

Evidence-based Practice Center Systematic Review Protocol

Project Title: Comparative Effectiveness of Intravascular Diagnostic Procedures and Imaging Techniques versus Angiography Alone

Amendment Dates: 3/1/12, 5/1/12
(see Appendix VII)

I. Background and Objectives for the Systematic Review

Coronary artery disease (CAD) is a leading cause of morbidity and mortality worldwide, accounting for 35 percent of all deaths in the United States and 30 percent of all deaths globally in 2005.¹ The diagnosis of CAD is made on the basis of stenosis within one or more coronary epicardial arteries. Treatment options for CAD include medical therapy and invasive revascularization with either percutaneous coronary intervention (PCI) or bypass surgery. Clinical recommendations for revascularization have traditionally been based on qualitative and quantitative coronary angiography. While angiograms are still regarded as the reference standard for anatomic visualization of coronary arteries, they are not without limitation.

Coronary angiograms only visualize an outline of the luminal wall and are generally ineffective in determining the functional importance of stenoses. Angiographic evidence of stenosis is usually not detected until the plaque approaches 40 to 50 percent of the total cross-sectional area of the coronary artery, because the outer wall of the artery enlarges to accommodate the growing plaque (positive remodeling).² Thus, for intermediate ranges of coronary stenoses (40 to 80 percent), there is considerable variability between physiologic and angiographic assessments of the severity of stenosis, often making it difficult to determine whether PCI is needed.³ In addition, most complex plaques do not reveal sufficient alterations by angiography, thereby limiting assessment of complex lesions with this technique (e.g., ostial, graft, or bifurcation lesions). Moreover, angiograms cannot provide information on the composition of the coronary plaque, which could be important in determining therapeutic choices.²

Several adjunctive intravascular diagnostic procedures and imaging techniques (collectively referred to as IVDx) have been developed for the purpose of providing more detailed anatomic and hemodynamic information. IVDx techniques do not preclude the need for angiography but rather are complementary in nature by assisting treatment decisionmaking.⁴

Among the IVDx imaging techniques used to visualize coronary anatomy, intravascular ultrasound (IVUS) is the most common. During PCI, IVUS provides high-resolution images of the vessel and lumen geometry and enables analysis of plaque composition and distribution, as well as guidance of coronary stent implantation. IVUS can also be used to quantitatively assess revascularization success or diagnose stent-related complications,^{5,6} but it does not directly measure the hemodynamic effects of a stenosis.

Fractional flow reserve (FFR), in contrast, is an IVDx technique used to determine the physiologic significance of a coronary stenosis. An FFR value <0.75 indicates inducible ischemia, 0.75–0.80 represents an intermediate “grey” zone, and a value >0.80 generally excludes ischemia related to a specific stenosis.^{3,7,8}

Other IVDx techniques that are less widely used or are still evolving include coronary flow reserve (CFR), IVUS-virtual histology (VH-IVUS), integrated backscatter IVUS, optical coherence tomography (OCT), near-infrared spectroscopy, angioscopy, thermography, and intravascular magnetic resonance imaging (MRI).

IVDx techniques are potentially valuable in a number of clinical scenarios. For example, as previously described, IVUS provides precise visualization of intracoronary anatomy, atherosclerotic plaque composition, and changes in vessel dimensions. Its use could diagnose patients who have coronary stenoses that might otherwise be missed, thereby improving long-term clinical outcomes. Conversely, FFR might help identify patients whose stenoses are not really impeding flow and thereby reduce the number of unneeded stents and limit patient exposure to blood thinners and repeat revascularizations.

Nevertheless, these techniques remain invasive, and their application can result in procedure-related complications or increased procedural times and initial costs and possibly generate additional unnecessary invasive tests or unnecessary treatments that can adversely impact long-term clinical outcomes. Therefore, their use should be weighed by considering the potential benefit of the additional diagnostic information gained versus noninvasive alternatives. These decisions are not always straightforward. Other, noninvasive imaging techniques for evaluating stenoses (e.g., cardiac computed tomography) that are available have a much lower resolution than IVUS. Moreover, invasive techniques such as IVUS are able to detect plaques much earlier than cardiac MRI, that is before the plaques attain maximum maturity.⁹ In addition, available noninvasive methods are not also without their own associated adverse events, costs, and technology-specific risks (e.g., exposure to radiation). Thus, despite their potential drawbacks, invasive IVDx modalities have emerged as potentially important complementary tools to angiography.

