Research Prioritization Topic Briefs

Topics 1-11

PCORI Scientific Program Area:
Assessment of Prevention, Diagnosis and Treatment Options

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

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TOPIC 1: Treatment Strategies for Atrial Fibrillation

Compare the effectiveness of treatment strategies for atrial fibrillation, with an emphasis on early use of catheter ablation for recently-diagnosed atrial fibrillation.

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION[1] • Atrial fibrillation (AF) is a heart rhythm problem that originates in the atria, or upper chambers of the heart. • AF causes the atria to contract in an uncoordinated manner and the ventricles, or lower chambers of the heart, to contract irregularly and often too rapidly. These changes can cause several problems, including fatigue, shortness of breath, and, most importantly, higher rates of stroke and earlier death. • AF can be "paroxysmal" (occurs for periods of less than 1 week, which resolve and recur), "persistent" (occurs for periods of greater than 1 week and may still come and go), or "permanent" (occurs continuously).
Relevance to patient-centered outcomes	SYMPTOMS[1] • AF may be asymptomatic; however, in many patients AF causes symptoms that include: o Severe fatigue o Lightheadedness or fainting o Shortness of breath o Chest pain or discomfort o Palpitations, heart racing, or a sense of irregular heartbeat OUTCOMES[1] • Stroke o Stroke is one of the most common and feared complications of AF. o It is caused when AF-related blood clots travel from the heart to the brain. o The risk of stroke in patients ranges from less than 1% to more than 7% per year, depending on the presence of other risk factors related to stroke.[2,3] o When stroke occurs in patients with AF, it is often severe or fatal.[1] • Other thromboembolic complications may occur when AF-related blood clots travel from the heart to other parts of the body (such as the gut or legs). • Heart attacks o May occur when the heart beats too rapidly in AF or (rarely) when blood clots travel from the heart to the coronary arteries.[4] • Heart failure o AF can worsen heart failure or even cause heart failure in some cases when the heart rate is too rapid over time.[5] • Death o AF is a risk factor for death—individuals with AF are approximately twice as likely to die as other patients.[1,6]
Burden on Society	
Recent incidence and prevalence in populations and subpopulations	INCIDENCE (NEW CASES) AND PREVALENCE (PROPORTION OF POPULATION LIVING WITH THE CONDITION) • AF is the most common rhythm abnormality seen in clinical practice—more than 2.3 million Americans have AF.[7] • AF incidence and prevalence increase with age; prevalence approaches 8% in patients older than 80 years of age.[8] • AF affects men and women equally, but 60% of patients older than 75 years of age

	are female.[1] • African Americans appear to be at lower risk for AF than Whites.[9]
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	QUALITY OF LIFE • Quality of life is impaired in many patients with AF, but treatment can lead to significant improvement in quality of life in symptomatic patients.[10] PRODUCTIVITY[11] • AF places significant cost, absence, and productivity burdens on employers. • For patients with AF, it leads to greater rates of sick leave and more frequent short-term disability absences compared with non-AF patients. FUNCTIONAL CAPACITY • Mental and physical functioning are significantly affected in AF patients compared with non-AF patients.[10] MORTALITY • Individuals with AF are at higher mortality risk—they are approximately twice as likely to die as other patients.[1,6]
How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• The management of AF and its complications is responsible for almost $16 billion in costs to the U.S. health care system each year[1] and causes substantial morbidity and higher mortality for patients. • The substantial public health impact of AF in the United States led the Institute of Medicine (IOM) to designate comparison of treatment strategies for AF as one of the top priority areas for comparative effectiveness research.[12]
Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	<u>Systematic reviews/available data:</u> • The most recent systematic review on AF treatment was sponsored by the Agency for Healthcare Research and Quality (AHRQ) and was completed in June of 2013.[1] (A more recent update of this literature search [through November 2013] and its findings will be published in June 2014.) o Comparing pharmacological rate- and rhythm-control strategies, there was moderate strength of evidence (SOE) supporting comparable efficacy with regard to all-cause mortality, cardiac mortality, and stroke in older patients with mild AF symptoms. o For rate-control therapies, conclusions were limited by the small number of studies comparing therapies and including outcomes of interest. o For the effect of rhythm-control therapies in reducing AF recurrence, there was high SOE favoring pulmonary vein isolation (PVI) versus antiarrhythmic medications in relatively younger patients with paroxysmal AF and no or mild structural heart disease. o There was high SOE for the surgical Maze (including PVI) procedure at time of other cardiac surgery as opposed to cardiac surgery alone. • The most recent systematic review on stroke prevention in AF was sponsored by AHRQ and was completed in August 2013.[13] o The continuous CHADS2 and continuous CHADS2-VASc scores have the greatest discrimination for stroke risk (low SOE), and the HAS-BLED score has the greatest discrimination for bleeding risk (moderate SOE). o Factor IIa inhibitor (dabigatran 150 mg) was superior to warfarin in reducing the incidence of stroke (including hemorrhagic) or systemic embolism, with no

significant difference in the occurrence of major bleeding (high SOE).
    - The Xa inhibitor rivaroxaban was not inferior to warfarin in preventing stroke or systemic embolism (moderate SOE), with similar rates of major bleeding and death (high SOE).
    - The Xa inhibitor apixaban was superior to warfarin in reducing the incidence of stroke or systemic embolism (high SOE), major bleeding (high SOE), and all-cause mortality (moderate SOE)
    - Apixaban was also superior to aspirin in reducing the incidence of stroke or systemic embolism, with similar hemorrhagic events, including major bleeding in patients who are not suitable for oral anticoagulation (high SOE).
    - Evidence for patients undergoing invasive procedures, switching among anticoagulant therapies, and starting or restarting anticoagulant therapy after previous major bleeding events was insufficient.
- AHRQ and the Centers for Medicare and Medicaid (CMS) are currently sponsoring a systematic review exploring the comparative safety, efficacy, and effectiveness of catheter ablation and medical therapy for AF. This review expands on existing reviews and specifically focuses on:
    - health outcomes at one year or longer
    - whether current ablation techniques reduces the risk of death and stroke
    - comparative safety and effectiveness of ablation techniques using different energy sources
    - what the evidence is regarding the comparative effectiveness and harms of catheter ablation in the Medicare population (age 65 years or older, females)
    - This systematic review is scheduled to be completed by January 2015.

SCREENING/EARLY DIAGNOSIS

- There have been few studies examining the value of screening for AF, but available evidence does suggest that screening increases the detection of AF.[14]

TREATMENT[1]

- Treatment of AF involves three distinct areas:
    - Rate control (treatments to slow the heart rate to a normal range)
    - Rhythm control (treatments to bring the heart rhythm back to normal)
    - Prevention of complications relating to blood clots

MANAGEMENT OPTIONS[1]

- There are multiple management options for each of the three domains of AF treatment:
    - Options for rate control include treatment with medications (primarily beta blockers and calcium channel blockers) and some procedural treatments (atrioventricular nodal ablation with pacemaker placement).
    - Options for rhythm control include a variety of antiarrhythmic medications and procedural treatments to help the heart regain its normal rhythm (achieved with medications or electrical cardioversion) or maintain its normal rhythm (achieved with medications or ***catheter-based or surgical ablation procedures***, older surgical "cut-and-sew" techniques).
        - AF ablation is typically recommended only for symptomatic patients; asymptomatic patients are usually managed with anticoagulation and/or rate control as needed
        - Catheter ablation for the treatment of AF is a commonly performed procedure for symptomatic patients in whom rhythm control medications are either ineffective or not tolerated.
        - Ablation seeks to restore normal sinus rhythm by delivering energy through catheters to targeted points in the heart at which the arrhythmia

	originates; this energy ablates or destroys these small focal areas of the heart and disrupts the abnormal electrical activity ○ Other types of catheter ablation are becoming available, such as cryoablation, which uses a pressurized refrigerant in the catheter tip to ablate the source of the arrhythmia, cryoballoon ablation, which involves cooling and freezing of the targeted tissue using coolant inside a balloon to alter abnormal electrical activity. ○ The most commonly used catheter ablation approaches to treat AF are pulmonary vein isolation (PVI) and pulmonary vein antrum isolation (PVAI). Other approaches are also used, including wide area circumferential ablation (WACA) and complex fractionated atrial electrograms (CFAE). ○ Recent systematic reviews have attempted to evaluate the efficacy of ablation approaches relative to each other. These reviews have highlighted the significant heterogeneity with regard to the approaches compared. This diversity of strategies studied and related heterogeneity precludes effective synthesis of data, and meaningful conclusions regarding optimal strategies are not currently possible. ○ Options for prevention of blood clot–related complications include antithrombotic medications (warfarin, newer medications like rivaroxaban, dabigatran, apixaban) and procedural treatments to remove or block the parts of the upper chambers of the heart where clots can form.
What could new research contribute to achieving better patient-centered outcomes?	• New research could potentially improve patient-centered outcomes within all three domains of AF treatment. • Future research should address uncertainties related to subgroups of interest and impact of different therapies on long-term clinical outcomes. • The role of rhythm control in AF, particularly procedural treatments geared toward maintenance of normal heart rhythm, is less well-established than rate control and prevention of blood clot–related complications ○ Because catheter ablation may be more effective than medical antiarrhythmic therapy,[1] new research on catheter ablation procedures for AF has strong potential to improve patient-centered outcomes. ○ The optimal timing of catheter ablation and whether it should be offered as first-line or second-line therapy is uncertain.
Have recent innovations made research on this topic especially compelling?	Recent innovations: • Continued refinement of catheter-based ablation techniques for AF, along with evidence showing effectiveness in younger populations,[1] makes early use of catheter ablation a compelling area for comparative effectiveness research. • AF is primarily a disease of the elderly, and although data on catheter ablation appear promising in younger patients, defining its role in older patients in whom AF is much more prevalent is a priority.
How widely does care now vary?	VARIABILITY IN CARE • The existence of gender and racial disparities in use of catheter ablation to treat AF is uncertain and should be explored in future studies. • In one large referral center, 77% of ablation procedures from 2001 to 2009 were performed in men and 93% were performed in Whites; these disparities in ablation utilization do not reflect known AF demographics.[15]
What is the pace of other research on this topic (as indicated by recent publications and	RECENT PUBLICATIONS • A MEDLINE search from 3/19/2009 through 3/19/2014 yielded a total of 263 citations potentially relevant to the topic of catheter ablation in AF: ○ 23 were labeled as randomized controlled trials/therapy. ○ 8 were labeled as meta-analyses or systematic reviews.

ongoing trials)?	ONGOING TRIALS • At least 59 ongoing studies listed in www.clinicalTrials.gov could be potentially relevant to the topic of catheter ablation in AF. • Most notably, the effect of catheter ablation on final outcomes including mortality is being assessed by the ongoing NHLBI-funded Catheter Ablation vs. Antiarrhythmic Drug Therapy for AF (CABANA) trial. This trial is estimating an enrollment of 2200 patients and is hoped to be completed by March 2018. The primary endpoint is a composite of total mortality, disabling stroke, serious bleeding, or cardiac arrest in patients warranting therapy for AF. Secondary outcomes include: ○ Total mortality ○ Cardiovascular hospitalization ○ Cardiovascular death ○ Disabling stroke ○ Arrhythmic death or cardiac arrest ○ Heart failure death ○ Freedom from recurrent AF ○ Medical costs, resource utilization, and cost effectiveness ○ Quality of life
How likely is it that new CER on this topic would provide better information to guide clinical decision making?	KEY UNCERTAINTIES IN CLINICAL DECISION MAKING[1] • The safety, efficacy, and effectiveness of catheter ablation early in the course of AF relative to other rate- and rhythm-control (pharmacologic) approaches • The comparative effectiveness of specific catheter ablation procedures on patient-centered outcomes, including quality of life, functional capacity, and long-term outcomes like stroke and mortality • Differential outcomes with catheter ablation in subgroups of patients based on demographics, underlying cardiac characteristics, or duration/type of AF • The need for ongoing anticoagulation after catheter ablation has achieved rhythm control, or the optimal timing for stopping anticoagulation if ever • The durability of the effect of the procedure over time (data suggest a high recurrence rate at 3–5 years, potential rare complications that can be detected only over longer followup/ large patient population) • Prognostic significance of early recurrence of AF after ablation • Examining predictors of good response to ablation (patient clinical characteristics, imaging factors, biomarkers) • Effect of antiarrhythmic drugs after ablation (it is expected that the effect may change after varying the substrate with ablation) LIKELIHOOD THAT CER WOULD BE ABLE TO REDUCE THESE UNCERTAINTIES • There is a high likelihood that appropriately designed comparative effectiveness studies would be able to effectively address these and other areas of uncertainty • Note, however, that current clinical trials (e.g., CABANA) are experiencing challenges including: ○ Slow enrollment since patients are referred to electrophysiologist for ablation and at that point it is difficult to randomize them to the nonablation arm ○ Evolving technologies, which may reduce the applicability of findings in longer studies that are (appropriately) trying to evaluate longer term outcomes but whose results may no longer be relevant to the changing clinical practice
Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that would affect the implementation	FACILITATORS • AF has a high prevalence, causes substantial morbidity and mortality, and is already considered a high-priority condition. • Many effective treatment strategies exist for AF that can reduce complications and improve quality of life for patients with AF.

of new findings in practice?	• Given the wide range of available treatment options and remaining areas of clinical uncertainty, CER in the area of AF is likely to have an important impact. BARRIERS • Catheter ablation is relatively costly, so its reach as a first-line therapy may be limited for under/uninsured patients. • Many different procedural variations exist, and effects may differ by patient subgroup, which may make trial design challenging.
How likely is it that the results of new research on this topic would be implemented in practice right away?	EVIDENCE OF BENEFIT • Findings would likely be implemented widely if evidence of better patient-centered outcomes was strong. EVIDENCE OF NO BENEFIT OR HARM • It is likely that research demonstrating no evidence for benefit of catheter ablation would also impact practice by supporting the continued early use of alternative therapies.
Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies?	• Although catheter ablation techniques continue to evolve, it is likely that new information regarding early use of catheter ablation, outcomes in different populations, and the need for ongoing anticoagulation in AF following catheter ablation would remain relevant.

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APPENDIX: TOPIC QUESTION

Proposed Topic:

Compare the effectiveness of treatment strategies for atrial fibrillation including surgery, catheter ablation, and pharmacologic treatment.

Revised Topic:

Compare the effectiveness of treatment strategies for atrial fibrillation, with an emphasis on early use of catheter ablation for recently-diagnosed atrial fibrillation.

TOPIC 2: Treatment Strategies for Intermittent Claudication

Compare the effectiveness of treatment strategies for patients with intermittent claudication

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION • Intermittent claudication is the most common symptom in patients who have peripheral artery disease (PAD) and is defined as leg pain that occurs with exertion. • Intermittent claudication is most frequently caused by atherosclerosis (narrowing of the arteries caused by cholesterol plaque) and impaired perfusion (blood flow) of the lower extremities. • Patients with intermittent claudication have poorer functional capacity, worse quality of life, and higher morbidity and mortality than age- and sex-matched control patients without intermittent claudication.
Relevance to patient-centered outcomes	SYMPTOMS • Symptoms include buttock, thigh, and calf muscle discomfort or pain that typically occurs with exertion and improves with rest. • Symptoms typically cause limitations in functional capacity and quality of life. OUTCOMES • Cardiovascular outcomes—patients with PAD have a significantly higher risk of all-cause death, myocardial infarction, and stroke than patients without PAD. • Disease-specific outcomes—patients with PAD have higher risk of amputation, poorer functional capacity, and worse quality of life than patients without PAD: o Major and minor amputation of the lower extremity o Decreased functional capacity (6-minute walk, claudication onset distance/time, maximal walking distance/time) o Quality of life (walking impairment questionnaire, peripheral artery questionnaire)
Burden on Society	
Recent incidence and prevalence in populations and subpopulations	PREVALENCE (PROPORTION OF POPULATION LIVING WITH THE CONDITION) • Approximately 8 million people in the United States have PAD, of which about 3 to 4 million people have intermittent claudication. • The prevalence of PAD and intermittent claudication is increased in patients with: o Cigarette smoking (smokers have a 10-fold higher relative risk of developing PAD than nonsmokers) o Diabetes mellitus (diabetics have a 2- to 4-fold higher risk of PAD than nondiabetics; patients with diabetes account for a large proportion [70%] of nontraumatic lower extremity amputations each year) o Older age o Hypertension (high blood pressure; hypertensive patients have a 2-fold higher risk of PAD than nonhypertensive patients) o Hyperlipidemia (high cholesterol; hyperlipidemic patients have a 2-fold higher risk of PAD than nonhyperlipidemic patients)

Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	QUALITY OF LIFE • Anxiety/depression due to lack of mobility and pain • Concern over impact of PAD diagnosis on prognosis AMPUTATION OF THE LOWER EXTREMITY • Major amputation (above the knee, below the knee, or the foot) • Minor amputation (toes) • Between 2000 and 2008, a total of 186,338 patients (6.8% of the overall hospitalized population with PAD) underwent lower extremity amputation. • Limb loss is both physically and psychologically devastating for patients. Not only does lower limb amputation cause major disfigurement, it also renders people less mobile and at risk for loss of independence. FUNCTIONAL CAPACITY • Walking distance/time is often limited in patients with claudication. MORTALITY • 20% to 30% of patients with intermittent claudication die by 5 years from diagnosis (mainly from cardiovascular events).
How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• PAD was identified by the Institute of Medicine as one of the top 100 priorities for comparative effectiveness research due to the large population of patients affected with significant morbidity and mortality and the high costs of care to the health care system. • In 2001, $4.37 billion was spent by Medicare on PAD-related treatments in the United States (88% on inpatient expenditures). • The increasing prevalence of diabetes mellitus and the increasing age of the population will likely lead to a rise in the overall prevalence of PAD and intermittent claudication.
Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	Five recent systematic reviews explored therapies for patients with intermittent claudication.[1-5] Their results suggest the following management options. CURRENT TREATMENT OPTIONS • Risk factor modification (e.g., smoking cessation, weight loss, treatment of hypertension/hyperlipidemia/diabetes mellitus) • Cardiovascular medical therapy (e.g., antiplatelet medications, HMG-CoA reductase (statin) medications, angiotensin-converting enzyme inhibitors) • Disease-specific medications to improve functional capacity (e.g., cilostazol, pentoxifylline, naftidrofuryl) • Exercise training • Endovascular revascularization • Surgical revascularization CLINICAL MANAGEMENT • Very few existing studies have directly compared risk factor modification, medical therapy, exercise training, endovascular revascularization, and surgical revascularization strategies. • Benefits: o *Functional capacity.* A random-effects meta-analysis of 16 RCTs compared the

