. Recent studies including ACCORD and others continue to make us question the relevance of hba1c-lowering, given that it is a poor predictor of macrovascular complications of disease, although the literature about hba1c lowering and microvascular complications (such as nephropathy and retinopathy) is relatively clear.[4] To that extent, hba1c might be considered a patient-centered outcome given its clear link to clinical outcomes about which patients care (need for dialysis, need for retinal treatments and vision loss).<br>• Patients are symptomatic and at risk of self-injury when hyperglycemic and when hypoglycemic so regimens that limit these excursions from good glycemic control are patient-centered. The medications under consideration are reasonably well tolerated in efficacy studies but tolerability with prolonged treatment and with the use of multiple other medications is unknown. Tolerability of a medication is clearly patient-centered.<br>• Therefore patient-centered outcomes include: medication tolerability, symptomatic hyperglycemia, symptomatic hypoglycemia, diabetes specific quality of life, and Hba1c. |
| **Patient-centeredness** | |
| Is the proposed research focused on questions and outcomes of specific interest to patients, their caregivers, and clinicians? | • If clinicians are able to select a second medication based on the medications tolerability, the avoidance of symptomatic hyper- and hypo-glycemia and it offers good control of Hba1c, patients will benefit. Clinicians benefit from the satisfaction of offering evidence-based, good clinical care. The caregivers of patients benefit as utilization of emergency or urgent healthcare may decrease if excursions of glucose of reduced, and the patient has improved quality of life.<br>• While the proposed pragmatic trial will be relatively short (approximately 3 years), we will have the capacity to propose to track patients longitudinally through their EHR and patient—reported outcomes for the long-term, providing the ability to examine the relationship between second line treatment and long-term outcomes such as morbidity, mortality, and patient quality of life. |
| **Burden on Society** | |
| Recent prevalence in populations and subpopulations | • Diabetes affects 25.8 million people in the U.S, that is 8.3 % of the population; 95% of the adult patients have type 2 diabetes [5]<br>• The prevalence is higher in some racial and ethnic groups within the United States including Hispanic-Americans, Native Americans, and African-Americans with prevalence rates of 11.8, 16.1, and 12.6%. Asians had lower prevalence at 8.4%.[5,6]<br>• The rates of type 2 DM are particularly elevated among individuals with the comorbid condition of obesity, and among individuals requiring certain medications for disease management such as antipsychotics and corticosteroids. |

**Topic 6: Optimal Second-Line Agents for Treatment of Type 2 Diabetes Mellitus**

| | |
|---|---|
| Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services | • In 2007 diabetes was the seventh leading cause of death in the U.S. However, this is likely an underestimate of its contribution to mortality, since diabetes is often an underlying cause of cardiovascular death. Patients with diabetes have double the risk of death than those without diabetes. [7]<br>• There is a high association of diabetes and congestive heart disease, coronary heart disease, acute coronary syndrome and stroke. Mortality rates for patients with diabetes after an acute myocardial infarction are double than for those without DM. [8]<br>• Almost half of the individuals with diabetes have some degree of limitation in their mobility due to peripheral arterial disease, neuropathy and wounds secondary to diabetes. [7] With progressing disease, these individuals have an 8-fold increased risk of lower extremities amputations (4-5 cases per 1000 person-years). [9]<br>• Painful diabetic neuropathy affects up to 16% of patients. Life with pain affects QOL. [10]<br>• Diabetic retinopathy affects up to 40% of patients in varying degrees, from severe or vision threatening (8%). Early diagnosis is fundamental as it is the leading cause of preventable blindness [7,11]<br>• Diabetes is the leading cause of renal failure; in 20-30% of these cases patients will progress to moderate to severe stages including need for renal replacement therapies. [1]<br>• Patients with diabetes are up to 50% more likely to develop mood disorders including depression and anxiety. [6]<br>• Diabetes accounts for 22% of all hospital charges. In 2007, an estimated cost of diabetes in the United States of $174 billion. This included $116 billion in direct medical care costs and $58 billion in indirect costs (disability, productivity loss, and premature death) [7]<br>• In 2011 there were more than 60,000,000 discharges with diabetes as diagnosis, 2/3 of the patients were between 45 and 84 years old. 2.7 % of those patients died in the hospital, with heart conditions the leading cause of hospitalization and septicemia the leading cause of death.[12] |