Recent clinical practice guidelines have indicated that FFR and IVUS can be useful in certain clinical contexts—specifically, FFR in determining the necessity of PCI and IVUS for providing technical guidance during PCI and optimizing PCI results.^{10,11} However, the currently available guidelines and systematic reviews do not comprehensively examine the role of IVDx techniques in relation to the settings of interest and are not generally applicable to contemporary practice, as recent literature (e.g., for drug-eluting stents) has not yet been thoroughly reviewed. Furthermore, variation in how IVDx techniques are adopted in clinical practice across catheterization laboratories reflects considerable uncertainty about the utility and role of these techniques.¹² Thus, a comparative effectiveness review on the use of IVDx applications in patients with CAD is timely and necessary to assess the clinical impact of incorporating such techniques into coronary catheterization procedures.

II. Key Questions

Response to Public Comments

The Key Questions (KQs) for our review were posted on the Effective Health Care Program Web site (<http://effectivehealthcare.ahrq.gov>) for public comment from March 22 to April 19, 2011. Public comments received through the Web site were considered in preparation of this protocol.

In response to a request to clarify the role of IVDx techniques in the choice of a specific PCI technique, we have defined the clinical context of each KQ and pointed out that KQ 2 would

address this clinical question specifically. We do not plan to evaluate technical attributes of each technique, since the focus of our review will be assessment of clinical outcomes. Despite the potential lack of evidence on clinical outcomes, we will include all relevant KQs and identify future research needs when appropriate.

We plan to evaluate the impact of IVDx techniques on the diagnostic thinking of physicians. In defining the outcomes to be analyzed in our review, we provide explicit examples of the terms “diagnostic thinking” and the types of outcomes that fall under its formal definition in the evaluation of diagnostic tests.¹⁵

On the basis of input from Key Informants during the Topic Refinement phase, this review will not examine diagnostic test performance (e.g., sensitivity and specificity) for the following reasons:

1. Other than FFR, whose diagnostic accuracy has been established in a previous meta-analysis,¹³ all other IVDx techniques concern the histopathological structure of lesions and thus require a histopathological specimen to confirm imaging findings.
2. Based on a previous literature review,¹⁴ we identified that such literature is limited.
3. Such an evaluation clearly falls outside the scope of our review, which is to evaluate the impact of the information provided by the application of IVDx techniques on a set of clinical outcomes.

Key Questions (KQ)

Our review will focus on the following five KQs:

- *Key Question 1:* For patients undergoing diagnostic coronary angiography to evaluate the presence/extent of CAD in order to decide on the necessity for coronary intervention, what is the impact of using an IVDx technique—when compared to angiography alone—on the diagnostic thinking and therapeutic decisionmaking, short-term outcomes, and long-term outcomes?
- *Key Question 2:* For patients undergoing PCI, what is the impact of using an IVDx technique to guide the PCI procedure (either immediately prior to or during the procedure)—when compared to angiography-guided PCI—on the diagnostic thinking and therapeutic decisionmaking, short-term outcomes, and long-term outcomes?
- *Key Question 3:* For patients having just undergone a PCI, what is the impact of using an IVDx technique to evaluate the success of PCI immediately after the procedure—when compared to angiography alone—on the diagnostic thinking and therapeutic decisionmaking, short-term outcomes, and long-term outcomes?
- *Key Question 4:* How do different IVDx techniques compare to each other in their effects on the diagnostic thinking and therapeutic decisionmaking, short-term outcomes, and long-term outcomes?
 - a) During diagnostic coronary angiography for the evaluation of the presence/extent of CAD and the potential necessity of coronary intervention?
 - b) During PCI to guide the procedure?
 - c) Immediately after PCI to evaluate the success of PCI?

- *Key Question 5:* What factors (e.g., patient/physician characteristics, availability of prior noninvasive testing, type of PCI performed) influence the effect of IVDx techniques—when compared to angiography (or among different IVDx techniques)—on the diagnostic thinking and therapeutic decisionmaking, short-term outcomes, and long-term outcomes?
 - a) During diagnostic coronary angiography for the evaluation of the presence/extent of CAD and the potential need for coronary intervention?
 - b) During PCI to guide the procedure?
 - c) Immediately after PCI to evaluate the success of PCI?

Eligibility Criteria

Eligible studies to be included in our review should fulfill the following inclusion criteria with respect to population, interventions, comparators, outcomes, timing, study designs, and settings (PICOTS).