	effect of multiple treatments on maximal walking distance or absolute claudication distance. Exercise training, pentoxifylline, and the combination of endovascular treatment with exercise were associated with large effects, while cilostazol and endovascular intervention were associated with moderate effects when compared with usual care. None of the other treatments were found to have a statistically significant effect when compared against each other. Similar results were observed in studies that were excluded due to measurement of peak walking time rather than distance. The strength of evidence was rated moderate for exercise; low for cilostazol, endovascular treatment, and the combination of endovascular treatment with exercise. ○ *Quality of life.* A random-effects meta-analysis of 10 studies examining the difference in the Short Form-36 measure of physical functioning assessed between 3 and 6 months showed a significant improvement in quality of life from cilostazol, exercise training, endovascular intervention, and surgical intervention—ranging from moderate to large effects compared with usual care. However, the comparisons of all active treatments with each other showed that none of the treatments are significantly different from each other. The strength of evidence was rated low for all comparisons. ○ Cardiovascular events (e.g., myocardial infarction, stroke, cardiovascular death), amputation, wound healing, analog pain scale score, repeat revascularization, and vessel patency were infrequently reported. The strength of evidence was rated insufficient for all comparisons. • Harms: ○ Very few studies reported adverse effects or harms of treatment.
What could new research contribute to achieving better patient-centered outcomes?	• Prior research in PAD patients has not been patient-centered, as evidenced by functional outcomes that involve distance and time walked on a treadmill rather than ability to perform activities of daily living and 6-minute walking distance • New research has the potential to more clearly define objective outcome measures that are important to patients with intermittent claudication: ○ Relationship between anatomy and clinical limb-specific outcomes ○ Measures of functional capacity (e.g., 6-minute walking distance) ○ Measurement of long-term outcomes ○ Study of patients stratified by anatomic severity criteria (e.g., iliac, femoropopliteal, infrapopliteal, multilevel disease)
Have recent innovations made research on this topic especially compelling?	Recent innovations include improved endovascular revascularization techniques (e.g., atherectomy devices, drug-coated balloons, drug-eluting stents). Also, the increasing occurrence of endovascular revascularization in the United States makes a CER of multiple treatment modalities more compelling.
How widely does care now vary?	VARIABILITY IN CARE • Significant geographic, physician specialty, and patient-specific variation exists in the use of major amputation of the lower extremities and endovascular/surgical revascularization procedures. • There is uncertainty about the degree of use of smoking cessation therapies and exercise training due to the lack of payer reimbursement and the ability to capture these data in administrative claims.
What is the pace of other research on this topic (as indicated by	RECENT PUBLICATIONS • A systematic review/meta-analysis performed at Duke Clinical Research Institute and funded by the Agency for Healthcare Research and Quality was published in May 2013 titled "Treatment Strategies for Patients with Peripheral Artery Disease."[1]

recent publications and ongoing trials)?	concluding that: ○ clopidogrel monotherapy is more beneficial than aspirin in the intermittent claudication patient ○ dual antiplatelet therapy (aspirin and clopidogrel) is not significantly better than aspirin at reducing cardiovascular events in intermitten claudication patients ○ exercise therapy, cilostazol, and endovascular intervention all had an effect on improving functional status and quality of life; the impact of these therapies on cardiovascular events and mortality is uncertain ○ advances in care in both medical therapy and invasive therapy have not been rigorously tested and thus provide an impetus for further comparative research • A MEDLINE search from 8/1/2012 through 3/24/2014 yielded a total of 549 publications: ○ 41 were randomized controlled trials/therapy. ○ 77 were systematic reviews or meta-analyses. ONGOING TRIALS • There are at least 58 ongoing studies listed in www.clinicaltrials.gov targeting treatment of PAD ○ 39 of these are Phase 3 or 4 trials with 27 studies directly comparing alternative pharmacologic and/or nonpharmacologic therapies ▪ interventions, sample sizes, outcomes assessed, and time horizons for the trials vary widely ▪ none of the identified studies looked at multimodal comparisons ○ The EUCLID (Examining Use of tiCagreLor In paD) study has finished enrollment (target 15,328 patients) and is evaluating the efficacy and safety of ticagrelor (an oral antiplatelet medication) for patients with PAD. It is expected to be completed early in 2016 ○ Drug-eluting stents and drug-coated balloons are being introduced for the endovascular treatment of intermittent claudication (currently being studied in ~13 comparative studies) ○ Multiple cell therapy and gene therapy early-phase trials are currently enrolling and being planned.
How likely is it that new CER on this topic would provide better information to guide clinical decision making?	KEY UNCERTAINTIES IN CLINICAL DECISION MAKING • Prior studies have examined single treatments (i.e., supervised exercise vs. home exercise; balloon angioplasty vs. balloon angioplasty plus stenting) rather than treatment strategies (i.e., combined supervised exercise plus endovascular revascularization vs. supervised exercise alone) or a sequential treatment strategy (i.e., supervised exercise first; if no improvement, endovascular revascularization vs. supervised exercise and endovascular revascularization), • There has been very little prior research on the importance of outcomes (i.e., functional capacity, quality of life) to patients. LIKELIHOOD THAT CER WOULD BE ABLE TO REDUCE THESE UNCERTAINTIES • Engaging patients to help identify which outcomes (functional capacity, quality of life, etc.) are important, and the impact of treatments or treatment strategies could be extremely useful.
Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that would affect the	FACILITATORS • Multiple ongoing studies have examined therapies to reduce cardiovascular morbidity/mortality in patients with PAD; thus current and future work are well suited to examine issues specific to patient preferences and patient-centered outcomes

implementation of new findings in practice?	BARRIERS • Physicians from multiple specialties (surgery, cardiology, radiology, vascular medicine) take care of patients with PAD and intermittent claudication. • Current reimbursement policies reward high-cost procedures (endovascular and surgical revascularization) and overlook low-cost management strategies (supervised exercise training, smoking cessation therapies).
How likely is it that the results of new research on this topic would be implemented in practice right away?	EVIDENCE OF BENEFIT • High likelihood of implementation if evidence of benefit EVIDENCE OF NO BENEFIT OR HARM • May reduce use of high-cost, low-value treatments if evidence of no benefit or harm
Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies?	• There is currently sparse evidence to show that one treatment is superior to another across the spectrum of patient-centered outcomes, and very few comparisons of treatment strategies in patients with intermittent claudication. • It is highly likely that new information on the management of intermittent claudication (specifically comparisons of treatment strategies) will be current for several years.

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APPENDIX: TOPIC QUESTION

Proposed Topic:
Compare the effectiveness of treatment strategies for vascular claudication (e.g., medical optimization, smoking cessation, exercise, catheter-based treatment, open surgical bypass).

Revised Topic:
Compare the effectiveness of treatment strategies for patients with intermittent claudication.

TOPIC 3: Behavioral Interventions for Posttraumatic Stress Disorder

Compare the effectiveness of behavioral interventions (e.g., cognitive behavioral individual therapy, generic individual therapy) treatment strategies for posttraumatic stress disorder stemming from diverse sources of trauma.

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION • Posttraumatic stress disorder (PTSD) is the "the complex somatic, cognitive, affective, and behavioral effects of psychological trauma."[1] • PTSD can stem from diverse trauma experiences that include, but are not limited to, military combat, child or adult sexual violence (e.g., incest, rape), severe physical injury, diagnosis of a life-threatening illness, natural disaster. • The majority of people who go through a trauma have some symptoms of PTSD early on; however, only some will develop PTSD over time.
Relevance to patient-centered outcomes	SYMPTOMS PTSD is characterized by the following symptoms: • Intrusive thoughts • Nightmares and flashbacks of past traumatic events • Avoidance of reminders of trauma • Negative feelings about self and others • Hypervigilance (e.g., jumpiness) • Sleep disturbance OUTCOMES • PTSD has an impact on many physical, emotional, and social aspects of patients' lives including: o Social dysfunction o Emotional issues (e.g., depression, anxiety) o Employment issues (e.g., difficulty obtaining or keeping a job) o Interpersonal problems (e.g., relationship problems, including divorce) o Drinking or drug problems o Physical symptoms (e.g., increased blood pressure and heart rate, rapid breathing, muscle tension, nausea, and diarrhea) o Chronic pain o Elevated risk of coronary heart disease[2] o Quality of sleep
Burden on Society	
Recent incidence and prevalence in populations and subpopulations	INCIDENCE (NEW CASES) & PREVALENCE (PROPORTION OF POPULATION LIVING WITH THE CONDITION) Risk factors for PTSD include lower socioeconomic status, family or personal history of a psychiatric condition, poor social support, and initial severity of reaction to the traumatic event.[3-5] • In the United States, 8.3% of the general population will experience PTSD in their lifetimes, and 4.7% will have experienced PTSD in the past 12 months.[6] • Prevalence can vary by key subgroups and exposures: o The lifetime prevalence of PTSD is higher among women than men (9.7% vs. 3.6%).[7] o Prevalence of PTSD varies by race/ethnicity, with African Americans[8] having higher rates compared with other groups.

	○ Among populations experiencing a life-threatening medical event, the prevalence can be much higher[9] (e.g., 23% for patients experiencing stroke or transient ischemic attack). ○ Among US veterans, the prevalence of PTSD is higher than the general population and varies by era of service (e.g., Vietnam era) and exposure to combat (range: 10% to 31%).[10,11]
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	QUALITY OF LIFE • PTSD has far-ranging effects on physical, interpersonal, social, and emotional function—all of which can affect quality of life.[12] PRODUCTIVITY • PTSD can have profound effects on productivity. The degree of work limitations varies by individual and PTSD severity. • On average, PTSD can contribute to 3.6 days of work impairment per month, which is comparable to the impact of major depression.[13] FUNCTIONAL CAPACITY • PTSD can negatively affect memory, concentration, time management, and organizational skills, which affect functional capacity. • Compared to people without PTSD, individuals with PTSD experience greater impairment in terms of lost work days, interference with work or daily activities, decreased time with people in personal life, and increased tensions or conflicts in interpersonal relationships.[14] MORTALITY • PTSD is associated with a significantly increased incidence of a variety of cardiovascular (coronary artery disease, incidence of heart attack, stroke), pulmonary (bronchitis, asthma), and other (arthritis, renal dysfunction) physical illnesses.[15-17] • PTSD is associated with increased suicide attempts.[15]
How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	Given the high prevalence of PTSD and the impact on functional status, productivity, and quality of life, high priority should be given for optimizing treatments to reduce symptoms, and improve functioning and quality of life.
Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	Systematic reviews/available date: The most recent systematic review on PTSD treatment was sponsored by the Agency for Healthcare Research and Quality and was completed in April, 2013[18] (see Management Options below for main findings). SCREENING/EARLY DIAGNOSIS • A diagnosis of PTSD is made for patients who meet all of these criteria: exposure to traumatic event, presence of intrusive symptoms (e.g., intrusive distressing memories), persistent avoidance of stimuli associated with the traumatic event, negative thoughts or feeling associated with event, and increased arousal and reactivity associated with the traumatic event.

	TREATMENT • The main treatments for people with PTSD are psychotherapy ("talk" therapy), medications, or both. However, trauma-focused psychological interventions (i.e., those that treat PTSD by directly addressing thoughts, feelings, or memories of the traumatic event) are considered empirically supported first-line treatments for adults with PTSD. MANAGEMENT OPTIONS[18] • For psychotherapy (see descriptions in Appendix): ○ Strong evidence supports the efficacy of exposure therapy for improving PTSD symptoms. ○ Evidence also supports efficacy of cognitive processing therapy (CPT), cognitive therapy (CT), cognitive behavioral therapy (CBT)–mixed therapies, eye movement desensitization and reprocessing (EMDR), and narrative exposure therapy for improving PTSD symptoms. • For medications, evidence supports the use of fluoxetine, paroxetine, sertraline, topiramate, and venlafaxine for improving PTSD symptoms.
What could new research contribute to achieving better patient-centered outcomes?	New research could contribute to achieving better patient-centered outcomes. There is still significant clinical uncertainty around which treatments to select for which patients. Specifically, existing evidence does not allow for conclusions about these questions: • Are some psychological treatments efficacious? • What is the comparative effectiveness of evidence-based psychological treatments? • Should patients starting treatment begin with a combination of psychological and pharmacological approaches compared with psychological treatment alone? While most guidelines view psychological treatments as the preferred first step and use medications as an adjunct or a next-line treatment, there is insufficient direct evidence (from head-to-head trials) to support this approach. • Do treatments differ in effectiveness for specific groups? Few studies explore how effects differ by key subgroups, including those with different trauma types. Do certain patient characteristics increase the chances of responding (or not responding) to specific treatments? • If and for how long are the effects of treatment maintained after treatment stops? • What is the optimal duration or number of treatments needed to achieve meaningful outcomes for patients? • What are the comparative risks of adverse effects for psychological treatments?
Have recent innovations made research on this topic especially compelling?	There have been no recent high-impact innovations related to strategies for improving patient-centered outcomes. Yet, there is a compelling argument for fostering comparative effectiveness research in this area, given the following: • High burden of disease, especially among certain subgroups, and large burden on patient-centered outcomes (quality of life, functional ability) • Existence of psychological interventions to effectively improve outcomes but a lack of comparative effectiveness of these approaches, including comparative risk of adverse effects
How widely does care now vary?	VARIABILITY IN CARE[19] • There is likely high variability in care, and many people with PTSD never seek care. In an analysis of a nationally representative sample of U.S. adults: ○ Only 50% of respondents with PTSD are receiving any type of medical or mental health treatment in the preceding 12 months. ○ Of those receiving any treatment, only 21% were receiving care that was minimally adequate. ○ Mental health treatment varied by educational status and geographic location.
What is the pace	RECENT PUBLICATIONS

of other research on this topic (as indicated by recent publications and ongoing trials)?	• A MEDLINE search from 2009 through 2014 yielded a total of 1,833 citations:
	  ○ 264 were labeled as randomized controlled trials/therapy.
	  ○ 132 were labeled as meta-analyses or systematic reviews.
	
	ONGOING TRIALS
	There are at least 117 ongoing studies listed in www.clinicaltrials.gov. Of note, this includes the "Comparative Effectiveness Research in Veterans With PTSD (CERV-PTSD)" study which is designed to compare the effectiveness of two types of psychotherapy, Prolonged Exposure and Cognitive Processing Therapy, for treating posttraumatic stress disorder in male and female Veterans. The primary outcome is improvement in PTSD symptoms after treatment. The outcome will be measured at regular follow-up visits that will occur at the middle and at the end of treatment and then 3 and 6 months later. Additional outcomes include additional mental health problems, functioning, quality of life, and use of treatments for mental and physical problems. The trial is targeting 900 participants and is estimated to be completed in the Fall of 2018.

How likely is it that new CER on this topic would provide better information to guide clinical decision making?	KEY UNCERTAINTIES IN CLINICAL DECISION MAKING • What psychological treatment or combination of treatments work best for key subgroups of patients? For example, do approaches differ by type of trauma? • Should patients starting treatment begin with a combination of psychological and pharmacological approaches compared with psychological treatment alone? • What is the optimal duration or treatment approach to maintain treatment gains in patient-centered outcomes? • What are effective strategies to foster long-term adherence to treatments? • What are the comparative benefits and harms of different psychological strategies? LIKELIHOOD THAT CER WOULD BE ABLE TO REDUCE THESE UNCERTAINTIES There is a high likelihood that appropriately designed comparative effectiveness studies would be able to effectively address these and other areas of uncertainty • There are few comparative effectiveness studies of psychological interventions; understanding the best interventions in this area could improve care and outcomes by establishing a set of "best practices" to be employed in health care and community settings. • There is little evidence about which patients do best with what treatments; CER in this area could help patients and providers to better select strategies according to patient characteristics.
Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that would affect the implementation of new findings in practice?	FACILITATORS • PTSD has relatively high prevalence with a wide impact on patient quality of life, functioning, and productivity. • Due to recent wars in Afghanistan and Iraq, PTSD is a high-profile disorder with significant public awareness. • There is evidence from previous studies that obtaining treatment improves outcomes. Thus, there are already evidence-based interventions for patients with PTSD. These "off-the-shelf" programs that have an evidence base can be adapted to different settings and patient groups and can be readily used in comparative effectiveness research and implementation research. BARRIERS • Lack of treatment-seeking by affected individuals • High variability in care • Lack of access to evidence-based treatments that vary by geographic location.

How likely is it that the results of new research on this topic would be implemented in practice right away?	• Several professional societies have developed guidelines for the care and management of PTSD, and the core components of these recommendations are agreed on. However, there is a need to give providers specific guidance on when each management strategy may be appropriate for patients. • Patient-based research that compares the effectiveness of different therapies is likely to be implemented right away if resources support these therapies and improvements in outcomes are easy to achieve and can be customized to the individual patient.
Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies?	CER priority areas that seek to identify which psychological interventions work best for which patients are needed. These types of findings are not likely to become obsolete quickly.

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APPENDIX: TOPIC QUESTION

Proposed Topic:
Compare the effectiveness of treatment strategies (e.g., cognitive behavioral individual therapy, generic individual therapy, comprehensive and intensive treatment) for Post-traumatic Stress Disorder stemming from diverse sources of trauma.

Revised Topic:
Compare the effectiveness of behavioral interventions (e.g., cognitive behavioral individual therapy, generic individual therapy) treatment strategies for Post-traumatic Stress Disorder stemming from diverse sources of trauma.

Psychotherapy descriptions from the 2013 AHRQ Report on Treatments for PTSD[18]

Exposure therapies: These types of therapies involve confrontation with frightening stimuli related to the trauma and are continued until anxiety is reduced. Imaginal exposure uses mental imagery from memory or introduced in scenes presented to the patient by the therapist. In some cases, exposure is to the actual scene or similar events in life: *in vivo* exposure involves confronting real life situations that provoke anxiety and are avoided because of their association with the traumatic event (e.g., avoidance of tall buildings following experiencing an earthquake). The aim is to extinguish the conditioned emotional response to traumatic stimuli. By learning that nothing "bad" will happen during a traumatic event, the patient experiences less anxiety when confronted by stimuli related to the trauma and reduces or eliminates avoidance of feared situations. Exposure

therapy is typically conducted for 8 to 12 weekly or biweekly sessions lasting 60 to 90 minutes.

Cognitive processing therapy: This therapy includes psychoeducation, written accounts about the traumatic event, and cognitive restructuring addressing the beliefs about the event's meaning and the implications of the trauma for one's life. The treatment is based on the idea that affective states, such as depressed mood, can interfere with emotional and cognitive processing of the trauma memory, which can lead to traumatic symptomatology. The manualized treatment is generally delivered over 12 sessions lasting 60 to 90 minutes.

Cognitive therapy: This therapy is largely based on the cognitive model, which states that an individual's perception of a situation influences his or her emotional response to it. The general goal of cognitive therapy is to help people identify distorted thinking and to modify existing beliefs, so that they are better able to cope and change problematic behaviors. Cognitive therapy is generally considered to be brief, goal-oriented, and time-limited.

Cognitive behavioral therapy: This is a broad category of therapies based on principles of learning and conditioning and/or cognitive theory to treat disorders. CBT includes components from both behavioral and cognitive therapy. In CBT, components such as exposure, cognitive restructuring, and various coping skills are used either alone or in combination. Most forms of CBT consist of a minimum of 8 to 12 weekly sessions lasting 60 to 90 minutes. CBT can be administered either as group or individual therapy.

Eye movement desensitization and reprocessing: During this therapeutic technique, a patient is asked to hold the distressing image in mind, along with the associated negative cognition and bodily sensations, while engaging in saccadic eye movements. After approximately 20 seconds, the therapist asks the patient to "blank it out," take a deep breath, and note any changes occurring in the image, sensations, thoughts, or emotions. The process is repeated until desensitization has occurred (i.e., patient reports little or no distress on the Subjective Units of Distress Scale), at which time the patient is asked to hold in mind a previously identified positive cognition, while engaging in saccadic eye movements, and rating the validity of this cognition while going through the procedure as outlined above. The saccadic eye movements were initially theorized to both interfere with working memory and elicit an orienting response, which lowers emotional arousal so that the trauma can be resolved. Current standards consist of 8 to 12 weekly 90-minute sessions.

TOPIC 4: Biologics for Treatment of Inflammatory Bowel Disease

Compare the effectiveness of different strategies of introducing biologics into the treatment algorithm for inflammatory bowel disease (Crohn's disease, ulcerative colitis), with an emphasis on induction of treatment and maintenance (not acute flares).