**Topic 6: Optimal Second-Line Agents for Treatment of Type 2 Diabetes Mellitus**

| **Assessment of Current Options** | |
|---|---|
| Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options? | • On behalf of the Agency for Healthcare Quality and Research, Johns Hopkins University Evidence-based Practice Center reviewed the literature about the comparative effectiveness and safety of oral hypoglycemic medications. The updated literature review was published in 2012.[13] We found metformin is safer and more efficacious than the other agents when used as first-line agent, except for gastrointestinal upset. Two drug combinations showed similar Hb1c reduction and metabolic response, but higher risk of hypoglycemia and other adverse events.<br>• Other systematic reviews have found similar results [14,15,16] while others have shown that DPP-4 can be an effective and safe alternative as monotherapy or combined with metformin.[14,17]<br>• The Cochrane group published a review of 72 RCTS in 2013, where they saw the different therapeutic effects and adverse events of the different groups and concluded there is still a lack of evidence to support a safe and efficacious single one.[18]<br>• Several systematic reviews have shown the therapeutic effects improve and the adverse events may be reduced when combining 2 or 3 medications.[19,20,21]<br>• No systematic review to date, has found enough evidence on the effect of these medications on the long -term clinical outcomes (all-cause mortality, cardiovascular disease, nephropathy, and neuropathy).<br>• There have been systematic reviews on the topic of insulin therapy for patients with type 2 DM, as well. These have found that the main barrier and concern for its use is hypoglycemia as well. A systematic review to evaluate insulin lispro found it is a valid option to reach therapeutic targets and avoid hypoglycemia risks.[22]<br>• When compared to insulin detemir, insulin glargine had the same therapeutic effect, but detemir had better outcomes regarding weight gain.[23]<br>• Another SR showed that short-term insulin therapy may be useful and safe as an early intervention.[24] |
| What could new research contribute to achieving better patient-centered outcomes? | New research will provide clinicians and patients with the necessary effectiveness information to make the best choice about second agents. The existing data from efficacy trials largely answers questions about Hba1c control in a narrowly selected, and highly-compliant patient population. Understanding the impact of these medications in a usual practice setting, among diverse and variably-compliant patients, on outcomes that they care about, will inform care. |
| Have recent innovations made research on this topic especially compelling? | There have not been recent innovations on this topic. The newest class of medications for treatment of type 2 DM is the SGLT-inhibitors which increases glucose excretion in the urine. The long term safety of these is as yet unknown and the complications of fungal disease and urinary tract infections may make these a less favored class. The existing classes have seen recent approvals of “me-too” agents which cannot be considered innovative. The fairly recent generic availability of some of these agents – including pioglizatone – has increased the accessibility of these medications and might be considered a compelling innovation. |

**Topic 6: Optimal Second-Line Agents for Treatment of Type 2 Diabetes Mellitus**

| | |
|---|---|
| How widely does care now vary? | • Care varies widely. Some clinicians practice in settings with formularies which restrict their prescription of all available drugs for treating type 2 DM. Some clinicians develop familiarity with a drug (such as glipizide) and are slow adopters of newer agents even in the face of efficacy data suggesting benefits from different agents.<br>• Even though there are existing guidelines for diabetes care, individualized care is valued by practitioners and patients; diabetes presentation, age, renal function and patient and practitioner preferences determine choices, with up to half of the patients not receiving any medication upon diagnosis.[25]<br>• Existing guidelines from the ADA, ACP, and others cite the lack of evidence about optimal second line treatment for gylcemic control, and recommend that any of 5 treatment options are acceptable (oral sulfonylurea vs DPP-IV inhibitor vs TZD vs GLP-1 agonist vs insulin), and that care should be individualized to patient needs.[1,2,3]<br>• Adherence to clinical guidelines vary among primary care providers and specialists,[26] as well as their response to patients with hyperglycemia or high HbA1c. Specialists tend to be more aggressive, while primary care doctors tend to "wait and see"[27]<br>• Clinical inertia (wait and see) is prevalent in the care of patients with diabetes and may limit the patient's response and overall outcomes.[28]<br>• Patients with diabetes are initially diagnosed by their primary care doctors and their care will require, as the disease progresses, comprehensive attention (primary care, community services, education, nurses, pharmacists and specialists) to improve management and outcomes. However, this type of care is not available to all patients (rural vs urban, community resources, limitations with reimbursement), limiting patient's access to optimal care. [29] |