Populations

- Adults (≥ 18 years)
- *For KQs 1, 4a, and 5a:* Patients who undergo diagnostic coronary angiography and are evaluated for the presence or extent of CAD in order to decide on the need for coronary intervention.

All patients considered to be candidates for coronary interventions can be evaluated on the basis of the following subgroups, as reported in individual studies:

- Intermediate coronary stenoses (>40 – 50 percent and <70 – 80 percent), either ischemic or nonischemic
- Left main artery lesions
- Any type of complex coronary lesions (e.g., long diffuse lesions, tandem lesions, bypass conduit vessel lesions, bifurcation lesions, total occlusions, ostial lesions, stent thromboses, thrombotic and nonthrombotic lesions; in-stent restenosis; and those with stent fractures)
- Nonobstructive coronary lesions (e.g., vulnerable plaques)
- *For KQs 2, 4b, and 5b:* Patients who need PCI and are evaluated with an IVDx technique and/or angiography to guide the PCI procedure (either immediately before or during the procedure)
- *For KQs 3, 4c, and 5c:* Patients evaluated with an IVDx technique and/or angiography immediately after PCI (stent placement or other type of PCI) to evaluate the success of PCI (and the potential need for reintervention).
- *Subgroups of interest for all KQs:*
 - Patients with different manifestations of CAD (ST segment elevation myocardial infarction [STEMI], non-STEMI, unstable angina, and stable angina)
 - Patients who have diabetes and those who do not

- Patients with chronic inflammation (e.g., systemic lupus erythematosus)
- Patients who have atherosclerosis following a heart transplant

Interventions

- *For all KQs:* Intravascular diagnostic procedures that evaluate morphological or physiological parameters of coronary lesions:
 - Interventions presently employed in clinical care, as recommended by technical expert panel:
 - FFR
 - IVUS
 - Interventions that are mainly investigational at present:
 - IVUS with virtual histology
 - Optical coherence tomography
 - Elastography
 - Near-infrared spectroscopy
 - Thermography
 - Angioscopy
 - Intravascular MRI
 - Other indices such as stenosis index and index of microcirculatory resistance

Comparators

- *For KQs 1–3 and 5:* Conventional coronary angiography
- *For KQs 4 and 5:* Any index IVDx technique (for head-to-head comparisons)

Outcomes

Outcomes of interest are categorized into two types: diagnostic and treatment thinking outcomes and process and patient-centered outcomes.

Diagnostic thinking and therapeutic decisionmaking outcomes include:

- *KQ 1:* During diagnostic workup of CAD, the change in the number of hemodynamically significant lesions after the application of IVDx, or the change in the decision about an interventional therapy (e.g., if PCI is needed) after the application of IVDx
- *KQ 2:* During PCI, the change in the number of diagnoses of a complex lesion requiring additional intervention after the application of IVDx, or the change in the type of PCI treatment after the application of IVDx
- *KQ 3:* Immediately after PCI, the change in the number of successful PCIs after the application of IVDx, or how frequently the decision about the need for reintervention planned before IVDx changed after the test

Process and patient-centered outcomes are further categorized into short-term outcomes and intermediate or long-term outcomes. They are as follows:

- Short-term (≤ 30 days) outcomes:
 - In-hospital procedural outcomes
 - Process outcomes (technical success rates assessed by quantitative coronary angiography [QCA], such as proportion of successful completion of attempted procedures or proportion of interpretable results in completed procedures, total procedural time required, fluoroscopy, and contrast agent exposure)
 - Periprocedural complications (e.g., MI, death, vessel dissection, bleeding, repeat PCI, or bypass surgery)
 - Stent-related complications (e.g., acute stent thrombosis, and dissection)
 - Clinical outcomes (e.g., acute MI, length of hospital stay)
 - Resource utilization (e.g., number of guide catheters, wires, balloons, and stents)
 - Discharge to 30-day outcomes
 - Surrogate outcomes (e.g., QCA parameters of PCI success, electrocardiographic ischemia, biochemical markers, noninvasive assessment using MRI, a high-intensity signal on the doppler flow wire during PCI, and lumen diameter)
 - Clinical outcomes (e.g., acute MI, length of hospital stay, rehospitalization, stent thrombosis, restenosis, and repeat revascularization)
- Intermediate (≥ 30 days to 1 year) and long-term (> 1 year) outcomes, including:
 - Stent-related outcomes (restenosis, thrombosis, repeat revascularization)
 - Surrogate outcomes (cardiac imaging findings [such as ventricular function or myocardial perfusion], electrocardiographic ischemia, biochemical markers, noninvasive assessment using MRI, a high-intensity signal on doppler flow wire during PCI, and lumen diameter)
 - Clinical outcomes (MI, death, revascularization or composites of major adverse cardiovascular events, freedom from angina, quality of life, and quality-adjusted survival).