Criteria	Brief Description
Introduction	

Overview/definition of inflammatory bowel disease	DESCRIPTION OF CONDITION[1]
	• Inflammatory bowel disease (IBD) comprises two primary disorders: ulcerative colitis (UC) and Crohn's disease (CD).
	• Both UC and CD are conditions that involve inflammation of the bowel that comes and goes over time.
	  o Both have distinct clinical and pathologic characteristics but can overlap.
	• UC is characterized by inflammation that is limited to the colon and involves the mucosa (the layer closest to the bowel lumen).
	  o This inflammation usually begins in the rectum and may extend upward in a continuous fashion to involve other parts of the colon.
	  o "Pancolitis" is a term used to describe UC that involves more than just the left side of the colon (for example, extends from the rectum to the cecum).
	• CD is characterized by inflammation that can occur anywhere in the gastrointestinal tract from mouth to anus, and it can involve the entire thickness of the intestinal wall (often called "transmural" inflammation).
	  o Commonly affected areas are the ileum of the small intestine and the first part of the colon (cecum).
	  o CD is characterized by "skip lesions," or patches of inflammation occurring in different parts of the intestine with areas of normal tissue in between.
	• The cause of IBD is not completely understood—it is likely that there are both genetic risk factors (e.g., there are higher rates with a positive family history, higher rates in people of Ashkenazi Jewish descent, lower rates in African Americans and Hispanics compared with Caucasians) and environmental risk factors (e.g., variations based on geographic variation, smoking, diet, physical activity, obesity, certain infections). Notably, observational studies have shown that CD is a disease of smokers and UC a disease of nonsmokers.

Relevance to patient-centered outcomes	SYMPTOMS
	• The most common symptoms of UC include bloody diarrhea and abdominal pain/cramping. The symptoms of CD can be quite variable but often include abdominal pain, diarrhea, nausea, vomiting, and sometimes fever and weight loss.
	• Both UC and CD may have extraintestinal manifestations (symptoms outside the intestines) such as arthritis, skin problems (e.g., erythema nodosum, pyoderma gangrenosum), vitamin deficiencies, liver abnormalities (e.g., primary sclerosing cholangitis), severe eye problems (e.g., uveitis), and others.
	
	OUTCOMES
	• UC
	  o Patients with UC are at increased risk for colon cancer. Estimates of that risk vary widely, but the risk is increased with longer disease duration and extent of colonic involvement.[2,3]
	  o Prior to the recent introduction of biologic therapies, up to 20% of patients with UC required surgery (colectomy) to treat their disease.[4]
	  o Mortality does not appear to be elevated in UC.[5]

	• CD
	  ○ Because the inflammation in CD involves the entire thickness of the intestinal wall, patients with CD are at risk of developing complications such as strictures (narrowing of the intestines) and fistulae (connections that form between the intestines and skin or other hollow organs like the bladder) by 10 years after diagnosis.[6]
	  ○ Many patients require one or more surgeries over their lifetime for such complications.
	  ○ Patients with CD involving the colon are also at higher risk for colon cancer.[2,7]
	  ○ Mortality may be increased among patients with CD.[5]

Burden on Society	
Recent incidence and prevalence in populations and subpopulations	INCIDENCE (NEW CASES)[8] • Annual incidence of UC is up to 19.2 per 100,000 person-years in North America compared with 24.3 per 100,000 person-years in Europe and 6.3 per 100,000 person-years in Asia and the Middle East. • Annual incidence of CD is up to 20.2 per 100,000 person-years in North America compared with 12.7 per 100,000 person-years in Europe and 5.0 person-years in Asia and the Middle East. • UC and CD are most often diagnosed in a person's late teens and early twenties, with a second, smaller peak between 50 and 80 years of age.[9] PREVALENCE (PROPORTION OF POPULATION LIVING WITH THE CONDITION)[8] • Prevalence of UC is up to 249 per 100,000 persons in North America compared with 505 per 100,000 persons in Europe. • Prevalence of CD is up to 319 per 100,000 persons in North America compared with 322 per 100,000 persons in Europe. • For the United States, a study based on 9 million health insurance claims showed a prevalence of UC of 238 per 100,000 persons and a prevalence of CD of 201 per 100,000 persons.[10]
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	QUALITY OF LIFE[11] • Both forms of IBD can have a significant impact on quality of life—over 75% of patients report that their IBD symptoms negatively affect their ability to enjoy leisure activities. • However, over half of patients indicate that their doctor has not asked about the impact of IBD on their quality of life. PRODUCTIVITY/FUNCTIONAL CAPACITY • Over 67% of patients report their IBD symptoms negatively affect their ability to perform at work.[11] MORTALITY • Although estimates have varied, CD may increase mortality, while UC does not appear to have a significant impact on mortality.[5]

How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given	• IBD can be devastating for patients with this condition, and the symptoms of both UC and CD have the potential to reduce quality of life substantially.
	• IBD is extremely costly to the U.S. healthcare system.[12]
	  ○ For 2003–2004, mean annual per-patient costs for UC and CD were $5066 and $8265, respectively.
	  ○ For both conditions, these costs were approximately evenly divided between inpatient, outpatient, and pharmaceutical costs.
	• This substantial public health impact has led the Institute of Medicine (IOM) to

high priority?	designate comparative effectiveness research evaluating the use of biologics (a particularly costly therapy) for IBD as a top priority area.
Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	SCREENING/EARLY DIAGNOSIS • IBD is typically diagnosed based on the presence of symptoms, and screening does not play a large role. • Early diagnosis can be challenging, as other conditions (gastroenteritis, irritable bowel syndrome, functional abdominal pain) can mimic IBD. • Distinguishing between UC and CD on clinical grounds can be challenging, and diagnosis often depends on tissue biopsy of affected areas. TREATMENT • Treatment for IBD involves a variety of medication classes and selective use of surgery. • Treatment recommendations vary based on IBD type, disease severity, and location/extent of involvement. • The following medication classes are often used to suppress inflammation in IBD: o Aminosalicylates (mesalamine, sulfasalazine) may be administered rectally or orally. o Corticosteroids (prednisone, prednisolone, budesonide) may be administered rectally, orally, or intravenously. o Immunomodulators (6-mercaptopurine, azathioprine, and methotrexate) may be administered orally or subcutaneously (methotrexate). o 'Biologics' such as TNF-alpha inhibitors (infliximab, adalimumab, certolizumab, etc.) or natalizumab may be administered subcutaneously or intravenously • In general, biologics are genetically engineered medications made using living organisms and their products – biologics used for IBD are antibodies that specifically target molecules involved in the body's inflammatory response[13] • The main advantage for biologics in IBD is that they reduce inflammation in a targeted fashion, as opposed to corticosteroids or immunomodulators, which reduce inflammation through more generalized suppression of the immune system MANAGEMENT OPTIONS • UC[14] o Recommended therapy for induction of remission in UC is typically a rectally administered aminosalicylate, along with an orally administered aminosalicylate for patients with more extensive colonic involvement. o If remission cannot be induced using aminosalicylates, or the clinical presentation is more severe, corticosteroids may be used to induce remission, with tapering of the dose as tolerated. o Recommended maintenance therapies for UC include aminosalicylates, immunomodulators, and anti-TNF agents. Corticosteroids are not recommended for maintenance therapy. o If corticosteroids cannot be tapered without worsening of symptoms, immunomodulators or anti-TNF agents may be indicated to induce or maintain remission.

	○ Surgery to remove the colon may be indicated for UC patients whose symptoms cannot be controlled with medical therapy or for those who develop complications such as precancerous change, hemorrhage, perforation, etc. • CD[13] ○ Historically, lower-toxicity but lower efficacy therapies were used to treat CD, with escalation to include more effective but more toxic therapies as symptoms dictated ("step-up" approach, similar to the approach described for UC above). ○ More recently, evidence supports use of the more effective medications such as biologics earlier in the disease course ("top-down" approach). ○ For severe, steroid-resistant, or steroid-dependent CD presentations, hospitalization for intravenous therapy may be required to achieve remission or symptom control, and early use of immunomodulators and biologics is generally recommended. ○ In cases of CD with fistulae, anti-TNF biologics and immunomodulators appear most effective. ○ Surgery may be indicated for intestinal strictures and other complications.
What could new research contribute to achieving better patient-centered outcomes?	New research could contribute to achieving better patient-centered outcomes: • Corticosteroids have traditionally been a mainstay of therapy for induction of remission in IBD (especially CD), with the goal of reducing use of steroids in the maintenance of remission phase. ○ However, steroid medications have significant side effects, including weight gain, increased blood sugar, and loss of bone density, so finding alternatives to steroid therapy is desirable. • Use of biologics, which suppress inflammation in a more targeted way than steroids and are more effective than immunomodulators, hold promise in improving patient-centered outcomes in IBD with fewer side effects. ○ There is no universal agreement as to the timing of introduction of biologics for the treatment of IBD, particularly for CD (e.g., use of a "step-up" approach [using biologics only after other treatments have failed] or a "top-down" approach [using biologics early in the disease course]).[14]
Have recent innovations made research on this topic especially compelling?	The growing number of biologic therapy options—which may have more favorable long-term side effect profiles than steroids—makes new comparative effectiveness in this area highly compelling.
How widely does care now vary?	VARIABILITY IN CARE[15,16] • Variation exists in care for IBD patients: ○ 11% of patients receive care that is not guideline-recommended and is potentially harmful. ○ One analysis revealed significant variation in use of diagnostic tests and treatment choices for children and adolescents with IBD. ○ Different clinical guidelines recommend introducing biologics at different points in the course of IBD.
What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	RECENT PUBLICATIONS • A search of PubMed covering 3/21/09 through 3/21/14 yielded 859 publications, including: ○ 22 randomized, controlled trials ○ 43 systematic reviews/meta-analyses ○ 5 clinical guidelines

	ONGOING TRIALS
	• A search of clinicaltrials.gov showed 36 potentially relevant studies (8 targeting UC patients, 23 targeting CD patients, 5 targeting both UC and CD patients)
	  ○ 23 addressing biological/drug therapy
	  ○ 10 addressing biological/cell therapies
	  ○ 3 met criteria, but were pediatric only
	Most identified studies are with approved treatments (e.g., infliximab, golimumab, adalimumab). There are several with stem cells but thus far, that has not shown dramatic results. Future studies will look at fecal transplant and other biologic targets such as MMP9, etc.

How likely is it that new CER on this topic would provide better information to guide clinical decision making?	KEY UNCERTAINTIES IN CLINICAL DECISION MAKING
	• Based on a recent AHRQ-sponsored future research needs prioritization project focusing on CD, the following 4 areas of uncertainty were designated as the highest priority for future research:[17]
	  ○ For maintenance of remission in adults and children diagnosed with CD, what is the comparative effectiveness of treatment with a TNF-alpha inhibitor and an immunomodulator (combination therapy) versus a TNF-alpha inhibitor alone (monotherapy) for the outcomes of steroid reduction, patient-reported outcomes, CD activity index, and mucosal healing?
	  ○ For induction of remission in adults and children diagnosed with CD, what is the comparative effectiveness of one TNF-alpha inhibitor versus another TNF-alpha inhibitor for the outcomes of mucosal healing, patient-reported outcomes, steroid reduction, and CD activity index?
	  ○ For induction of remission in adults and children diagnosed with CD, what is the comparative effectiveness of a TNF-alpha inhibitor versus natalizumab for the outcomes of mucosal healing, patient-reported outcomes, steroid reduction, and CD activity index?
	  ○ For maintenance of remission in adults and children diagnosed with CD, what is the comparative effectiveness of one TNF-alpha inhibitor versus another TNF-alpha inhibitor for the outcomes of steroid reduction, patient-reported outcomes, CD activity index, and mucosal healing?
	• Because the timing of the use of biologics is also not clearly defined in UC, these comparisons may also be of interest in this condition.
	• Other potentially important areas for future research include:
	  ○ Specific IBD subpopulations that may benefit from earlier use of biologics
	  ○ Additional comparisons of specific biologics versus other biologics, immunomodulators, and other medications, both alone and in combination
	  ○ Further research to better define patient-centered outcomes of interest in IBD
	  ○ The use of fecal transplantation as a treatment for IBD
	
	LIKELIHOOD THAT CER WOULD BE ABLE TO REDUCE THESE UNCERTAINTIES
	• There is a high likelihood that appropriately designed randomized comparative effectiveness trials would address these areas of uncertainty.

Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that would affect the implementation of new findings in practice?	FACILITATORS • IBD is a common and costly condition that has significant effects on patient-centered outcomes and can be devastating for patients and their families. • Recent developments in medical therapy hold promise to improve patient-centered outcomes. • Evaluation of the use of biologics in IBD has already been identified as a high priority area for comparative effectiveness research by IOM.[18]

	BARRIERS • Though there is some overlap, UC and CD are different conditions, and findings for one may not pertain to the other. • Within UC and CD, there are different subclassifications based on severity, location, phenotype (for CD, stricturing, fistulizing, inflammatory) and the extent of the areas involved, which may complicate the design of comparative effectiveness studies.
How likely is it that the results of new research on this topic would be implemented in practice right away?	EVIDENCE OF BENEFIT • Findings would likely be implemented widely if there is evidence for better patient-centered outcomes. EVIDENCE OF NO BENEFIT OR HARM • It is likely that research demonstrating no evidence for benefit would also have an impact on practice by supporting current practice.
Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies?	• Although medical options continue to evolve, it is likely that new information regarding the optimal timing for use of biologics in IBD on patient-centered outcomes in different populations would remain relevant for years.

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APPENDIX: TOPIC QUESTION

Proposed Topic:
Compare the effectiveness of different strategies of introducing biologics into the treatment algorithm for inflammatory diseases, including Crohn's disease, ulcerative colitis, and rheumatoid arthritis

Revised Topic:
Compare the effectiveness of different strategies of introducing biologics into the treatment algorithm for inflammatory bowel disease (Crohn's disease, ulcerative colitis), with an emphasis on induction of treatment and maintenance (not acute flares).

TOPIC 5: Major Depressive Disorder

The comparative effectiveness of pharmacologic treatment versus (or in combination with) behavioral interventions in managing major depressive (unipolar) disorders in adults and adolescents in diverse treatment settings.

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION • Major depressive disorder (MDD) is a serious mental illness that persists and cause significant distress or interferes with a person's basic functioning. • In the United States, MDD ranks second among all diseases and injuries as a cause of disability.[1] • MDD is an illness that affects the body, mind, and thoughts. It is a mental disorder characterized by a depressed mood, diminished interest or pleasure, sleeping problems and tiredness, and negative thoughts. MDD affects the way patients feel about themselves and the people around them. • MDD can include a single episode or be recurrent. Also MDD can be mild, moderate, or severe and associated with psychotic features.
Relevance to patient-centered outcomes	SYMPTOMS An episode of MDD is a period lasting at least 2 weeks, with 5 or more of the following symptoms: • Depressed mood • Loss of interest or pleasure in any activities (i.e., anhedonia) • Insomnia or excessive sleeping • Significant weight loss or weight gain • Agitation • Fatigue or low energy • Decreased ability to concentrate, think, or make decisions • Thoughts of worthlessness or excessive or inappropriate guilt • Recurrent thoughts of death or suicidal ideation, or a suicide attempt OUTCOMES MDD has an impact on many physical, emotional, and social aspects of patients' lives including: • Emotions (e.g., depressed mood, feeling worthless, excessive guilt) • Employment issues (e.g., difficulty obtaining or keeping a job) • Interpersonal problems (e.g., relationship problems) • Quality and quantity of sleep • Increased risk of mortality, including suicide • Drinking or drug problems • Unhealthy weight (obesity or severe underweight) • Decreased physical functioning and pain (headaches, digestive disorders, chronic pain) • Slower recovery from physical illnesses
Burden on Society	
Recent incidence and prevalence in populations and	INCIDENCE (NEW CASES) & PREVALENCE (PROPORTION OF POPULATION LIVING WITH THE CONDITION) • In a given year, MDD affects approximately 14.8 million American adults (6.8% of the US population).[2]

subpopulations	• For children, 1-year prevalence of MDD is 8%, and the lifetime prevalence is 13%. Moreover, risk for depression increases during childhood.[3] • Among both children and adults,[4,5] the risk for developing depression is greater in females than males. • A history of an episode of major depression puts patients at a higher risk of having MDD in the future, compared with people without a prior history of MDD. • Patients with chronic medical conditions, like cancer, diabetes, and heart disease, are at greater risk of developing MDD.[6-9]
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	QUALITY OF LIFE • MDD has significant impacts on physical, emotional, interpersonal, and social functioning—all of which negatively affect quality of life. PRODUCTIVITY • MDD is a leading cause of work-related disability and lost work productivity.[10,11] Patients with MDD can feel irritable, fatigued, and have difficulty concentrating; all have an impact on the ability to work. Thus, untreated MDD can lead to significant absenteeism from work and overall lost productivity. • Compared with workers with other chronic medical conditions, people with MDD are more likely to keep working. Thus, depressive symptoms are associated with "presenteeism" or decreased job performance and at-work productivity as well.[12] • In the United States, depression-related productivity loss has been estimated at $2 billion per month.[13] FUNCTIONAL CAPACITY • Patients with MDD experience significant functional impairment; MDD is the second leading cause of disability in the United States.[1] MORTALITY • Patients with depression are at an increased risk of death compared to those without MDD (1.80-fold higher mortality risk).[14] • MDD is an independent predictor of mortality among those with heart disease.[15] • MDD is associated with an increased risk of suicide. Approximately 60% of suicide victims suffer from MDD (and other mood disorders).[16]
How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	Given the high prevalence of MDD and the impact on functional status, productivity, quality of life, and mortality, high priority should be given for optimizing treatments to reduce symptoms and improve functioning and quality of life.
Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the available management	Systematic reviews/available date: • There have been several recent, high-quality systematic reviews assessing strategies for treating MDD (see Management Options below for main findings). SCREENING/EARLY DIAGNOSIS • There are many validated tools available for depression screening. Also, there have been several initiatives to improve routine screening of depression in primary care settings and enhance training of primary care providers in appropriate evaluation and

options?	evidence-based treatment of MDD. • A diagnosis of MDD is made through a clinical interview and is characterized by a history of 1 or more major depressive episodes and no history of mania (or hypomania). • An episode of MDD is defined as 5 or more of the following symptoms for at least 2 consecutive weeks, and at least 1 symptom must be either depressed mood or loss of interest or pleasure: depressed mood; loss of interest or pleasure in most or all activities; insomnia or hypersomnia; significant weight loss or weight gain; psychomotor retardation or agitation; fatigue or low energy; decreased ability to concentrate, think, or make decisions; thoughts of worthlessness or excessive or inappropriate guilt; and recurrent thoughts of death or suicidal ideation, or a suicide attempt. TREATMENT • The goal of initial treatment for depression is symptom remission and restoring baseline functioning. Another major goal involves safety and managing risk around suicidal or self-harm behavior while working toward symptom remission and restoring baseline functioning. • Main treatments for people with MDD are psychotherapy (behavioral interventions like problem-solving therapy, cognitive behavior therapy, interpersonal therapy), pharmacotherapy (e.g., antidepressants), or both. • Severity of depression may be an important consideration; different treatments may be effective in patients with mild depression than severe depression. MANAGEMENT OPTIONS • Combination therapy (counseling and antidepressant medication) may be especially helpful for those who have severe depression or a history of recurrent depression. • Some studies have found that the benefits of pharmacotherapy alone compared with psychotherapy alone in depressed outpatients were comparable. Moreover, psychotherapy may be associated with lower risks or side effects compared with possible significant side effects of pharmacotherapy (e.g., diarrhea, sexual dysfunction, weight gain).[17] While psychotherapy has fewer risks than pharmacotherapy, it may not be risk-free, and psychotherapy has a burden of care (e.g., visits, time, expense) that may exceed that for pharmacotherapy. • The use of antidepressants alone had been studied more than combination treatment (i.e., antidepressants + psychotherapy) or psychotherapy alone. • Multiple reviews of different evidence-based psychotherapies (see Appendix for brief explanation of each type) demonstrate that:[18,19] ○ Psychotherapy improves depression over no treatment and is comparable to pharmacotherapy for initial MDD treatment. ○ Psychotherapy may have greater lasting effects post-treatment than pharmacological approaches.[20,21] ○ While no one psychotherapy has been demonstrated to be superior, a recent review of diverse psychotherapies found that interpersonal psychotherapy, cognitive behavior therapy (CBT), and behavior therapy (including problem-solving therapy) are efficacious. Brief dynamic therapy and emotion-focused therapy are possibly efficacious. CBT is efficacious and specific. Mindfulness-based cognitive therapy is efficacious. ○ Brief dynamic therapy and emotion-focused therapy are possibly efficacious in the prevention of relapse/recurrence following treatment termination, and interpersonal psychotherapy and CBT are each possibly efficacious in the prevention of relapse/recurrence if continued or maintained. ○ Overall, studies of psychotherapies have had small sample sizes and were of low

	quality, which reduce confidence in results.[22] ○ For patients with treatment-resistant depression (i.e., patients who have not responded to previous treatment for depression), no identified trials assess the comparative effectiveness of psychotherapy compared with pharmacotherapy, somatic therapies (e.g., electroconvulsive therapy), or other psychotherapies.[23]