**Topic 6: Optimal Second-Line Agents for Treatment of Type 2 Diabetes Mellitus**

| | |
|---|---|
| What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)? | ClinicalTrials.gov provided relevant information:<br>• 4384 entries included "Diabetes Mellitus Type 2" as a term. 3742 of those studies are interventional and 810 are currently open.<br>• There are 1716 for Diabetes Mellitus type 2 started in the United States, 1558 are interventional and 302 are currently open (258 excluding those with unknown status)<br>• Open -Interventional studies in the U.S (258)<br>o 62 have metformin as intervention (plus/versus other interventions such as glimepiride, sitagliptin, saxagliptin, liraglutide, insulins as glargine, detemir or other insulins or investigational drugs. 6 studies compare different doses of metformin.<br>o 64 have different types of Insulin as intervention<br>o 146 have investigational drugs as intervention (not FDA approved) Examples of the interventions are canaglifozin, empaglifozin, ertuglifozin, dapaglifozin, colesevalam, MK-3102, MN-504, PF-05175157, ORMD-0801, HM11260C, ITCA 650, CANA/MET XR FDC<br>o 124 studies have placebo as control<br>• The ongoing research covers all phases of investigation:<br>o 4 studies are in phase 0<br>o 30 studies are in phase 1<br>o 37 studies are in phase 2<br>o 65 studies are in phase 3<br>o 34 studies are in phase 4<br>o 88 studies do not specify current phase<br>• There is a high interest in treatment choices in the senior population, more than half of the studies include patients older than 65 years old (187 studies)<br>o 23 studies are specifically designed for children and adolescents<br>o 240 studies are recruiting adults<br>• The main outcome measured is efficacy; mainly glycemic and Hb1c response.<br>o 80 studies measure safety<br>o 14 studies are looking for quality of life outcomes<br>Cochrane Review protocols of ongoing systematic reviews are available for bromocriptine,[30] dapaglifozin,[31] probucol,[32] and extended vs immediate release metformin[33] as well as comparison of different insulins[34] and fibrates.[35] |
| **Potential for New Information to Improve Care and Patient-Centered Outcomes** | |
| How likely is it that new CER on this topic would provide better information to guide clinical decision making? | It is highly likely that new CER would provide better information to guide clinical decision making. Existing trials, largely sponsored by pharmaceutical companies, are conducted in settings and patient-populations with limited relevance to practice. The GRADE trial underway is similarly limited. Observational studies provide some information from usual care settings but are challenged by confounding by indication. A pragmatic trial that demonstrates clinical benefit of a magnitude that is meaningful to patient care can be expected to guide clinical care. |

**Topic 6: Optimal Second-Line Agents for Treatment of Type 2 Diabetes Mellitus**

| | |
|---|---|
| What are the facilitators and barriers that would affect the implementation of new findings in practice? | • There are still some barriers to widespread use of some medications:<br>o formulary restrictions,<br>o lack of generic availability<br>o high-tier pricing.<br>• Some of the medications under consideration require more patient teaching (the injectable drugs) which may prove a barrier to acceptance. Clinical inertia affects the addition of second agents and can be expected to be a challenge when encouraging clinicians to change their practices regarding choice of second agent.<br>• However, the support of professional societies who review the proposed trial's results and include them in practice recommendations or guidelines would be a powerful facilitator that would impact implementation of trial results in practice. Active dissemination of trial results will be necessary, presumably through the professional societies (endocrine, internal medicine, family practice). |
| How likely is it that the results of new research on this topic would be implemented in practice right away? | New research results should be quickly implementable – the medications are available, and covered by most insurance plans. Doctors are eager to receive guidance about the choosing a second-line treatment option. |
| Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies? | We anticipate that this study would have direct and long-term impact on management of diabetes. This information would be made quickly obsolete if there were soon to be a medication for type 2 DM that is a "game changer" – this would be a medication that proved to be well-tolerated and highly effective in phase III trials and without toxicity or substantial side-effects. We are unaware of any such medication pending approval soon. |
| **Feasibility of the clinical trial within health systems** | |
| Does this trial meet the requisite technical, governance and regulatory constraints described below*? | **Yes** |