What could new research contribute to achieving better patient-centered outcomes?	New research could contribute to achieving better patient-centered outcomes. Specifically, existing evidence does not allow for conclusions about the following questions: • What are the efficacies of some of the traditional psychotherapies? There are many randomized controlled trials of psychological interventions that evaluate the efficacy of newer interpersonal or CBT treatments—yet little is known about the efficacy of more traditional dynamic or experiential–humanistic approaches (e.g., Gestalt therapy), in which psychological illness is a result of the alienation, lack of genuine meaning, and loneliness of the modern world. Even for well-studied modalities, more comparative effectiveness research is needed that directly compares two treatment strategies. Many studies have allowed co-treatments to vary, which make conclusions difficult to draw about the direct benefits of one treatment versus another. • Could brief psychotherapies be developed that would lend themselves to implementation in primary care? Could these brief psychotherapies be delivered by primary care providers or other trained providers with the same comparative effectiveness as those delivered by mental health professionals? • Do treatments differ in effectiveness for specific groups? Few studies explore how effects differ by key subgroups (e.g., sex, age, baseline depression severity, chronicity of depression). Do certain patient characteristics increase the chances of responding to specific treatments? • How do medical and psychiatric comorbidities that are common with MDD affect treatment in community patients with MDD where these comorbidities are common? • Do treatments mapped to patient preferences (e.g., after a shared decision making process) lead to better outcomes? • What are the most important patient-centered outcomes in treating MDD, and what trade-offs are patients willing to make to avoid use of medications and their possible side effects? • Does appropriate evidence-based treatment provided earlier in the course of an initial episode of MDD reduce the risk of chronic, recurrent episodes and associated poor outcomes? • Often, treatments used for MDD are based on availability of treatments and provider comfort rather than on patient preferences for treatment choices. Thus proven, evidence-based treatments are often unavailable to patients. How do patients choose treatments when choice may be limited by availability? • How do the effects of psychotherapy delivered in the real world compare with effects seen in carefully controlled trials? • What are the best nonpharmacological approaches for patients with difficult-to-treat MDD? What is the optimal sequence of treatments after a patient has not responded to initial treatments? Comparative research on nonpharmacologic interventions for treatment-resistant depression is relatively new. In a recent AHRQ review, no identified trials assessed the comparative effectiveness of psychotherapy compared with pharmacotherapy, procedures such as electroconvulsive therapy, or other psychotherapies. Many clinical questions about efficacy and effectiveness remain unanswered.[23] • How many trials of medications are needed before switching to therapy or using combination therapy? • What is the role of other nonpharmacological approaches (e.g., self-help, exercise, mind-body interventions) in conjunction with psychotherapy and pharmacotherapy? • Are the effects of treatment maintained after treatment stops, and if so for how long? What is the optimal duration or number of treatments needed to achieve meaningful outcomes for patients? Do these differ by key patient characteristics? • Does the comparative strength of treatment approaches vary based on the phase of

	treatment (e.g., acute vs. followup phase)? • What are the comparative risks of adverse effects for psychological treatments? Few studies expressly assess adverse outcomes of approaches that do not include medications or procedures. • When designing for wide implementation, what are the common factors and elements of health care delivery systems, providers, patients, and treatment strategies that produce positive outcomes or help sustain change? For example, many psychotherapies include common underlying components or elements that contribute to effectiveness such as psychoeducation, patient and family engagement, goal setting, communication skills, activity scheduling, self-monitoring, or relapse prevention. What are these key elements?
Have recent innovations made research on this topic especially compelling?	Recent innovations: • There is increasing interest in delivery of psychotherapy over the Web. This is a delivery platform that warrants further testing. • There are some new somatic therapies that may show promise for treating patients with difficult-to-treat MDD, such as deep-brain stimulation or magnetic seizure therapy. • Recently, the FDA has approved atypical antipsychotics as an adjunctive treatment for depression; however, there are no long-term trial data to assess adverse effects or studies when used for MDD. • Fostering comparative effectiveness research in this area would be compelling because of the high burden of disease, especially among certain subgroups, and the large impact on patient-centered outcomes (quality of life, functional ability). • For patients with difficult-to-treat MDD, there is very little evidence on nonpharmacological approaches to treatment, including comparative risk of adverse effects.
How widely does care now vary?	VARIABILITY IN CARE • There is high variability in care. • Most patients seek treatment in primary care[24] where antidepressants are the most commonly prescribed treatments.[25] • Only about half of people with depression seek treatment, so the risk of undertreatment is substantial.[26] • Of those who seek treatment, only 20% receive adequate treatment using evidence-based treatment guidelines.[26] • Despite undertreatment, there may be an excessive use of antidepressants for mild cases of MDD[27] as many of the trials of antidepressants were among those with severe depression and not the milder forms to MDD more commonly seen in primary care.
What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	RECENT PUBLICATIONS • MEDLINE search from 2009 through 2014 yielded a total of 1138 citations: o 305 were labeled as randomized controlled trials/therapy. o 111 were labeled as meta-analyses or systematic reviews. ONGOING TRIALS • There are at least 220 ongoing studies listed in www.clinical.trials.gov (using the search terms major depressive disorder AND behavior AND drug): o Intervention: ✓ Most of these trials are drug vs. drug, or drug vs. placebo. ✓ Only 9 appear to be ongoing studies of pharmacologic treatment vs. psychological interventions.
How likely is it that new CER on this topic would	KEY UNCERTAINTIES IN CLINICAL DECISION MAKING • What treatment or combination of treatments works best for key subgroups of

provide better information to guide clinical decision making?	patients? • For patients who do not respond to initial treatments, what is the best sequence of treatments? • For patients who do not respond to initial treatments, what nonpharmacological approaches are effective? • What is the optimal duration or treatment approach to maintain treatment gains in patient-centered outcomes? • What are effective strategies to foster long-term adherence to treatments, such as ways to organize care (e.g., collaborative care models), innovations to deliver established care (e.g., Web-based therapies), or preference-matching approaches (e.g., shared decision making)? • What are the comparative benefits and harms of different psychological interventions? LIKELIHOOD THAT CER WOULD BE ABLE TO REDUCE THESE UNCERTAINTIES There is a high likelihood that appropriately designed comparative effectiveness studies would be able to effectively address these and other areas of uncertainty. • Understanding the best interventions in this area could improve care and outcomes by establishing a set of "best practices" to be employed in health care and community settings. • There is little available evidence about which patients do best with what treatments; CER in this area could help patients and providers to better select strategies according to patient characteristics.
Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that would affect the implementation of new findings in practice?	FACILITATORS • Relatively high prevalence with wide impact on patient quality of life, functioning, and productivity. • Evidence from previous studies that obtaining treatment improves outcomes. Thus, there are already evidence-based interventions for patients with MDD. These "off-the-shelf" programs can be adapted to different settings and patient groups and can be readily used in comparative effectiveness research and implementation research. BARRIERS • Lack of treatment-seeking by affected individuals • High variability in care • Lack of access to evidence-based treatments, particularly evidence-based psychotherapies, which vary by geographic location
How likely is it that the results of new research on this topic would be implemented in practice right away?	• Several professional societies have developed guidelines for the care and management of MDD, and there is agreement about the core components of these recommendations. However, there is a need to give providers specific guidance on when each management strategy may be appropriate for patients. • Patient-based research that compares the effectiveness of different therapies is likely to be implemented right away if there are improvements in outcomes that are easy to achieve and can be customized to the individual patient across diverse settings. • In contrast, implementing different ways to organize or deliver care is likely more difficult to implement—yet could be equally important.
Would new information from CER on this topic remain current for several years, or	CER priority areas that seek to identify which interventions, combinations of interventions, or sequence of interventions work best for which patients are needed. These types of findings are not likely to become obsolete quickly.

would it be rendered obsolete quickly by subsequent studies?	

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APPENDIX: TOPIC QUESTION

Compare the effectiveness of pharmacologic treatment versus (or in combination with) behavioral interventions in managing major depressive (unipolar) disorders in adults (and adolescents) in diverse treatment settings.

Types of Psychotherapies

Cognitive therapy: This therapy is largely based on the cognitive model, which states that an individual's perception of a situation influences his or her emotional response to it. The general goal of cognitive therapy is to help people identify distorted thinking and to modify existing beliefs, so that they are better able to cope and change problematic behaviors. Cognitive therapy is generally considered to be brief, goal-oriented, and time-limited.

Cognitive behavioral therapy (CBT): This is a broad category of therapies based on principles of learning and conditioning and/or cognitive theory to treat disorders. CBT includes components from both behavioral and cognitive therapy. In CBT, components such as exposure, cognitive restructuring, and various coping skills are used either alone or in combination. Most forms of CBT consist of a minimum of 8 to 12 weekly sessions lasting 60 to 90 minutes. CBT can be administered either as group or individual therapy.

Interpersonal psychotherapy (IPT): This is a time-limited psychotherapy that focuses on interpersonal issues, which are understood to be a factor in the genesis and maintenance of psychological distress. The targets of IPT are symptom resolution, improved interpersonal functioning, and increased social support. Typical courses of IPT range from 6 to 20 sessions with provision for maintenance treatment as necessary.

Behavior therapy: This is a group of treatments that helps change potentially self-destructive behaviors. Behavioral approaches vary; however, they focus mostly on how some thoughts or behaviors may accidentally get "rewarded" within one's environment, contributing to an increase in the frequency of these thoughts and behaviors. Typical courses of treatment range from 6 to 20 sessions.

Brief dynamic therapy: This is a time-efficient treatment in which the therapist maintains a focus on specific client issues and goals, all within a basic psychodynamic conceptual framework. Many different approaches fit this general definition, but each shares the brief dynamic characteristics of time management, defined focus, circumscribed goals, active therapist participation, rapid assessment, prompt intervention, an awareness of unconscious processes, and techniques that quickly foster a strong alliance with the client.

Emotion-focused therapy: A major underpinning of this approach is that emotion is fundamental to the construction of the self and is a key determinant of self-organization. Emotions are framed as a way to rapidly alert patients to situations important to advancement and to prepare/guide patients in these important situations to take action toward meeting their needs. Patients undergoing emotion-focused therapy focus on ways to better identify, experience, explore, make sense of, transform, and flexibly manage their emotional experiences. This therapy is usually a short term (8 to 20 sessions).

TOPIC 6: Nonsurgical Treatment for Cervical Disc and Neck Pain

Compare the effectiveness of nonsurgical treatment strategies (e.g., pharmacologic treatment and physical therapy) in delaying or preventing surgery for cervical disc and neck pain.

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION • Neck pain is a common, bothersome, and potentially debilitating problem. • Most neck pain results from problems affecting the structures of the cervical spine, which include the 7 cervical vertebrae, the pads between them (intervertebral discs), and the other joints between the vertebrae. o Neck pain can also result from other nonspinal disorders, which will not be addressed in this brief. o Acute trauma-related neck pain likewise will not be discussed. • Options for addressing neck pain depend greatly on its cause and chronicity. o Only a minority of people with neck pain seek healthcare; seeking care is likely determined by multiple factors, including perceived pain severity, speed of onset, presence of trauma at onset, previous experience, costs, and availability of care.[1] o When neck pain causes chronic symptoms, it becomes necessary to consider the full range of management options.
Relevance to patient-centered outcomes	SYMPTOMS[1] • Pain symptoms originating from the cervical spine typically cause neck pain or pain/weakness/sensation changes in the shoulders or arms. o Problems that primarily cause neck pain include: ▪ Cervical strain (injury to cervical ligaments and muscles) ▪ Discogenic pain (from injury to the pads between the vertebrae) ▪ Cervical facet pain (from injury or inflammation in the “facet joints” between vertebrae) [see Appendix for figure of the cervical vertebrae anatomy] ▪ Cervical "whiplash" syndrome (traumatic injury resulting from motor vehicle collision or sports-related injuries) o Disorders that primarily cause symptoms in the shoulders or arms include: ▪ Cervical radiculopathy (pain due to pressure on nerves that emerge from the spinal cord and pass between vertebrae) ▪ Cervical spondylotic myelopathy (pain due to pressure on the spinal cord resulting from degenerative problems in the vertebrae and discs) • Neck pain that is severe enough to cause patients to seek care can be graded using the following system: o Grade I: No signs of major pathology and no (or little) interference with daily activities. This is frequently the case for patients, and reassuring them might be all that is required. o Grade II: No signs of major pathology, but interference with daily activities. This occurs less frequently (<10% of people report having experienced this severity of pain during the previous year). Clinical intervention may be sought to decrease symptoms. o Grade III: Neck pain with neurological signs or symptoms (radiculopathy). This is uncommon, but may require specific tests and treatments. o Grade IV: Neck pain with signs of major pathology (e.g., serious instability or spinal infection). This is rare but might require urgent tests and treatments. OUTCOMES[2,3] • Though many patients have full resolution, neck pain can be a disabling condition

	with a course marked by periods of remission and exacerbation. ○ Up to a third of patients with neck pain report ongoing problems with pain that do not resolve after 1 year. • Clinical prediction rules can help identify patients that are likely to develop chronic neck pain.
Burden on Society	
Recent incidence and prevalence in populations and subpopulations	INCIDENCE (NEW CASES)[4] • Neck pain incidence varies depending on the definition used: ○ Incidence of survey-reported new neck pain is 146 to 179 per 1000 person-years. ○ Incidence of healthcare visits for new neck pain is 15.5 to 78.5 per 1000 person-years. ○ Incidence of diagnosed disc herniation with radiculopathy is 0.055 per 1000 person years. PREVALENCE (PROPORTION OF POPULATION LIVING WITH THE CONDITION)[4] • Neck pain prevalence also varies depending on the definition used: ○ 12-month prevalence of any neck pain ranges from 12.1% to 71.5% for adults. ○ 12-month prevalence of activity-limiting neck pain for adults is 1.7% (limited ability to work); 2.4% (limited social activities); and 11.5% (limited activities overall). • Neck pain prevalence peaks in middle age and is higher among women than men. • Though some studies have demonstrated an association between neck pain prevalence and employment/lower education, most show no association between neck pain and socioeconomic status. • Other risk factors for neck pain include poor psychological health (e.g., depressed mood) and exposure to tobacco.
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	QUALITY OF LIFE[5] • Neck pain is associated with significantly decreased quality of life as demonstrated by validated scales. • Depressive symptoms are much more common among sufferers of neck pain than the general population. PRODUCTIVITY[6] • In one large cohort of nurses and midwives with neck pain, 19% reported taking sick leave for this issue within the prior year. Factors contributing to this loss of productivity included severity of pain and fear of movement. FUNCTIONAL CAPACITY[5] • In a study using the Neck Disability Index, 87% of neck pain sufferers reported at least moderate disability, and 55% reported at least severe disability. MORTALITY • Common causes for neck pain are unlikely to result in mortality.
How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• While many cases of neck pain are self-limited, the condition can be devastating for those who develop persistent or chronic symptoms. • Evaluation of treatment options for neck pain has already been identified as a high priority area for comparative effectiveness research by the Institute of Medicine.[7]
Options for Addressing the Issue	

Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	DIAGNOSIS[8]
	• Clinical evaluation consists of a history and physical exam that evaluate "red-flag" symptoms that might necessitate further radiographic evaluation.
	  ○ Red-flag symptoms include trauma, symptoms of spinal cord compromise (pain/weakness/sensory loss in arms/legs, incontinence of bowel/bladder), fever or other signs of infection, history of cancer, severe pain with tenderness palpable over the spine, or prior neck surgery.
	• Radiographic evaluation is indicated with red-flag symptoms, advanced age, or persistent pain.
	  ○ X-rays are relatively insensitive though may show vertebral fractures, evidence of significant spinal misalignment, loss of disc height suggestive of disc herniation, or facet joint arthritis.
	  ○ CT and MRI are more sensitive for disc herniation, spinal cord compression, infection, and malignancy.
	  ○ Of note, the extent to which radiographic findings correlate with clinical neck pain is highly variable; patients with severe cervical spine degeneration may have minimal symptoms, while others with normal radiographic findings may report severe pain.[4,9]
	
	TREATMENT[10,11]
	• The goals of treatment for neck pain are:
	  ○ To reduce pain and muscle spasm
	  ○ To reestablish normal cervical alignment
	  ○ To improve functionality
	• Most cases of neck pain improve within a few weeks with conservative management.
	• For patients whose pain does not improve, more aggressive treatment is warranted.
	
	MANAGEMENT OPTIONS[10,11]
	• Pharmacotherapy:[12]
	  ○ Compared with back pain, there appear to be relatively few comparative effectiveness data for pharmacologic neck pain treatments.
	  ○ Preferred options appear to include acetaminophen and nonsteroidal anti-inflammatory drugs.
	  ○ Muscle relaxants and narcotics are options for acute pain relief, but should not be used indefinitely.
	• Nonpharmacologic, noninvasive management:
	  ○ Options include physical therapy, massage therapy, manual therapy (spinal manipulation), transcutaneous electrical nerve stimulation, acupuncture, electromagnetic therapy, Qigong (e.g., Tai Chi), low-level laser therapy, and cognitive behavioral therapy.
	  ○ One systematic review suggests that manual therapy, supervised exercise interventions, low-level laser therapy, and perhaps acupuncture are more effective than no treatment, sham, or alternative interventions; however, none of the active treatments was clearly superior to any other in either the short- or long-term.[10]
	• Injections:
	  ○ Options include epidural corticosteroid injections, cervical facet joint injections, radiofrequency neurotomy, cervical medial branch blocks, trigger point injections, and botulinum toxin injections.
	  ○ There is evidence for short-term symptomatic improvement of neck pain with radicular symptoms with epidural corticosteroid injections.

	○ One systematic review suggests that cervical facet joint injections and radiofrequency neurotomy for neck pain without radiculopathy are not supported by current evidence.[11] ○ There is limited evidence available for cervical medial branch blocks, trigger point injections, or botulinum toxin injections. • It is unclear whether surgical treatments like cervical fusion and cervical arthroplasty improve long-term outcomes for neck pain (with or without radicular symptoms) compared with nonoperative approaches, though relief may be achieved in some cases of cervical radiculopathy.
What could new research contribute to achieving better patient-centered outcomes?	New research could contribute to achieving better patient-centered outcomes: • Given the apparent lack of rigorous comparative effectiveness research in the area of pharmacologic and nonpharmacologic (including noninvasive and invasive strategies) treatments for neck pain, it is likely that new research would be helpful in better defining the impact of the many available interventions on patient-centered outcomes. • Additionally, research to better understand relevant patient-centered outcomes may be needed. • An updated comparative effectiveness review may also be helpful to better define the landscape of the current evidence base ○ The last review comprehensively comparing non-surgical approaches to neck pain treatment was done in 2008; systematic reviews (including Cochrane reviews) evaluating individual techniques have been done since although have not been comparative between interventions.
Have recent innovations made research on this topic especially compelling?	Recent innovations: • The arsenal of nonpharmacologic treatment strategies for neck pain is increasing in size but is doing so in the absence of rigorous comparative effectiveness research. Thus, this would be a compelling area for new research.
How widely does care now vary?	VARIABILITY IN CARE • It appears that the use of various nonpharmacologic treatment strategies for neck pain varies widely depending on what options are available locally. • For example, use of spinal manipulation in older adults in different regions is highly correlated with the availability of chiropractors.[13]
What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	RECENT PUBLICATIONS • A search of PubMed from 4/8/09 through 4/8/14 yielded a total of 2,390 publications, including: ○ 185 randomized, controlled trials ○ 90 systematic reviews/meta-analyses ONGOING TRIALS • A search of www.clinicaltrials.gov showed 90 potentially relevant ongoing studies. ○ Most studies are small (<100 patients) and don't compare across modes of nonsurgical treatments
How likely is it that new CER on this topic would provide better information to guide clinical decision making?	KEY UNCERTAINTIES IN CLINICAL DECISION MAKING[14] In 2008, a task force laid out a series of evidence gaps and research priorities relating to neck pain, including: • Understanding the actual course of neck pain and determinants of that course. • Investigations of modifiable risk and prognostic factors in neck pain. • Studies on the course and prognostic factors of neck pain in children. • How to prevent neck pain–related activity limitations and/or disability. • Good-quality studies testing the widespread view that degenerative disc changes are risk factors for onset of neck pain and are prognostic of recovery for patients with neck pain.

	• How physical, psychological, and societal factors interact in both the risk of neck pain and recovery from neck pain. • Studies directly examining cultural factors in the onset or prognosis of neck pain, or studies directly comparing neck pain incidence, risk factors, or prognosis across cultures. • Understanding the role of work-related vibration (such as use of a jack hammer) or long hours of work-related driving (such as driving a truck or bus) in risk or prognosis of neck pain. LIKELIHOOD THAT CER WOULD BE ABLE TO REDUCE THESE UNCERTAINTIES There is a high likelihood that appropriately designed randomized comparative effectiveness trials would address these areas of uncertainty.
Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that would affect the implementation of new findings in practice?	FACILITATORS • The high frequency of neck pain symptoms in clinical practice would make this a high priority for practitioners and healthcare organizations. • There is an expanding number of possible interventions for neck pain, which would clearly benefit from comparative effectiveness research. • While systematic review may help better establish the current research landscape, several areas of uncertainty have been fairly well-outlined by prior reviewers[14] BARRIERS • Interventions may have different effects in different populations (e.g., workers vs. nonworkers, claimants vs. nonclaimants, litigants vs. nonlitigants), and intervention effects may also vary by type of outcome measure (e.g., pain, disability, global improvement, return to work) and by follow-up time (e.g., days, weeks, months, years).[10] • The high number of nonpharmacologic options may complicate study design. • Treatment options for neck pain are aligned with different professional disciplines (e.g., acupuncture, physical therapy, spinal manipulation); existing referral patterns and availability of providers may limit implementation of new comparative effectiveness research.
How likely is it that the results of new research on this topic would be implemented in practice right away?	EVIDENCE OF BENEFIT • Findings are likely to be implemented widely if there is evidence for better patient-centered outcomes. EVIDENCE OF NO BENEFIT OR HARM • It is likely that research demonstrating no evidence for benefit would also have an impact on practice by supporting current practice.
Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies?	Although nonsurgical treatment options for cervical disc and neck pain continue to evolve, it is likely that new information regarding the effects of available treatments on patient-centered outcomes in different populations would remain relevant for years.

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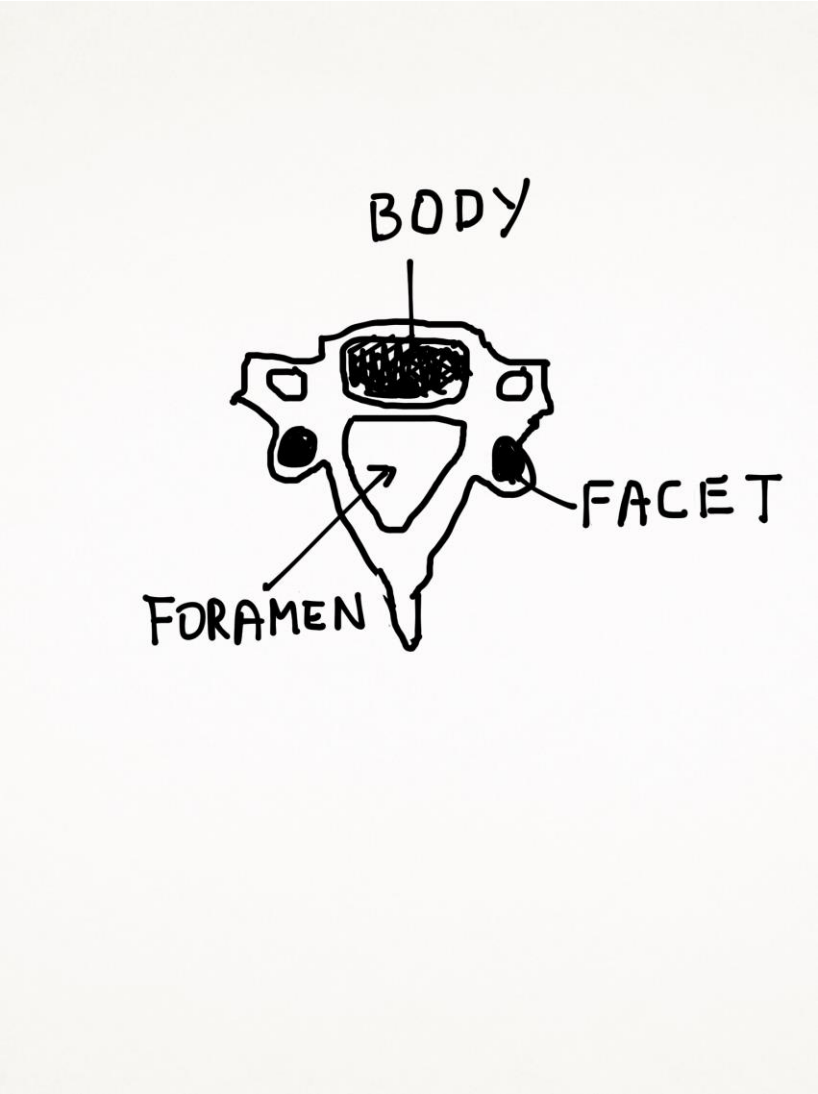
APPENDIX: TOPIC QUESTION

Proposed Topic:
Compare the effectiveness of treatment strategies (e.g., artificial cervical discs, spinal fusion, pharmacologic treatment with physical therapy) for cervical disc and neck pain.

Revised Topic:
Compare the effectiveness of nonsurgical treatment strategies (e.g., pharmacologic treatment and physical therapy) in delaying or preventing surgery for cervical disc and neck pain.

Cervical Vertebrae Anatomy:



TOPIC 7: Renal Replacement Therapies

Compare the effectiveness of peritoneal dialysis versus hemodialysis on survival, quality of life, hospitalization, and costs in different patient subgroups.

Criteria	Brief Description
Introduction	

Overview/definition of topic	DESCRIPTION OF CONDITION[1]
	• Chronic kidney disease (CKD) is defined as the presence of kidney damage (usually detected by excess protein in the urine) or decreased kidney function (measured using the estimated glomerular filtration rate or eGFR) for 3 or more months.
	  o CKD is distinct from acute kidney injury (AKI). Although these conditions may overlap, AKI may have different causes and usually resolves with appropriate treatment.
	• End-stage renal disease (ESRD) is the final stage of CKD, when symptoms of kidney failure require patients to undergo dialysis or transplantation.
	• There are many potential causes of CKD and ESRD, with common causes including diabetes (44% of cases) and hypertension (28%), and less common causes including glomerulonephritis (6%) and polycystic kidney disease (2%).[2]
	• In earlier stages of CKD, progression to ESRD can be slowed or prevented.
	• Once ESRD is present, renal replacement therapy must be initiated to preserve life. The most common types of renal replacement therapy are:
	  o Hemodialysis (HD)—After placement of a fistula or graft in the arm or a catheter in a large vein, approximately 1 pint of blood is in constant circulation in a dialysis machine. Toxins and extra fluid are removed in this manner for usually 4 hours every other day.
	  o Peritoneal dialysis (PD)—A catheter is placed in the abdomen, allowing a special fluid to be instilled into the peritoneal space of the abdomen, which helps filter the blood, and then the fluid is drained. Usually patients undergo peritoneal dialysis every night while they sleep aided by a specialized device called a "cycler."
	  o Renal transplantation—Surgery is performed to implant a kidney from a deceased or living donor.
	  o HD is the predominant dialysis modality with 9 out of 10 patients undergoing HD as opposed to PD. Use of PD varies greatly regionally in the US and in international comparison. This is due to nephrology practice patterns, availability of in-center HD clinics, compensation for service, and patient attitudes.

Relevance to patient-centered outcomes	SYMPTOMS
	• In its earlier stages, CKD is asymptomatic.
	• As CKD advances, different symptoms and signs may develop, which reflect loss of the normal functions of the kidney:
	  o Fluid overload leading to leg swelling and difficulty with breathing
	  o Life-threatening imbalances of electrolytes like potassium and calcium
	  o Acidosis, or buildup of acid in the blood
	  o Anemia, or low red blood cell levels leading to weakness and fatigue
	  o Loss of bone strength
	  o Buildup of toxins that are normally disposed of by the kidney, which leads to "uremia" (may cause poor appetite, nausea/vomiting, confusion, coma, and other symptoms)
	
	OUTCOMES
	• Patients with CKD and ESRD are at higher risk for heart disease, including heart attacks and arrhythmias, hospitalizations, and death.[3]

	○ This risk is high enough that having CKD/ESRD is considered a coronary disease risk equivalent.[4] • Mortality[2] ○ CKD is an independent risk factor for all-cause and cardiovascular mortality.[5] ○ Though mortality rates have declined in the prevalent dialysis population over the past few decades, adjusted rates of all-cause mortality are 6.5-7.9 times greater for dialysis patients than for individuals in the general population. ○ Among those starting ESRD therapy in 2006, only 52% of HD patients and 61% of PD patients were still alive 3 years after starting dialysis.
Burden on Society	
Recent incidence and prevalence in populations and subpopulations	INCIDENCE (NEW CASES)[2] • According to the 2013 U.S. Renal Data System (USRDS) Annual Data Report, the incidence of ESRD in 2011 was 357 per million in the United States. ○ Overall, the ESRD incidence rate fell 3.8% in 2011 after remaining stable through the 2000s. This decrease is assumed to be due to the turning tide on early starts of renal replacement therapy and that the nephrology community embraces "conservative" measures more readily—rather than the clinical field reducing the ESRD epidemic. ○ The ESRD incidence rate in 2011 varied by race (White: 280 per million, Black/African American: 940, Native American: 453, Asian: 399) and ethnicity (518 for Hispanic patients, 1.5 times the rate for non-Hispanic patients). PREVALENCE (PROPORTION OF POPULATION LIVING WITH THE CONDITION)[2] • According to the 2013 USRDS Annual Data Report, the prevalence of ESRD by the end of 2011 was 1,901 per million in the U.S. ○ Overall, the ESRD prevalence rate increased by 1.3% in 2011, the slowest growth in 30 years. ○ The ESRD prevalence rate in 2011 varied by race (White: 1,395 per million, Black/African American: 5,583, Native American: 2,701, Asian: 2,265) and ethnicity (2,818 for Hispanic patients, higher than the rate for non-Hispanic patients).
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	QUALITY OF LIFE[6,7] • In general, patients with CKD and ESRD have lower quality of life than other patients, but renal replacement therapy improves quality of life in ESRD. ○ Although kidney transplant patients consistently appear to have higher quality of life than dialysis patients, differences in quality of life between patients on HD compared with PD are less clear. PRODUCTIVITY[8] • On adjusted analysis of individuals on renal replacement therapy, patients with kidney transplants had the highest rates of employment, followed by those on PD, and those on home HD. Patients on in-center HD had the lowest rates of employment. FUNCTIONAL CAPACITY[9] • A systematic review of 46 studies suggested that kidney transplant patients may experience better rates of participation in life activities when compared with dialysis patients, whereas HD patients and PD patients may experience similar rates. MORTALITY[2,10,11] • The rate of all-cause mortality is 6.3 to 8.2 times greater for dialysis patients compared with the general population. • Mortality does not appear vary by gender, but does appear to vary by race. ○ 5-year survival on dialysis is 42% among African Americans, but only 34% among

	White patients. • Data on the relative effects on mortality of HD, PD, and transplantation are variable and conflicting. o Patients on PD may have a slight overall survival advantage compared with those on HD during the first 3 years of therapy; however at 5 years, survival appears to be equal (about 34%). o Nonrandomized comparisons of PD and HD are difficult to interpret due to systematic differences between patients on PD and HD (e.g., in comorbid diseases)[12] and between-study differences in design, time from initiation of dialysis, and comorbidities. o Additionally, the benefits of PD may vary depending on patient factors like age and the presence of heart failure, further confounding comparisons.
How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• The prevalence of ESRD requiring dialysis continues to grow, and dialysis patients have significant reductions in quality of life, productivity, functional status, and survival. o African-American, Native American, and Hispanic patients appear to be disproportionately affected by ESRD in the U.S. • ESRD is extremely costly to the U.S. healthcare system. o Total healthcare expenditures for ESRD in 2011 were $49.3 billion ($34.9 billion for Medicare, which automatically covers anyone with ESRD requiring dialysis or kidney transplant). o By dialysis type, Medicare expenditures for ESRD in 2011 were: ✓ $87,945 total Medicare expenditures per person per year for HD ✓ $71,630 total Medicare expenditures per person per year for PD ✓ $32,922 total Medicare expenditures per person per year for transplantation • This substantial public health impact led the Institute of Medicine (IOM) to designate comparison of treatment strategies for ESRD as a priority area for comparative effectiveness research.[13]
Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	SCREENING/EARLY DIAGNOSIS[2] • Early identification of CKD is possible using standard lab testing, and it is crucial because it allows the initiation of treatments to help prevent CKD from progressing to ESRD. TREATMENT • After CKD has progressed to ESRD, it is necessary to replace the normal functions of the kidney. • As described above, the main options for renal replacement therapy are HD, PD, and renal transplantation. • Recently, nondialytic or palliative regimens for ESRD have gained traction, particularly in the elderly. MANAGEMENT OPTIONS[2] • As of 2011, 615,899 patients were receiving treatment for ESRD in the U.S.; 430,273 were on dialysis and 185,626 had a functioning kidney transplant. o The number of patients starting dialysis in 2011 was 112,788. o In contrast, 2,855 patients received a kidney transplant as their first ESRD treatment (this does not include patients receiving a kidney transplant after initiating dialysis). • Of the 430,273 patients receiving dialysis as of 2011, approximately 92% were receiving HD and 8% were receiving PD. o Although the proportion of patients starting PD as their first-line treatment for ESRD is slowly growing in the U.S., the utilization of PD lags well behind most

	developed countries.[15] ○ PD in the U.S. is less costly than HD (total per patient Medicare expenditures in 2011 were $87,945 for HD patients vs. $71,630 for PD patients). ○ Rates of PD use are lower in African American and Native American patients compared with White patients. ○ 5,535 patients receive home HD—a number that continues to grow.
What could new research contribute to achieving better patient-centered outcomes?	New research could potentially improve patient-centered outcomes in ESRD treatment by informing choice of dialysis modality (e.g., HD vs. PD) in different populations, reducing racial and ethnic disparities in use of different ESRD treatments, and exploring the impact of emerging approaches to care (e.g., continuous cycling PD, home HD) on patient-centered outcomes.
Have recent innovations made research on this topic especially compelling?	Recent innovations: • HD and PD technologies continue to evolve, and options for dialysis are expanding—further increasing the need for patient-centered outcomes research. ○ In HD, home-based therapy is increasing in use and may be an alternative to traditional in-center HD. ○ In traditional continuous ambulatory PD, fluid in the peritoneal cavity needs to be manually exchanged ~4 times daily, but alternatives have emerged, such as continuous cycling PD (where a machine continually exchanges the fluid in the peritoneal cavity over 10-12 hours including overnight during sleep).
How widely does care now vary?	VARIABILITY IN CARE • Clear racial and ethnic disparities exist in ESRD, both in terms of incidence and prevalence and in terms of utilization of available therapeutic options[2]
What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	RECENT PUBLICATIONS • A MEDLINE search from 3/28/2009 through 3/28/2014 yielded a total of 3,125 citations potentially relevant to the effectiveness of renal replacement therapy (both HD and PD) on survival, hospitalization, quality of life, and costs in patients of different ages, races, and ethnicities. ○ 153 were labeled as randomized controlled trials/therapy. ○ 120 were labeled as meta-analyses or systematic reviews. ONGOING TRIALS • A search on www.clinicaltrials.gov for open studies that included both HD and PD found 36 trials. Of those: ○ 18 are believed to contain interventions and collect outcomes that address the research question. ○ One ongoing trial ("Survival on Peritoneal Dialysis (PD) Versus Hemodialysis (HD) in China") is a large trial randomizing patients (target 1,370) to HD versus PD, powered to detect a mortality differences. Note that a similar trial failed in the Netherlands several years ago because patients refused to be randomized to either modality; instead, they felt strongly one way or the other after screening. This ongoing trial could answer the ultimate question if one modality (PD or HD) is superior, even though the nephrology community has probably settled that both modalities are likely similar in regard to outcomes. This trial is targeted to be completed in August 2016.
How likely is it that new CER on this topic would provide better information to guide clinical decision	KEY UNCERTAINTIES IN CLINICAL DECISION MAKING • Donated kidneys are scarce, so most patients with ESRD receive dialysis, and so selecting the most appropriate dialysis modality for a given patient is crucial. ○ This selection depends on understanding patient-centered outcomes with each modality • There is evidence that PD is less costly than HD, and may be associated with reduced mortality and higher productivity and quality of life compared with HD

making?	(because PD does not need to be done at a dialysis center). o However, PD is underutilized in the U.S. compared with other developed countries, and understanding barriers and facilitators to increasing PD use will be crucial. • There are racial and ethnic disparities not only in rates of ESRD in the U.S, but also in use of PD and renal transplant. For example, African American patients are less likely on a per-patient basis to receive PD and transplant than White patients o Understanding barriers and facilitators to equitable use of PD and renal transplantation is an important area of research. • Home HD may hold promise for improving quality of life and other outcomes and is a potentially valuable area for patient-centered outcomes research. LIKELIHOOD THAT CER WOULD BE ABLE TO REDUCE THESE UNCERTAINTIES • There is a high likelihood that appropriately designed comparative effectiveness studies would be able to effectively address these and other areas of uncertainty. • There are however several barriers to having feasible HD vs PD comparative effective studies. These include: o Close to all patients can undergo in-center HD. However, not all patients can undergo PD, there are medical and psychosocial contraindications. o Randomization to either PD or HD in a trial comparing the two is difficult o This occurred in a large Dutch trial, which was able to recruit some 5% of patients screened and eligible. This is because informed patients have strong opinions as to what they want to do as it pertains to dialysis modality, hence, opt out if randomization is not in their favor. o There are huge differences between HD and PD and how this impacts patients and which patients prefer which treatment. The biggest difference is that HD suits a passive patient who does not want to deal with the challenge of learning a technique, and who prefers the safety of a HD clinic. PD patients in contrast are proactive and independent, and thrive on the challenge of making PD at home work. • Note that PD is currently underutilized in the US for the following reasons: o The compensation structure in the last two decades favored in-center HD. Given that 90% of dialysis patients are being cared for by for-profit HD providers, underutilization of PD was driven by financial disincentive. o Given that PD utilization was low over the last two decades, nephrologists did not have the opportunity to train in a PD friendly environment, hence, did not learn to do it well. If you can't do something well, you don't do it and less exposure occurs.
Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that would affect the implementation of new findings in practice?	FACILITATORS • ESRD has a high prevalence, causes substantial morbidity and mortality, is extremely costly, and is already considered a high-priority condition. • Many treatment strategies exist for ESRD, all of which may affect quality of life and other patient-centered outcomes in different ways. o Treatment of ESRD is automatically covered by Medicare, so availability should not be an issue regardless of patient resources. • Racial and ethnic disparities exist, both in rates of ESRD and utilization of treatment options. • Given the wide range of available treatment options and remaining areas of clinical uncertainty, CER in the area of treatment for ESRD is likely to have an important impact. BARRIERS

	• In-center HD is by far the most common strategy for treating ESRD, and there may be inertia leading to continued utilization of this approach. • Many factors may complicate the design of comparative studies, such as the types of HD catheters used and different types of PD. Note that the biggest game changer in terms of incidence/prevalence for the use of PD is the "bundled payment system for dialysis services" by the Centers for Medicare and Medicaid (CMS), which was introduced several years ago. This new payment system offers a monetary incentive for large dialysis providers to increase penetrance of PD. This change is having a tremendous impact on the dialysis landscape in the U.S.
How likely is it that the results of new research on this topic would be implemented in practice right away?	EVIDENCE OF BENEFIT • Findings would be likely to be implemented widely if there is evidence for better patient-centered outcomes. EVIDENCE OF NO BENEFIT OR HARM • It is likely that research demonstrating no evidence for benefit would also impact practice by supporting current practice.
Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies?	Although technologies continue to evolve, it is likely that new information regarding use of PD vs. HD and resultant patient-centered outcomes in different populations would remain relevant for years.