**Topic 6: Optimal Second-Line Agents for Treatment of Type 2 Diabetes Mellitus**

| | |
|---|---|
| Is the trial characterized by operational simplicity? | This trial could meet several criteria for operational simplicity:<br>• Patients can be identified through the EHR by searching for ICD-9 criteria for diabetes, medication lists for metformin monotherapy, and, A1C levels.<br>• Patients could potentially be recruited and consented electronically. Randomization to study drug could also occur centrally/electronically.<br>• Health care providers would need to agree to prescribing the assigned second line agent and discussing risks/benefits of this agent with the patient. We anticipate that this would be reasonable, since the 5 treatment options are all part of usual care.<br>• As a pragmatic trial, health care providers would have the ability to alter treatment over time, as they chose, and in accordance with their usual practices.<br>• Outcome data could be collected through extraction of key variables from the EHR. In addition, web-based surveys could be used to collect patient reported outcomes over time. |
| Does the trial make use of EHR to identify patients and measure outcomes? | **Yes.**<br>• Individuals with diabetes are easily identified with EHR; there are well-validated algorithms for identifying these individuals based on ICD codes and medication disbursements.<br>• Most of the outcomes of interest are measured as usual care or are processes of care (e.g. Hba1c, hospitalization). The recording of *quality of life* measures will be within the EHR; a process that is both novel and feasible. Patients will have the flexibility of responding to queries regarding quality of life during clinic visits or remotely online or via their mobile devices. |

**Topic 6: Optimal Second-Line Agents for Treatment of Type 2 Diabetes Mellitus**


1. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes care.* Jun 2012;35(6):1364-1379.
2. ADA. Standards of medical care in diabetes--2011. *Diabetes care.* Jan 2011;34 Suppl 1:S11-61.
3. Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. *Annals of internal medicine.* Feb 7 2012;156(3):218-231.
4. Buse JB, Bigger JT, Byington RP, et al. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods. *The American journal of cardiology.* Jun 18 2007;99(12A):21i-33i.
5. CDC. 2011 National Diabetes Fact Sheet. Diabetes Public Health Resource 2011; http://www.cdc.gov//diabetes/pubs/factsheet11.htm. . Accessed Accessed April 4, 2014.
6. Naranjo D, Hessler DM, Deol R, Chesla CA. Health and psychosocial outcomes in U.S. adult patients with diabetes from diverse ethnicities. *Current diabetes reports.* Dec 2012;12(6):729-738.
7. CDC. Diabetes Complications. *Diabetes Public Health Resource* 2013; http://www.cdc.gov/diabetes/statistics/complications_national.htm. Accessed Apr 3, 2014.
8. Vasiliadis I, Kolovou G, Mavrogeni S, Nair DR, Mikhailidis DP. Sudden cardiac death and diabetes mellitus. *Journal of diabetes and its complications.* 2014(0).
9. Margolis DJ, Jeffcoate W. Epidemiology of Foot Ulceration and Amputation: Can Global Variation be Explained? *Medical Clinics of North America.* 2013;97(5):791-805.
10. Bril V, England JD, Franklin GM, et al. Evidence-based guideline: treatment of painful diabetic neuropathy--report of the American Association of Neuromuscular and Electrodiagnostic Medicine, the American Academy of Neurology, and the American Academy of Physical Medicine & Rehabilitation. *Muscle & nerve.* Jun 2011;43(6):910-917.
11. Cheung N, Mitchell P, Wong TY. Diabetic retinopathy. *The Lancet.*376(9735):124-136.
12. HCUP. H-CUPnet National Statistics. 2013; HCUPnet is a free, on-line query system based on data from the Healthcare Cost and Utilization Project (HCUP). It provides access to health statistics and information on hospital inpatient and emergency department utilization. Available at: http://hcupnet.ahrq.gov/HCUPnet.jsp. Accessed April 4 2013.
13. Bennett WL, Wilson LM, Bolen S, et al. Oral Diabetes Medications for Adults With Type 2 Diabetes: An Update. Vol Report No.: 11-EHC038-EF. Rockville MD: Agency for Healthcare Research and Quality (US) 2011: http://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=644. Accessed April 7, 2014.
14. Wu D, Li L, Liu C. Efficacy and safety of dipeptidyl peptidase-4 inhibitors and metformin as initial combination therapy and as monotherapy in patients with type 2 diabetes mellitus: a meta-analysis. *Diabetes, obesity & metabolism.* Jan 2014;16(1):30-37.
15. Liu X, Xiao Q, Zhang L, Yang Q, Xu L, Cheng W. The long-term efficacy and safety of DPP-IV inhibitors monotherapy and in combination with metformin in 18 980 patients with type-2 diabetes mellitus-a meta-analysis. *Pharmacoepidemiology and drug safety.* Mar 18 2014.

**16.** Landman GW, de Bock GH, van Hateren KJ, et al. Safety and efficacy of gliclazide as treatment for type 2 diabetes: a systematic review and meta-analysis of randomized trials. *PloS one.* 2014;9(2):e82880.