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APPENDIX: TOPIC QUESTION

Original nominated question:
Compare the effectiveness (including survival, hospitalization, quality of life, and costs) of renal replacement therapies (e.g., daily home hemodialysis, intermittent home hemodialysis, conventional in-center dialysis, continuous ambulatory peritoneal dialysis, renal transplantation) for patients of different ages, races, and ethnicities

Revised Question:
Compare the effectiveness (including survival, hospitalization, quality of life, and costs) of continuous ambulatory peritoneal dialysis versus hemodialysis (primarily conventional in-center dialysis, but also daily home hemodialysis, intermittent home hemodialysis) for patients of different ages, races, and ethnicities.

TOPIC 8: Imaging Technologies in Cancer

Compare the effectiveness of imaging that includes positron emission tomography (PET) vs. other non-PET imaging for monitoring patients with lymphoma, breast, lung, or melanoma cancer.

(Note: This topic brief includes dedicated PET or integrated PET/CT, typically using FDG as the tracer in both cases.)

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF INTERVENTION • Positron emission tomography (PET) is an imaging technique that that uses a radioactive substance called a tracer to look for disease in the body by measuring cell metabolism; it produces a 3-dimensional image of processes in the body. Currently, the most commonly used tracer is [18F]-fluorodeoxyglucose or FDG. • Since its introduction in 2000, the combined PET/CT (computerized tomography) modality has largely replaced conventional PET; almost all scanners now in use worldwide are PET/CT scanners. • The primary rationale for using PET, or other advanced imaging techniques like CT or MRI, for surveillance following the initial treatment of cancer is to determine if and where the tumor has spread (metastasized) and to detect early tumor recurrence so that an intervention can increase survival and/or improve quality of life, *though this assumption of an increase in either outcome has not been validated*. • For the purpose of this topic brief, surveillance is defined as posttreatment monitoring of cancer survivors in the absence of clinical or other diagnostic suspicion of recurrence.
Relevance to patient-centered outcomes	CONDITIONS FOR WHICH INTERVENTION MIGHT BE INDICATED • PET/CT is used for many cancers for initial staging, assessment of treatment response, restaging, detection of clinically suspected recurrence, and surveillance. For the purpose of this topic brief, we will be focusing on the following cancers: **lymphoma, breast, lung, or melanoma.** *Note however that there is also significant uncertainty surrounding use of PET and other imaging modalities for numerous additional cancers (e.g. colorectal cancers, head and neck cancers) which could be considered for inclusion.*[1,2] OUTCOMES ASSOCIATED WITH INTERVENTION • PET can be used to monitor cancer treatments to detect disease that is not responding to treatment and to allow for a change to a more effective treatment strategy or less exposure to treatments (and the side effects of such treatments) that are not effective.[3] • The use of PET/CT may impact a patient's emotional distress (depression, anxiety) from coping with cancer treatment sequelae and posttreatment surveillance/monitoring. • Depending on insurance coverage, many patients can face a significant financial burden of posttreatment surveillance for these cancers. • PET (plus or minus CT) can be very sensitive to pick up new cancer recurrences and distant metastases, which may allow for earlier intervention of these recurrences. • PET strategies, however, also may have a higher number of false-positives (i.e., test indicates cancer when cancer is not present[4]) compared with other advanced imaging technologies, which then leads to additional testing and potential treatments. • Possible risks of using PET/CT for surveillance include unnecessary follow-up testing (including invasive biopsy) and overtreatment based on false-positives, and

	unnecessary radiation exposure.[5]
Burden on Society	
Recent incidence and prevalence in populations and subpopulations	PREVALENCE OF USE • Despite the lack of current evidence for benefit, PET is commonly used for surveillance of some cancer survivors.[6] For example, PET may be used in clinical practice for some particularly high-risk subpopulations (e.g. low-grade lymphoma); however which subpopulations may benefit from such surveillance has not been established. INCIDENCE & PREVALENCE OF KEY CONDITIONS[7] Breast cancer: • Almost 3 million women within the United States have a history of breast cancer; this constitutes over 40% of female cancer survivors.[7] • While most breast cancer survivors are women, approximately 2,000 men[8] are diagnosed with breast cancer annually in the United States, and most will go on to become breast cancer survivors requiring surveillance as well. Lymphoma: • Half a million men and women in the United States have a history of non-Hodgkin lymphoma, which is approximately 4% of all cancer survivors in the United States. • It is estimated that there were 9,060 new cases of Hodgkin lymphoma and 70,130 new cases of non-Hodgkin lymphoma in the United States in 2012. Lung cancer: • There are approximately 226,000 cases of lung cancer and 165,000 deaths per year, making it the most common cause of cancer death for both men and women in the United States. Most patients present with advanced disease, and 5-year survival is only 16%. Thus, while lung cancer is one of the most prevalent non–skin cancers, survivors of lung cancer make up only 3% of the total cancer survivor population in the United States. • Imaging is often used to plan radiation therapy (in stage III disease), monitor response to chemotherapy (in stages II-IV disease) and/or monitor for recurrence following surgery (in stages I-II disease). Melanoma: • There are approximately 980,000 melanoma survivors in the United States, which is approximately 7% of all cancer survivors in the United States. • The 5- and 10-year survival rates for persons with melanoma are 91% and 89%, respectively. • While 84% of melanomas are found in an early stage (i.e., localized), there are significant disparities in stage of diagnosis between whites and African Americans in the United States (84% vs. 58% for localized cancer at diagnosis, respectively).

Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	EFFECTS ASSOCIATED WITH THE CONDITIONS
	• Lymphoma, breast cancer, lung cancer, and melanoma are associated with many physical, emotional, financial issues, many of which affect the length and quality of life for an individual cancer survivor.
	• Many cancer patients experience negative impacts on their health as a result of cancer treatments. These include but are not limited to:
	  ○ Lymphedema, an abnormal buildup of lymph fluid that causes swelling and pain
	  ○ Physical disfigurement from treatments, which may cause body image or relationships issues
	  ○ Decreased sexual function; women cancer patients may experience menopausal symptoms that result from chemotherapy, and hormonal therapy may decrease enjoyment in sexual activities or make these activities painful
	  ○ Changes in fertility
	  ○ Heart problems, which may include swelling of the heart muscle, problems with the heart's ability to pump blood (congestive heart failure), or heart disease
	  ○ Lung problems (e.g., difficulty breathing, inflammation of the lungs)
	  ○ Fatigue and reduced sleep quality
	  ○ Digestive problems
	  ○ Increase risk of secondary cancers from treatment exposures
	
	EFFECTS ASSOCIATED WITH THE INTERVENTION
	• Use of PET for diagnosis and staging of cancers may improve initial care for cancers, which may reduce expose to ineffective or unnecessary treatments that negatively affect a patient's quality of life.
	• However, inappropriate (i.e., not evidence-based) use of PET/CT for surveillance can lead to overtreatment based on false-positives and unnecessary radiation exposure. Inappropriate use of PET/CT for surveillance can also contribute to delays in care.
	• Using advanced imaging, including PET, for posttreatment surveillance of patients is controversial because it may not reduce mortality from a recurrence or secondary primary cancer or improve survival.

How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	Given the high prevalence of people living with a past diagnosis of these cancers who are in need of monitoring approaches; the impact of these cancers on functional status, productivity, quality of life, and mortality; and the level of uncertainty around the use of PET for monitoring these patients, high priority should be given to exploring the use of PET to optimize important patient-centered outcomes and enhance survival.

Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the intervention of interest?	Systematic reviews/available date: There have been multiple systematic reviews on the use of advanced imaging techniques for cancer diagnosis, staging, treatment response, and surveillance. For this topic brief, we focus on the recent data on the use of PET for surveillance of survivors of lymphoma, breast cancer, melanoma, and lung cancer.[9] LYMPHOMA A recent systematic review identified no studies that assessed the role of PET in monitoring lymphoma survivors. Thus, there is insufficient evidence to draw conclusions on the clinical impact of PET or PET/CT surveillance for lymphoma. PET currently has no recognized role in the routine surveillance of lymphoma patients.[6] BREAST CANCER The American Society of Clinical Oncology does not recommend PET for routine follow-up in an otherwise asymptomatic patient after initial treatment for breast cancer.[10] MELANOMA[4] A recent systematic review identified 34 studies of advanced imaging techniques for assessing the diagnostic accuracy for surveillance of melanoma patient. • For melanoma surveillance of lymph node involvement, ultrasonography had the highest sensitivity (96%, 95% Credible Interval (CrI) = 85% to 99%), specificity (99%, 95% CrI = 95% to 100%), and diagnostic odds ratio (1675, 95% CrI = 226.6 to 15,920). • For distant metastases, PET/CT had the highest sensitivity (86%, 95% CrI = 76% to 93%), specificity (91%, 95% CrI = 79% to 97%), and diagnostic odds ratio (67, 95% CrI = 20.42 to 229.7). However, for patients with low risk of melanoma recurrence, the positive predictive value was only 33%, which would indicate that it is not a good test to use for this population. LUNG CANCER[11] • For non–small cell lung cancer, recurrence may be detected at an earlier point by PET than by clinical examination or other type of imaging; however, there is limited evidence that patient management or survival would be affected. An economic evaluation from 2009 found that FDG-PET/CT applied 3 months after chemotherapy plus radiation therapy or radiation therapy alone detected progressions that were possibly amenable to curative treatments.[12] • For small cell lung cancer, recurrence is considered to be incurable, and while PET may provide adequate detection of recurrence, it is considered inappropriate.[13]
What could new research contribute to achieving better patient-centered outcomes?	New research could contribute to achieving better patient-centered outcomes. There are limited randomized studies on which to base decisions regarding the trade-offs of monitoring with PET. • Does the use of PET improve survival or reduce mortality from a recurrence or a secondary primary cancer? PET and other advanced imaging technologies are able to detect cancer; however, using advanced imaging, including PET, for posttreatment surveillance of patients is controversial because it may not improve survival. • Which patients will be helped most by surveillance via PET? A broad area of uncertainty is the subpopulation for which monitoring by PET / CT is appropriate. There are multiple sources of heterogeneity such as cancer type, cancer site, stage or cancer, and prior treatments. • At what frequency and time interval is monitoring by PET/CT appropriate? Past

	research has not provided detailed descriptions of surveillance protocols. • What is the best way to utilize PET/CT scanning in monitoring specific subpopulations? Appropriate utilization is a relevant area of research that has a potentially high impact and high significance. Patient outcomes could be the ultimate standard for determining appropriateness. • What frequencies of PET surveillance are tolerated by patients that can optimize adherence to long-term followup protocols? Patient compliance to surveillance frequency may be affected by multiple factors, ranging from inconvenience, significant emotional distress and uncertainty of results to financial stress if patients have large out-of-pocket expenses. • How can FDG PET/CT be used to assess more conventional measures of patient outcome such as response to therapies and the potential for reducing therapeutic toxicities? • What are the most important patient-centered outcomes for patients being monitored for these cancers? • What trade-offs or level of uncertainty are patients willing to deal with to avoid unnecessary testing that may lead to unnecessary treatments? • What study data would provide patients with the assurance that they do not have recurrent disease and allow both clinicians and patients a high degree of confidence that further testing (biopsy, surgery, or other intervention) is not necessary? • Can the use of blood biomarker(s) improve appropriate patient selection for surveillance PET scans? Many serum biomarkers (e.g., CA 125) have not been well characterized for sensitivity/specificity of recurrence in combination with PET.
Have recent innovations made research on this topic especially compelling?	Recent innovations: • PET and CT are the 2 primary imaging modalities for monitoring patients with cancer, and these modalities are now combined into a single hybrid modality. The vast majority of clinical PET scanners sold today have a state-of-the-art CT scanner integrated with PET. • The 3 major manufacturers of PET scanners are investigating the advantages of combined PET/MRI over PET/CT; however, this investigation is in the very early stages.
How widely does care now vary?	VARIABILITY IN PRACTICE • It is difficult to ascertain the true variability in clinical practice; however, there appears to be significant variability in use. PET and PET/CT are being used for a variety of cancer indications—none of which are based on high or moderate strength of evidence. • PET facilities are not distributed evenly across the United States, and so use may have significant geographic variations.
What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	RECENT PUBLICATIONS • A MEDLINE search from 2009 through 2014 yielded a total of 7,088 citations: o 105 were labeled as randomized controlled trials/therapy. o 132 were labeled as meta-analyses or systematic reviews. ONGOING TRIALS There are 157 ongoing studies listed in www.clinicaltrials.gov that are assessing PET and are relevant to the cancers of interest. However only 6 of these appear to evaluate the use of PET in *monitoring* patients (2 lung cancer studies, 3 breast cancer studies, 1 lymphoma study) and none of these studies appearing to be true comparative effectiveness studies of PET versus other non-PET imaging modalities.

How likely is it that new CER on this topic would provide better information to guide clinical decision making?	KEY UNCERTAINTIES IN CLINICAL DECISION MAKING • Does the use of PET improve survival or reduce mortality from a recurrence or a secondary primary cancer? • For which subpopulation, and at what frequency and time interval, is monitoring by PET/CT appropriate? • What are effective strategies to foster long-term adherence to monitoring? • What are the comparative benefits and harms of PET? Do these vary by frequency or time interval of PET scanning? LIKELIHOOD THAT CER WOULD BE ABLE TO REDUCE THESE UNCERTAINTIES There is a high likelihood that appropriately designed CER would be able to effectively address these and other areas of uncertainty. There is little available evidence about the appropriate utilization of PET for monitoring patients with these cancers, or which patients may benefit from PET. CER in this area could help patients and providers to better select monitoring strategies according to patient characteristics.
Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that would affect the implementation of new findings in practice?	FACILITATORS • There is much uncertainty around the optimal use of PET for surveillance, making CER in this area particularly attractive. • There is a relatively high prevalence of these cancers that have a wide impact on patient quality of life, functioning, and productivity. • Use of PET for surveillance could be significantly influenced by practice guidelines. BARRIERS • There is variability in evidence-based use. • There is geographic variability in the availability of PET. • For patients, adherence to a surveillance protocol could be significantly influenced by insurance coverage (i.e., if patients have a large out-of-pocket expenses).
How likely is it that the results of new research on this topic would be implemented in practice right away?	EVIDENCE OF BENEFIT • Because of the high level of uncertainty about the effect on survival, there is a high likelihood of implementation if evidence of benefit is shown. EVIDENCE OF NO BENEFIT OR HARM • Implementation of less aggressive surveillance techniques may be difficult because of residual patient anxieties about risk. • Relative weighting of harms may also create barriers (e.g., some patients/providers may feel that the risks of overtreatment are worth the benefits of finding a recurrence earlier).
Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies?	CER priority areas that seek to identify the subpopulation, frequency, and time interval for appropriate monitoring by PET/CT is needed. It is highly likely that new information on the appropriate surveillance of cancer survivors will be current for several years.

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APPENDIX: TOPIC QUESTION

Original topic:
Compare the effectiveness of imaging technologies in diagnosing, staging, and monitoring patients with cancer including positron emission tomography (PET), magnetic resonance imaging (MRI), and computed tomography (CT).

Modified topic:
Compare the effectiveness of imaging that includes positron emission tomography (PET) vs. other non-PET imaging for monitoring patients with lymphoma, breast, lung, or melanoma cancer. (Note: This topic brief includes PET alone, PET/CT, and PET/FDG)

TOPIC 9: Eye Disease

Compare the effectiveness of different treatment options (with an emphasis on anti-vascular endothelial growth factor [anti-VEGF]) for diabetic retinopathy and macular degeneration

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION[1] • Over 3.4 million patients in the United States are either visually impaired (i.e., visual acuity worse than 20/40) or legally blind (i.e., visual acuity worse than 20/200 or a visual field of less than 20 degrees)—at least 3% of the U.S. population. o Despite the large number of people with, or at risk for, significant vision loss and its consequences, many have not taken advantage of available early detection and effective treatments. • Two of the most common causes for vision loss in the United States are age-related macular degeneration and diabetic retinopathy. • Age-related macular degeneration (AMD) o AMD affects the macula—the central part of the retina that allows the eye to see fine details, which facilitates common tasks like reading and driving. o AMD is the most common cause for visual impairment (though not blindness) in the United States. o There are 2 types of AMD, both of which increase with age: ▪ In wet AMD (10% to 30% of cases), abnormal blood vessels behind the retina grow under the macula (neovascularization), causing leakage of blood/fluid. This leads to scarring and damage in the macula, which can cause rapid central vision loss. ▪ In dry AMD (70% to 90% of cases), the macula thins out as part of the aging process, causing gradual vision loss. o Along with age, other risk factors for AMD include family history/genetics, smoking, nutritional factors (e.g., lack of antioxidants), atherosclerotic disease, aspirin, and, possibly, surgery for cataracts.[2] • Diabetic retinopathy (DR) o DR causes progressive damage to the blood vessels of the retina and is a leading cause of blindness in the United States. o Patients with DR usually progress through 4 stages: ▪ Mild nonproliferative DR is characterized by microaneurysms (small areas of blood vessel enlargement). ▪ Moderate nonproliferative DR is where blockage occurs in some retinal vessels. ▪ Severe nonproliferative DR is where more vessels are blocked, depriving areas of the retina of blood supply, which leads to new blood vessel growth (neovascularization). ▪ Proliferative retinopathy, the most advanced stage, is characterized by significant vision loss. o Diabetic macular edema (DME) refers to swelling of the macula that can occur in the presence of DR. DME can occur at any stage of DR and is responsible for much of the vision loss that occurs with DR. o Good control of diabetes and associated risk factors like hypertension can help prevent the development DR and its progression to vision loss.[3]

Relevance to patient-centered outcomes	SYMPTOMS[1]
	• AMD is often asymptomatic early in its course. While significant central vision loss sometimes results, peripheral vision is generally spared, and patients usually do not progress to complete blindness.[4]
	  ○ Vision loss is usually gradual in dry AMD and may affect one or both eyes. Patients may note difficulty reading or driving, and they may see gaps in their vision or the need for brighter light or magnification.
	  ○ In wet AMD, vision loss may be more rapid in onset and typically appears in one eye before the other (though developing symptoms in one eye increases the likelihood of involvement of the other eye). A common early symptom of wet AMD is the perception of straight lines as wavy or curved (also called metamorphopsia).
	• DR
	  ○ DR is classically asymptomatic through its early course, and by the time symptoms develop, it is sometimes too late to effectively treat it.
	  ○ Patients may notice decreased visual acuity, which does not respond to glasses, or "floaters" in their vision.
	
	OUTCOMES
	• Vision loss in general can lead to loss of functionality, depression, and falls.[5]
	• DR is associated with an increase in cardiovascular events and cardiovascular mortality, even after adjustment for some comorbid cardiovascular disease risk factors.[6]

Burden on Society	
Recent incidence and prevalence in populations and subpopulations	INCIDENCE/PREVALENCE (PROPORTION OF POPULATION LIVING WITH THE CONDITION)[1] • In the United States, approximately 1.8 million people have AMD, and an additional 7.3 million have drusen (yellow-white deposits in the retina, often seen with early AMD) and so are at substantial risk of developing AMD. • An estimated 4.1 million people in the United States are affected by DR, and 899,000 have vision-threatening retinopathy. • During the next three decades, the prevalence of both AMD and DR is estimated to double due to the rapidly aging population and the epidemic of diabetes.[1,7]
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	QUALITY OF LIFE[1,8,9] • Vision loss from AMD and DR drastically reduces quality of life as measured using reliable scales and can lead to higher rates of depression. . PRODUCTIVITY[10] • Vision loss is responsible for significant productivity losses in the United States. For example, among patients younger than 40 years of age, vision loss causes up to $13 billion in indirect costs annually, primarily due to $12.2 billion in lost productivity each year. FUNCTIONAL CAPACITY[1] • Vision loss is among the top 10 disabilities among adults over 18 years of age and is one of the most prevalent disabling conditions among children. MORTALITY[6] • As noted above, DR is associated with an increase in cardiovascular mortality.

How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• The prevalence of vision loss from AMD and DR is high and—due to population aging and increasing rates of diabetes—is growing. • These conditions cause significant decrements in quality of life, productivity, and functional capacity, and the financial burden of major adult visual disorders is high (over $35 billion annually).[11,12] • This substantial public health impact led the Institute of Medicine (IOM) to designate comparative effectiveness research evaluating different treatment options for AMD and DR as a high-priority area (listed in third quartile).[13]
Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	SCREENING/EARLY DIAGNOSIS[1] • Early detection and timely treatment of eye conditions such as diabetic retinopathy has been found to be efficacious and cost effective, since delays in detection and treatment generally lead to permanent, irreversible vision loss. • An estimated 61 million adults in the United States are at high risk for serious vision loss, but only half visited an eye doctor in the past 12 months. TREATMENT • AMD o Dry AMD—No effective treatment options exist, though antioxidants, zinc, and laser treatment have been investigated with limited success.[4] o Wet AMD—A range of treatments can alter the disease course. ▪ Of note, by targeting the process of neovascularization, anti-vascular endothelial growth factor (anti-VEGF) therapy has "revolutionized" the treatment of wet AMD,[14] providing treatments in which there were no prior successful options to improve vision, with the possible exception of photodynamic therapy which had been shown to stabilize vision in some cases. • DR o A wide range of treatment are options available that can alter the disease course and preserve vision.[1] o Anti-VEGF therapy also represents a significant advance in the treatment of vision-threatening forms of DR (proliferative DR and DME) by interfering with neorevascularization.[15] Because of its overall efficacy, anti-VEGF therapy has become the first-line treatment for diabetic macular edema. MANAGEMENT OPTIONS • AMD (focusing on wet AMD given the absence of effective treatments for dry AMD)[4] o Anti-VEGF therapies are medications administered via injection into the globe of the eye (usually monthly).[14] ▪ Multiple trials have shown *ranibizumab* to be effective compared with placebo and photodynamic therapy. ▪ Although not FDA-approved for AMD, *bevacizumab* appears to have similar efficacy for AMD compared with ranibizumab and is much less expensive ($50 vs. $1900 per injection). However, it may be associated with increased systemic adverse events. ▪ *Aflibercept* has a longer half-life than ranibizumab, and when given every other month, appears to be noninferior to monthly ranibizumab. ▪ *Pegaptanib* is an older anti-VEGF agent that is less effective for AMD and is rarely used in current practice. o Other older approaches have been largely replaced by anti-VEGF therapies.[4] ▪ *Laser photocoagulation* uses high-intensity thermal laser energy to treat

	areas of the retina with neorevascularization but is a destructive therapy that causes visual scarring and is now used very infrequently. ▪ With *photodynamic therapy,* a light-sensitive dye is given intravenously and concentrates in areas of neorevascularization, where it is then activated with a laser beam focused over the macula, causing localized thrombosis. This approach is used relatively infrequently, primarily as an adjunct to anti-VEGF therapies. ▪ *Surgical procedures* can be done to remove neovascularization or surgically move the macula to a healthier part of the retina but are of questionable efficacy and are seldom used since the development of anti-VEGF therapies. o Antioxidant vitamins appear to have a beneficial effect on progression of AMD. o Quitting smoking reduces the risk for progression of AMD. o Combination therapy with anti-VEGF agents and other current and/or novel treatments (adjuvant therapy) may have more impact than anti-VEGF alone. • DR[15] o With nonproliferative DR, vision may not be affected, and emphasis is on control of risk factors for progression, including diabetes, hypertension, and lipids. ▪ If clinically significant DME is present with nonproliferative DR, then treatment with anti-VEGF therapies, intravitreal steroids, or focal laser photocoagulation is indicated to preserve vision (see below). o Proliferative DR ▪ *Panretinal laser photocoagulation* is the primary treatment for high-risk and severe proliferative DR. In cases with significant hemorrhage from new blood vessels or with associated traction retinal detachments, vitrectomy surgery (removal of the fluid inside the eye) may be necessary. ▪ *Anti-VEGF therapy* involving treatment with ranibizumab, bevacizumab, and pegaptanib has been shown to be effective in reducing neovascularization in proliferative DR; however, long-term effects are less clear than for panretinal laser photocoagulation. Unlike the permanent effects of laser, anti-VEGF therapy is a temporary measure for treating proliferative DR. ▪ *Intravitreal steroids* may reduce diabetic macular edema but appear to be associated with significant toxicity (e.g., infections and increased pressure inside the eye, which may cause cataracts and glaucoma) and so are not used frequently. o Regardless of the stage of DR with which DME is associated, DME generally requires treatment to preserve vision. ▪ There are ample data supporting the use of *anti-VEGF therapy* (ranibizumab, bevacizumab, pegaptanib) in DME, and it is considered by many to be the first-line treatment. ▪ Use of *focal laser photocoagulation* is a well-established therapy for DME but causes scarring that can impact vision and has been largely replaced by anti-VEGF, particularly for DME involving the center of vision. ▪ Compared with anti-VEGF therapy, *intravitreal steroids* appear similar in effectiveness for DME but may be associated with increased side effects, including elevation of pressure inside the eye and cataract development.
What could new research contribute to achieving better patient-centered outcomes?	New research could contribute to achieving better patient-centered outcomes.[15] • Additional comparative effectiveness studies evaluating different anti-VEGF agents are indicated in AMD and DR: o Though bevacizumab lacks an FDA indication for any retinal disease, the potential for cost savings with this agent (versus ranibizumab or aflibercept) makes it a valuable target for research. o Longer term studies are needed that compare anti-VEGF agents with each other and procedural treatments for proliferative DR in order to determine whether anti-

	VEGF therapy might replace laser photocoagulation as a treatment of choice. ○ New studies that evaluate combinations of anti-VEGF agents and procedural treatments are indicated to develop contemporary treatment algorithms based on current advances in treatment and diagnostic modalities. • Given the need for monthly eye injections with anti-VEGF agents, studies evaluating reduced injection burdens could be helpful in improving patient-centered outcomes in AMD and DR. ○ Novel delivery mechanisms (e.g., ocular implants) that might prolong the effects of anti-VEGF agents require evaluation. • Studies to address apparent racial and ethnic disparities in vision loss should be conducted. • Further research to better define and measure patient-centered outcomes of interest in AMD and DR should be conducted.
Have recent innovations made research on this topic especially compelling?	Recent innovations: • The development of anti-VEGF therapies is an important innovation in the care of vision-threatening conditions like wet AMD and DR, which are disorders of neovascularization. • The development of optical coherence tomography to image the retina has revolutionized diagnosis of retinal disease, but "gold standard" treatment algorithms, particularly for DME, were established prior to this development and do not yet incorporate its use in diagnosis and management strategies. • New research further exploring applications of anti-VEGF therapy in these conditions would likely have a high impact on patient outcomes and health.
How widely does care now vary?	VARIABILITY IN CARE • More than half of adult Americans do not seek eye care due to lack of awareness or costs, and this is often exacerbated by lack of adequate health insurance.[1] • With the recent and rapid development of novel therapeutic modalities, particularly anti-VEGF agents, and novel diagnostic modalities, particularly optical coherence tomography, previously established gold standards for treatment are often no longer applicable and need updating. These existing treatment algorithms are often based on anecdotal rather than rigorous evidence, resulting in significant variation in individual physician treatment approaches. • While AMD is more common in White patients, DR is more common in African American and Hispanic patients.[16] • Significant visual impairment is more common in African American and Hispanic patients than White patients, suggesting that African American and Hispanic patients may benefit from earlier initiation of vision-preserving therapies.[16]
What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	RECENT PUBLICATIONS • A search of PubMed covering 3/24/09 through 3/24/14 yielded a total of 1,678 publications, including: ○ 118 randomized, controlled trials ○ 80 systematic reviews/meta-analyses ○ 5 clinical guidelines ONGOING TRIALS • A search of www.clinicaltrials.gov showed 43 potentially relevant ongoing studies focusing on AMD or DR and anti-VEGF. ○ Most studies are small (~50 patients). ○ Several RCTs are either recently completed or estimated to finish soon comparing bevacizumab with ranibizumab in patients with AMD (e.g., CATT, LUCAS, IVAN, GEFAL, and MANTA trials). ○ There is an ongoing RCT evaluating Fovista (an antiplatelet derived growth factor) administered in combination with either bevacizumab or aflibercept compared with

	bevacizumab or aflibercept monotherapy in patients with AMD. Fovista is a novel agent currently being tested that gets a lot of attention and holds promise (target 622 patients, estimated completion 2016). o For diabetic retinopathy, there are fewer rigorous trials.
How likely is it that new CER on this topic would provide better information to guide clinical decision making?	KEY UNCERTAINTIES IN CLINICAL DECISION MAKING • Specific subpopulations of patients with AMD or DR that could benefit from anti-VEGF therapy • Additional comparisons of specific anti-VEGF agents with other anti-VEGF agents, alone and in combination with procedural therapies or other medications • Further research to better define and measure patient-centered outcomes which are of most interest to patients with AMD and DR LIKELIHOOD THAT CER WOULD BE ABLE TO REDUCE THESE UNCERTAINTIES • There is a high likelihood that appropriately designed randomized comparative effectiveness trials would address these areas of uncertainty.
Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that would affect the implementation of new findings in practice?	FACILITATORS • Vision loss is a common and costly condition that has significant effects on patient quality of life and can be devastating for patients. • Recent developments in medical therapy hold promise to improve patient outcomes in AMD and DR. • Comparative effectiveness research evaluating different treatment options for AMD and DR has already been designated as a high-priority area by IOM.[13] BARRIERS • Though both conditions involve neorevascularization, AMD and DR are different from each other, and findings for one may not pertain to the other. • AMD and DR can vary based on severity and extent of involvement, which may complicate the design of comparative effectiveness studies.
How likely is it that the results of new research on this topic would be implemented in practice right away?	EVIDENCE OF BENEFIT • Findings would be likely to be implemented widely if there is evidence for better patient outcomes. EVIDENCE OF NO BENEFIT OR HARM • It is likely that research demonstrating no evidence for benefit would also have an impact on practice by supporting the ongoing use of past treatment strategies rather than modifications to these strategies to include anti-VEGF therapies.
Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies?	Although medical treatment options continue to evolve, it is likely that new information regarding the impact of anti-VEGF therapies and other medications on patient-centered outcomes in different populations would remain relevant for years.

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APPENDIX: TOPIC QUESTION

Proposed Topic:

PCORI Topic Brief: Assessment of Prevention, Diagnosis and Treatment Options

Compare the effectiveness of different treatment options (e.g., laser therapy, intravitreal steroids, anti-vascular endothelial growth factor [anti-VEGF]) for diabetic retinopathy, macular degeneration, and retinal vein occlusion.

Revised Topic:
Compare the effectiveness of different treatment options (with an emphasis on anti-vascular endothelial growth factor [anti-VEGF]) for diabetic retinopathy and macular degeneration

TOPIC 10: Mindfulness-Based Interventions

Compare the effectiveness of mindfulness-based interventions for the treatment of anxiety, depression, and pain.

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF INTERVENTION • Mindfulness is a term that is generally considered to describe a focus on attention and awareness. • Mindfulness essentially aims to foster a more attentive way of seeing and way of being, rooted in a growing self-awareness, with the intention of living in a way that is more conscious, deliberate, kind, and compassionate and less reactive, automatic, and judgmental. • Mindfulness-based interventions refer to programs that are centered on daily mindfulness meditation practice and designed to grow these core qualities. • A wide variety of clinical, spiritual, or religious practices strive to help people achieve a state of mindfulness. Some mindfulness practices or interventions focus explicitly on mindfulness training: examples include mindfulness-based stress reduction (MBSR), transcendental meditation (TM), other meditation-based interventions, and some forms of prayer. Other interventions may achieve a state of mindfulness indirectly by engaging in a prescribed set of movements (e.g., Tai chi), "postures" (e.g., some forms of yoga), or breathing exercises (e.g., qi gong and some forms of yoga). o The specific inclusion/exclusion criteria for mindfulness-based interventions vary. Note that for this brief we follow the definition of mindfulness-based interventions used in the recent AHRQ-funded systematic review by Goyal and colleagues,[1] in which ▪ Included interventions were structured meditation programs (any systematic or protocol meditation programs that follow predetermined curricula) consisting of, at a minimum, ≥4 hours of training with instructions to practice outside the training session, including mindfulness-based programs (i.e., mindfulness-based stress reduction, mindfulness-based cognitive therapy, vipassana, Zen, and other mindfulness meditation), mantra-based programs (i.e., TM, other mantra meditation), and other meditation programs. ▪ Excluded interventions were programs in which meditation is not the foundation of the intervention, including dialectical behavioral therapy; acceptance and commitment therapy; any of the movement-based meditations, such as yoga (e.g., Iyengar, Hatha, shavasana), tai chi, and qi gong (chi kung); aromatherapy; biofeedback; neurofeedback; hypnosis; autogenic training; psychotherapy; laughter therapy; therapeutic touch; eye movement desensitization reprocessing; relaxation therapy; spiritual therapy; breathing exercise; pranayama exercise; or any intervention that is given remotely or only by video or audio to an individual without the involvement of a meditation teacher physically present. • Mindfulness interventions have been used and studied for a wide range of conditions, including depression, anxiety disorders, acute and chronic pain conditions, HIV, irritable bowel syndrome, cancer survivorship, fall prevention, and sleep disorders. This topic brief focuses specifically on its use for *anxiety*, *depression*, and *pain*, as these conditions frequently occur on their own and as

	comorbid conditions with other mental and medical illnesses. • Mindfulness-based interventions fall under the larger umbrella category of "mind and body practices," which according to the NIH National Center for Complementary and Alternative Medicine (NCCAM) includes other types of meditation, tai chi, yoga, qi gong, relaxation techniques such as breathing exercises, and movement therapies. Whereas many of these practices involve a component of mindfulness, mindfulness is not the primary focus or desired outcome of all mind and body practices.
Relevance to patient-centered outcomes	OUTCOMES • Anxiety disorders are the most common form of mental disorder,[2] affecting about 40 million American adults each year. Outcomes associated with anxiety disorders include impaired functional status, decreased work productivity, substance abuse, and increased use of health care services.[3] Nearly one-half of those diagnosed with depression are also diagnosed with an anxiety disorder. • Depression is the leading cause of disability worldwide, with an estimated global prevalence of 350 million people.[4] Outcomes associated with depression include significantly impaired functional status, substance abuse, decreased quality of life, and suicide. • Chronic pain affects about 100 million American adults—more than the total affected by heart disease, cancer, and diabetes combined—and costs the United States up to $635 billion annually in medical treatment and lost productivity.[5] Outcomes associated with unrelieved pain include longer hospital stays, increased rates of rehospitalization, increased outpatient visits, and decreased function. POTENTIAL BENEFITS ASSOCIATED WITH MINDFULNESS INTERVENTIONS • Past reviews have demonstrated small to moderate effectiveness of a variety of mindfulness interventions in reducing emotional symptoms (e.g., anxiety, depression, stress) and physical symptoms (e.g., pain). POTENTIAL HARM ASSOCIATED WITH MINDFULNESS INTERVENTIONS • Movement-based mindfulness interventions (e.g., tai chi and some forms of yoga and qi gong) could involve falls or musculoskeletal injury while performing the exercises, although any increase in the rate of such injuries compared with those occurring in other activities of daily living may be negligible. Note that these movement-based interventions are not included in the AHRQ definition of mindfulness interventions as defined above. • Few trials report on potential harms of meditation programs, in the AHRQ systematic review, of the 9 trials reporting this information, none reported any harms[1]
Burden on Society	
Recent incidence and prevalence in populations and subpopulations	There are few published estimates of the extent to which mindfulness interventions are used or prescribed for patients with depression, anxiety, or pain conditions. Results of a national survey suggest that about 4.1% of the U.S. population has used meditation in the past 12 months.[6]
Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	Meditation and mindfulness-based interventions are thought to benefit participants though effects on blood pressure, cardiac functioning, and immunity.[7-10]

How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	Alternative approaches are available for the treatment or management of depression, anxiety, and pain, but no single approach is considered to be universally effective and safe. CER on the adherence to, or effectiveness and safety of, mindfulness interventions for depression, anxiety, or pain conditions has the potential to have a significant impact on the very large societal burden associated with depression, anxiety, and pain.
Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the intervention of interest?	Systematic reviews/available data: There have been several systematic reviews related to mindfulness-based interventions.[11, 14-17] Most notably and relevant, however, is a recent AHRQ-funded systematic review by Goyal and colleagues[1] that evaluated the efficacy of meditation programs in improving stress-related outcomes (anxiety, depression, stress/distress, positive mood, mental-health related quality of life, attention, substance use, eating habits, sleep, pain, and weight) in diverse adult clinical populations. • This review of 47 trials (3515 participants) found that mindfulness meditation programs had moderate evidence of relieving symptoms of anxiety (effect size, 0.38 [95% CI, 0.12-0.64] at 8 weeks and 0.22 [0.02-0.43] at 3-6 months), depression (0.30 [0.00-0.59] at 8 weeks and 0.23 [0.05-0.42] at 3-6 months), and pain (0.33 [0.03- 0.62]) and low evidence of improved stress/distress and mental health–related quality of life. • Authors found low evidence of no effect or insufficient evidence of any effect of meditation programs on positive mood, attention, substance use, eating habits, sleep, and weight. • Authors found no evidence of any harms of meditation programs, although few trials reported on harms. • The review found insufficient evidence that meditation programs were better than any active treatment (i.e., drugs, exercise, and other behavioral therapies). • Note that this review *did not* include trials that used a "usual care" or "treatment as usual" comparison. • The review highlights that there have been very few RCTs of mindfulness-based interventions compared with active, established treatments, much less multiple good-quality trials within the same diagnosis. As such, the evidence base cannot really be determined at this time. Many more good-quality comparative effectiveness studies are required.
What could new research contribute to achieving better patient-centered outcomes?	Currently, medical management is the mainstay of treatment for depression, anxiety, and pain conditions. Some pain conditions also frequently involve surgical interventions. Counseling, psychotherapy, and cognitive behavioral therapies are also important. These interventions are often expensive and may be associated with undesirable side effects or adverse events. In contrast, mindfulness interventions are relatively inexpensive and generally do not seem to harm patients. Many are also potentially more widely accessible than interventions that must be administered or supervised by a physician, psychologist, or other healthcare professional. The time and resources required to teach a patient specific breathing exercises, or mindfulness meditation techniques, or tai chi movements is not usually excessive. New research on mindfulness interventions has the potential to achieve a wide variety of improved patient-centered outcomes for patients with depression, anxiety, or pain, including: • Better overall health among persons who engage in daily mindfulness exercises