**17.** Craddy P, Palin HJ, Johnson KI. Comparative Effectiveness of Dipeptidylpeptidase-4 Inhibitors in Type 2 Diabetes: A Systematic Review and Mixed Treatment Comparison. *Diabetes Ther.* Mar 25 2014.

**18.** Hemmingsen B, Schroll JB, Lund SS, et al. Sulphonylurea monotherapy for patients with type 2 diabetes mellitus. *The Cochrane database of systematic reviews.* 2013;4:CD009008.

**19.** Zhang F, Xiang H, Fan Y, et al. The effects of sulfonylureas plus metformin on lipids, blood pressure, and adverse events in type 2 diabetes: a meta-analysis of randomized controlled trials. *Endocrine.* Dec 2013;44(3):648-658.

**20.** Boland CL, Degeeter M, Nuzum DS, Tzefos M. Evaluating second-line treatment options for type 2 diabetes: focus on secondary effects of GLP-1 agonists and DPP-4 inhibitors. *The Annals of pharmacotherapy.* Apr 2013;47(4):490-505.

**21.** Poolsup N, Suksomboon N, Setwiwattanakul W. Efficacy of various antidiabetic agents as add-on treatments to metformin in type 2 diabetes mellitus: systematic review and meta-analysis. *ISRN endocrinology.* 2012;2012:798146.

**22.** Ceriello A, Cremasco F, Romoli E, Rossi A, Gentilella R. Insulin lispro protamine suspension in the treatment of patients with type 1 and type 2 diabetes mellitus: a systematic review of published data. *Expert opinion on pharmacotherapy.* Feb 2012;13(2):255-281.

**23.** Zhuang YG, Peng H, Huang F. A meta-analysis of clinical therapeutic effect of insulin glargine and insulin detemir for patients with type 2 diabetes mellitus. *European review for medical and pharmacological sciences.* Oct 2013;17(19):2566-2570.

**24.** Kramer CK, Zinman B, Retnakaran R. Short-term intensive insulin therapy in type 2 diabetes mellitus: a systematic review and meta-analysis. *The lancet. Diabetes & endocrinology.* Sep 2013;1(1):28-34.

**25.** Raebel MA, Xu S, Goodrich GK, et al. Initial antihyperglycemic drug therapy among 241 327 adults with newly identified diabetes from 2005 through 2010: a surveillance, prevention, and management of diabetes mellitus (SUPREME-DM) study. *The Annals of pharmacotherapy.* Oct 2013;47(10):1280-1291.

**26.** Seidu S, Khunti K. Non-adherence to diabetes guidelines in primary care - the enemy of evidence-based practice. *Diabetes research and clinical practice.* Mar 2012;95(3):301-302.

**27.** Shah BR, Hux JE, Laupacis A, Zinman B, van Walraven C. Clinical inertia in response to inadequate glycemic control: do specialists differ from primary care physicians? *Diabetes care.* Mar 2005;28(3):600-606.

**28.** Davis J, Chavez B, Juarez DT. Adjustments to diabetes medications in response to increases in hemoglobin a1c: an epidemiologic study. *The Annals of pharmacotherapy.* Jan 2014;48(1):41-47.

**29.** Stellefson M, Dipnarine K, Stopka C. The chronic care model and diabetes management in US primary care settings: a systematic review. *Preventing chronic disease.* 2013;10:E26.

**30.** Ooi Cheow P, Loke Seng C. Bromocriptine for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews, Protocol*: John Wiley & Sons, Ltd; 2013.

**Topic 6: Optimal Second-Line Agents for Treatment of Type 2 Diabetes Mellitus**


**31.** Raval Amit D, Chovatiya K, Bhavsar Ankit B, Patel Megha H. Dapagliflozin for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews, Protocol*: John Wiley & Sons, Ltd; 2011.

**32.** Yang Yong J, Li Cheng C, Yang Y, Tian Jin H, Yang Ke H. Probucol for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews*: John Wiley & Sons, Ltd; 2009.

**33.** Al-Shareef Mohammed A, Kalo B, Sabban S. Extended-release metformin versus immediate-release metformin for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews, Protocol*: John Wiley & Sons, Ltd; 2007.

**34.** Farmer Andrew J, Lasserson Daniel S, Perera R, Glasziou Paul P, Holman R. Different insulin regimens for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews, Protocol*: John Wiley & Sons, Ltd; 2013.

**35.** Bonates Milla C, Carvalho Alan PV, Albergaria B-H, Valente O. Fibrates for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews, Protocol*: John Wiley & Sons, Ltd; 2012.