	• Decreased severity and/or frequency of condition-specific symptoms • Improved quality of life, functional status, and/or productivity • Improved mood and/or decreased pain and suffering • Decreased use of medications, with concomitant decreased risk of medication-related adverse events or effects
Have recent innovations made research on this topic especially compelling?	A relatively new innovation is the development and broad dissemination of structured training programs for both novices and teachers of MBSR. In addition, recent technological advances in brain imaging, molecular biology, and genetics have allowed more careful and more refined study of the potential underlying mechanisms through which mindfulness training can relieve physical and mental symptoms and enhance health and wellness.
How widely does care now vary?	VARIABILITY IN PRACTICE • There is great variability in the practice of mindfulness interventions because of the large number of traditions or forms or practice philosophies. However, the *process* of practicing mindfulness meditation is generally the same regardless of the object of meditation (breath, body, sounds, thoughts, etc.). These practices all include bringing nonjudgmental attention and awareness to one's present-moment experience and intentionally returning to that state whenever one notices becoming distracted. • Disciplined leadership in the MBSR community, however, has resulted in standardized and reproducible MBSR training.
What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	RECENT PUBLICATIONS A search of PubMed covering the past five years yielded 150 publications, including: ○ 51 randomized controlled trials ○ 22 systematic reviews/meta/analyses ○ 1 clinical guideline Note that most publications of mindfulness may not appear in the medical literature (and therefore may not be captured by PubMed); instead many occur in psychology, education, or business/corporate health sectors of study. Other databases of the published (and gray) literature would need to be explored to see the scope of available evidence. ONGOING TRIALS A search on www.clinicaltrials.gov for open studies that included "mindfulness" and the conditions of "pain," "anxiety," or "depression" found 44 potentially relevant ongoing trials. These studies vary in terms of the number of patients included (ranging from 8 to 320 patients, median 115), outcomes assessed, and interventions studied. About half of these studies compare active interventions within the study, although the specific mindfulness interventions (and comparators) and the underlying patient populations included vary widely.
How likely is it that new CER on this topic would provide better information to guide clinical decision making?	KEY UNCERTAINTIES IN CLINICAL DECISION MAKING • Which mindfulness interventions, specifically, are appropriate for which conditions, and are associated with which clinical outcomes? • What are the risks associated with any given mindfulness intervention? • Do mindfulness interventions decrease medication use and other forms of healthcare utilization? • What are the most appropriate outcomes for mindfulness interventions in general, and interventions for given clinical conditions specifically? • What are the specific contributions of the mindfulness component of mindfulness interventions to observed clinical outcomes, as opposed to the contributions of other components (e.g., exercise, relaxation, time away from stressful activities, etc.) or

	nonspecific effects of the intervention? • What is the appropriate dose (e.g., length or intensity of a given exercise/meditation session, frequency of sessions, duration of an intervention course, etc.) of a given mindfulness intervention for a given clinical condition? • Is mindfulness training (e.g., MBSR) equivalent to standard care for depression, anxiety, and/or chronic pain? • Is mindfulness training (e.g., MBSR) consistently effective across major demographic subgroups (age, gender, race, ethnicity, education, SES, region of the country, etc.)? • Is mindfulness training effective even if patients do not have a high level of commitment or expectation? • Are self-help, phone-based, or Internet-based mindfulness training programs essentially equivalent to traditional, classroom-based classes? LIKELIHOOD THAT CER WOULD BE ABLE TO REDUCE THESE UNCERTAINTIES • Mindfulness interventions comprise many different practices, most of which are difficult to standardize. It is also difficult to design and conduct high-quality trials that involve one or more comparators that control for nonspecific effects. Whereas individual studies of specific mindfulness interventions for specific clinical conditions should provide better information to guide clinical decision making, it may be difficult to design and conduct new CER that would, by itself, likely have a major impact on clinical decision making. • Note that Davidson and colleagues developed the Health Enhancement Program (HEP) in collaboration with the NIH.[12,13] This program uses an active control condition, which allows for rigorous evaluations of MBSR and testing mindfulness as an active ingredient.
Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that would affect the implementation of new findings in practice?	FACILITATORS • There is relatively high interest in this general topic. A variety of stakeholders would be willing and able to help implement new findings in practice (e.g., current leadership at the Department of Veterans Affairs). • There is strong interest in this general topic by a variety of patient/consumer/lay groups. Compelling evidence of effectiveness might be relatively widely disseminated via social media venues. BARRIERS • There is a diverse set of stakeholders; the most efficient mechanism for disseminating new and relevant information to most of the stakeholders may be through the media (Time Magazine, New York Times, nightly news, etc). • In the absence of placebo comparators, there is likely to be skepticism on the part of many people, even if many large and well-designed clinical trials and meta-analyses all demonstrate a consistently strong and positive effect. Although the development of HEP mentioned above aims to decrease this limitation in mindfulness-based evaluations, this barrier is high for many/most nonpharmacologic and nonsurgical interventions, and is likely to also remain high for all/most mindfulness interventions. • There are concerns about the generalizability of studies of one mindfulness technique to the efficacy of other techniques. Note, however, that if mindfulness meditation generally involves a common process, then the results could generalize across conditions, to the extent that the conditions share some common cause like stress, anxiety, depression, or pain. • Similar to the barriers associated with research on alternative therapies in general, there may be a high barrier to incorporation of findings into mainstream clinical practice.
How likely is it that	EVIDENCE OF BENEFIT

the results of new research on this topic would be implemented in practice right away?	• New research that demonstrates benefit of a given mindfulness intervention in a well-defined sample of patients with a depressive, anxiety, or pain condition may result in more patients with that condition engaging in that intervention. • Likelihood of healthcare providers recommending a mindfulness intervention more often as the result of new research may be relatively low, however, in part because of limited dissemination through professional channels and therefore the healthcare providers are not sufficiently informed; or because the new research is unlikely to be placebo-controlled. EVIDENCE OF NO BENEFIT OR HARM • New research on this topic that demonstrates no benefit is not likely to have much impact on practice. Research that demonstrated harm (without benefit) may have a modest impact on patients' enthusiasm for trying or continuing with a mindfulness intervention.
Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies?	Although mindfulness techniques continue to evolve—and there are debates within the field in terms of which interventions to specifically include as mindfulness-based interventions—it is likely that new information regarding their use for pain, depression, or anxiety, as well as the comparative effectiveness of these techniques once established with high-quality CER would remain relevant.

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APPENDIX: TOPIC QUESTION

Compare the effectiveness of mindfulness-based interventions for the treatment of anxiety, depression, and pain.

TOPIC 11: Concussion Management

What is the comparative effectiveness of complete rest, complete rest with the addition of pharmacotherapy, rest with gradual introduction of normal home activities, rest with gradual introduction of vestibular/ocular rehabilitation, rest with gradual introduction of cognitive rehabilitation, or combinations, in term of the average duration before the affected person is deemed fit to return to full activities?

Criteria	Brief Description
Introduction	
Overview/definition of topic	DESCRIPTION OF CONDITION • Concussion is a term used to describe a form of traumatic brain injury (TBI). It is defined as "a complex pathophysiological process affecting the brain, induced by biomechanical forces."[1] • A concussion may occur when the head hits an object, or a moving object strikes the head. It can affect how the brain works for a brief period of time. A concussion can lead to a bad headache, changes in alertness, or loss of consciousness.

Relevance to patient-centered outcomes	SYMPTOMS
	• Concussion typically results in the rapid onset of short-lived impairment of neurologic function that resolves spontaneously, but symptoms and signs can evolve over minutes or hours.
	• After a concussion, a person may have trouble concentrating and may be unable to remember things. The person may be irritable or have headaches, dizziness, blurry vision, and nausea that come and go.
	• In a small proportion of patients, symptoms of concussion do not go away.
	
	OUTCOMES
	• Concussion may result in neuropathological changes without detectable abnormalities on standard structural neuroimaging studies.
	• Concussion results in a graded set of clinical symptoms that may or may not involve loss of consciousness.
	• 80% to 90% of concussions resolve within 7 to 10 days, with a typically longer recovery timeframe in children and adolescents.[1]
	  ○ 3 months after a concussion, children 8 to 16 years of age have been found to have persistent deficits in processing complex visual stimuli.[2]
	• Although the majority of athletes who experience a concussion are likely to recover, an unknown number of these individuals may experience chronic cognitive and neurobehavioral difficulties related to recurrent injury (i.e., postconcussion syndrome). Symptoms may include:
	  ○ Chronic headaches
	  ○ Fatigue
	  ○ Sleep difficulties
	  ○ Personality changes (e.g., increased irritability, emotionality)
	  ○ Sensitivity to light or noise
	  ○ Dizziness when standing quickly
	  ○ Deficits in short-term memory, problem-solving, and general academic functioning
	• Compared with similar young athletes without a history of concussion, athletes with 2 or more concussions demonstrated statistically significant lower grade-point averages.4 (Moser 2008)
	• Long-term effects of concussion or concussions are not known.
	  ○ There is a potential relationship between chronic traumatic encephalopathy and concussions/contact sports.

Burden on Society	

Recent incidence and prevalence in populations and subpopulations	INCIDENCE AND PREVALENCE
	• In 2009, an estimated 248,418 children (aged 20 or younger) were treated in U.S. emergency departments for sports and recreation-related injuries that included a diagnosis of concussion or TBI.[3]
	  ○ From 2001 to 2009, the rate of emergency department visits for sports and recreation-related injuries with a diagnosis of concussion or TBI, alone or in combination with other injuries, rose 57% among children (aged 20 or younger).
	• Concussion risk appears to be greater for females than males in basketball and soccer,[4] possibly due to smaller neck muscle mass.[5]
	• Preexisting learning disabilities may increase the negative effect of concussions on cognitive performance.[6]
	• The risk of repeated concussion is highest within the first 10 days following a concussion.[4]
	• The American Academy of Neurology Position Statement attributes the increasing incidence of recreation-related concussion to:
	  ○ Increased recognition
	  ○ Increased exposure
	  ○ Possibly decreasing physical fitness
	  ○ More youth engaged in collision sports year-round
	• Symptoms consistent with concussion are frequently underreported by student athletes.[7]

Effects on patients' quality of life, productivity, functional capacity, mortality, use of health care services	QUALITY OF LIFE, PRODUCTIVITY, AND FUNCTIONAL CAPACITY
	• During the days or weeks after a concussion, quality of life, productivity, and functional capacity are often significantly affected by pain, cognitive symptoms, other symptoms, and restriction of daily activities.
	• Evidence pertaining to long-term effects of concussion is inconsistent.
	  ○ In one study of 214 patients with mild traumatic brain injury (mTBI), 50% of patients that were followed prospectively reported long-term consequences 3 years after the injury.[8]
	  ○ Another study of 37 patients reported relatively normal functionality and quality of life 12 months after mild closed head injury.[9]
	  ○ Among 120 children aged 5 to 17 years who sustained mTBI, health-related quality of life was not found to differ before mTBI compared with after mTBI at various time points up to 12 months.[10]
	  ○ A study of 302 collegiate athletes demonstrated that a history of 1 or more concussions was associated with statistically significant lower scores on the bodily pain, vitally, and social function subscales of a quality-of-life questionnaire (SF-36).[11]
	  ○ A cross-sectional cohort study with 3214 individuals without a history of concussion and 254 patients who experienced mTBI with altered consciousness demonstrated that mTBI was associated with poorer psychosocial outcomes, including an increased likelihood of self-reported disability, underemployment, low income, and marital problems.[12]
	• With proper diagnosis and management, most patients with mTBI recover fully.

How strongly does this overall societal burden suggest that CER on alternative approaches to this problem should be given high priority?	• The incidence of recognized concussion is on the rise among children, adolescents, and young adults. • There is also a growing awareness of the potential for long-term cognitive decline secondary to repeated concussions. • A high proportion of young people engage in activities/sports that put them at risk for concussion. • There is currently great uncertainty regarding optimal management after concussion. • State laws, sport-wide policies, school policies, and clinical guidelines are actively being developed to guide postconcussion management and return-to-play protocols. • CER of current and alternative approaches to postconcussion management has the potential to have a high impact on the relatively high overall societal burden associated with concussion.
Options for Addressing the Issue	
Based on recent systematic reviews, what is known about the relative benefits and harms of the available management options?	Systematic reviews/available data: • No recent systematic reviews were identified that compared alternative approaches for postconcussion management. • A systematic review that aimed to identify predictors of persistent concussion symptoms (PCS) in children following concussion, which identified 15 studies, concluded that "minimal, and at times contradictory, evidence exists to associate clinically available factors with eventual development of PCS in children."[13] • The question, "What is the evidence for concussion therapies?" was addressed at the 4th International Conference on Concussion in Sport held in 2012 and led to the statement that "The current evidence evaluating the effect of rest and treatment following sport-related concussion is sparse. An initial period of rest may be of benefit. However, further research to evaluate the long-term outcome of rest, and the optimal amount and type of rest, is needed."[1] SCREENING/EARLY DIAGNOSIS • Multimodal assessment instruments such as the Sport Concussion Assessment Tool (SCAT) is useful in early diagnosis. The Consensus Statement on Concussion in Sport[1] recommends improvement of the SCAT2 and that a new tool (Child SCAT3) be developed for young children. • If any of the following symptoms or signs are present after a head injury, a concussion should be suspected: o Somatic, cognitive, or emotional symptoms o Physical signs o Behavioral changes o Cognitive impairment o Sleep disturbance

	TREATMENT AND MANAGEMENT OPTIONS[1]
	• Concussion management includes physical and cognitive rest until the acute symptoms resolve as well as a graded program of exertion prior to medical clearance and return to play.
	  ○ The current published evidence evaluating the effect of rest following a sport-related concussion is sparse.
	• The Graduated Return to Play Protocol consists of 5 sequential rehabilitation stages, with a recommendation of at least 24 hours in each stage before returning to play:
	  1. No activity
	  2. Light aerobic exercise
	  3. Sport-specific exercise
	  4. Noncontact training drills
	  5. Full contact practice
	
	In 2009, Washington State passed the first concussion sports law (known as the Zackery Lystedt Law); Oregon followed shortly after with Max's Law. Between 2009 and 2012, 43 states and the District of Columbia passed laws on concussion in sports for youth and/or high school athletes often referred to as "return to play" laws.[14] Four more states have pending legislation.

What could new research contribute to achieving better patient-centered outcomes?	New research could contribute to achieving better patient-centered outcomes: • Nearly all the studies that informed the new American Academy of Neurology guideline on the relationship between concussion and neurocognitive outcomes in athletes were cross-sectional or retrospective studies.[15] • Use of a symptom-based definition of concussion would increase the accuracy of reporting for both research and clinical purposes.[4] • Further research is needed to evaluate the long-term outcome of rest and the optimal amount and type of rest.
Have recent innovations made research on this topic especially compelling?	There are no specific innovations in this domain that make this topic especially compelling, but the evidence base for optimal management strategies is particularly sparse.
How widely does care now vary?	VARIABILITY IN CARE • The level of awareness about concussion among young athletes and their parents is relatively high, but evidence suggests that mothers are more likely than fathers to consider concussion a "critical issue," and female athletes appear to report less peer pressure regarding "caring about concussions" than their male counterparts.[16] • There does not appear to be a universally accepted standard of care for postconcussion care or return-to-play protocols. There is variability among state laws that support the recognition and management of student athletes with concussion. • The Consensus Statement recommends a 5-stage graduated return-to-play protocol (listed above).[1]

What is the pace of other research on this topic (as indicated by recent publications and ongoing trials)?	RECENT PUBLICATIONS A PubMed search of the English-language literature published in the past 5 years using search terms that included “brain concussion/therapy” or “brain concussion/diagnosis” in children and young adults identified 17 systematic reviews, 1 published guideline, 15 RCTs, and 187 cohort studies. ONGOING TRIALS There are 39 ongoing trials listed in www.clinicaltrials.gov that are studying concussions. A few notable studies include: • “Exercise for Adolescents Following Sport-Related Concussion: A Randomized Control Trial” plans to evaluate outcomes associated with an active rehabilitation program compared with treatment as usual among 30 children and young adults. • “Aerobic Training for Management of Post-Concussion Syndrome in Adolescents” compares aerobic training with stretching among 30 children with postconcussion syndrome. • “Clinical Trial of a Rehabilitation Game—SuperBetter” evaluates the outcomes associated with a behavioral intervention among 40 children and adults postconcussion. • An mTBI registry is being established to determine which biomarkers and/or clinical variables correlate with long-term symptoms of mTBI.

How likely is it that new CER on this topic would provide better information to guide clinical decision making?	KEY UNCERTAINTIES IN CLINICAL DECISION MAKING
	Comparative effectiveness data are very sparse in this field. Therefore, the key uncertainties are broad and include:
	• What are the optimal strategies to prevent, predict, manage, objectively grade, and follow concussions?
	• What is the comparative effectiveness of the following strategies in terms of the average duration before the affected person is deemed fit to return to full activities?
	  ○ Complete rest
	  ○ Complete rest with the addition of pharmacotherapy
	  ○ Rest with gradual introduction of normal home activities
	  ○ Rest with gradual introduction of vestibular/ocular rehabilitation
	  ○ Rest with gradual introduction of cognitive rehabilitation
	  ○ Combinations of strategies
	
	LIKELIHOOD THAT CER WOULD BE ABLE TO REDUCE THESE UNCERTAINTIES
	• There is a paucity of reliable and valid information about the comparative effectiveness of available strategies for concussion management in children and young adults.
	• Evaluations to perform comparisons of these strategies may potentially have study design issues related to needed sample sizes, standardizations of strategies, assessment and validation of patient-reported outcomes, and ethical and legal barriers.
	• If such CER studies were performed, there is, however, a high likelihood that most or all of the many stakeholders (e.g., patients, parents, clinicians, policymakers, coaches, and trainers) would refer to findings from new CER on this topic to guide clinical decision making.

Potential for New Information to Improve Care and Patient-Centered Outcomes	
What are the facilitators and barriers that would affect the implementation of new findings in practice?	FACILITATORS • Since 2009, 43 states have passed laws supporting proper recognition and management of student-athletes with concussion (4 additional states have pending legislation). Most of these laws stipulate that fitness to return to activity be assessed exclusively by a licensed healthcare professional. • There seems to be a growing awareness that concussion incurred as a child or young adult may have long-term sequelae. BARRIERS • Athletes may continue to underreport symptoms if they want to continue to engage in physical or cognitive activities after sustaining a head injury that may have resulted in a concussion. • Parents may apply pressure on their children and/or their children's coaches or trainers to minimize disruption of training or time engaged in sports activities. • Coaches or trainers may want certain athletes to return to play as soon as possible (or not miss any playing or training time). • Leagues or schools or other institutions may resist guidelines that result in prolonged return-to-play protocols. • There is a possibility that evidence clearly linking concussion during one's youth with serious cognitive deficits later in life is not yet universally compelling.
How likely is it that the results of new research on this topic would be implemented in practice right away?	EVIDENCE OF BENEFIT, NO BENEFIT, OR HARM • There is a high likelihood that results of new research on this topic would be implemented in practice right away. The stakes pertaining to this topic are generally considered to be high. Any compelling evidence associated with the many possible approaches to the management of concussion among children and young adults is likely to be implemented quickly, irrespective of whether the evidence suggests benefit, no benefit, or harm associated with one or more possible approaches. • However, much effort and political capital have been expended in recent years to enact statewide laws and institutional policies that are intended to protect children and young adults from long-term harm resulting from concussion. Consequently, new research on this topic that suggests the appropriateness of less rest or faster return-to-play protocols, relative to the policies and protocols reflected in recently passed statewide laws, may not likely be implemented in practice.
Would new information from CER on this topic remain current for several years, or would it be rendered obsolete quickly by subsequent studies?	Research in this area is difficult to conduct, in part because of existing laws that prescribe general or specific protocols. Also, there is currently both a paucity of reliable and valid information on this topic and a strong desire for such information to help inform clinical decision making. As such, new information from CER on this topic that helps guide clinical or individual decision making is likely to remain current for several years, and information that informs policy or legislative action is also likely to remain current for many years.

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APPENDIX: TOPIC QUESTION

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