Timing

- Any duration of followup

Study designs of interest

- For diagnostic thinking and therapeutic decisionmaking outcomes, the following study designs will be considered eligible:

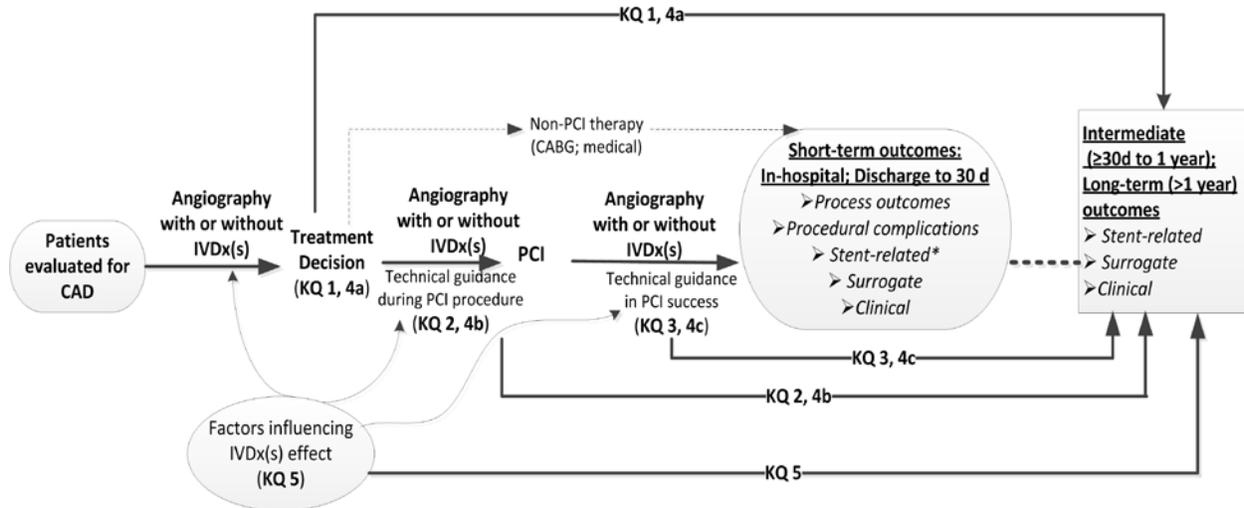
- Randomized clinical trials (RCTs)
- Nonrandomized comparative cohort (observational) studies
- Cohort studies that provide data comparing IVDx technique and angiography with angiography alone
 - *For KQs 1–3 and 5:* Studies that compared diagnostic thinking and decisionmaking by applying an IVDx technique in angiographically demonstrated lesions within the same population
 - *For KQs 4 and 5:* Studies that compared diagnostic thinking and decisionmaking by applying two IVDx techniques within the same population
- For process and patient-centered outcomes, the following study designs will be considered eligible:
 - RCTs
 - Nonrandomized comparative cohort (observational) studies
- No minimum sample size requirement (to be re-evaluated when the literature is being screened; if there are sufficient data from large trials such that adding the smaller trials would not influence the final conclusions, then a minimum sample size will be imposed after consulting with the TEP)

Settings

- Application of IVDx techniques and use in the following settings:
 - Tertiary care centers or community hospitals
 - In-hospital or stand-alone catheterization laboratories
 - Emergent and nonemergent catheterizations

III. Analytic Framework

Figure 1. Analytic framework for intravascular diagnostic procedures and imaging techniques compared with angiography alone in patients with coronary artery disease



*Undergoing stent implantation.

Abbreviations: CABG = coronary artery bypass grafting; CAD = coronary artery disease; IVDx = intravascular diagnostic technique; KQ = key question; PCI = percutaneous coronary intervention.

This figure depicts the KQs described in the previous section within the context of the PICOTS (population, intervention, comparators, outcomes, timing, study designs, and settings) criteria. In general, the figure illustrates how intravascular diagnostic procedures and imaging techniques—when compared with angiography—may aid treatment decisionmaking during diagnostic angiography, allow procedure optimization and assessment of immediate results in patients undergoing PCI, and improve short-term (in hospital or discharge to 30 days), intermediate (≥ 30 days to 1 year), and long-term (> 1 year) outcomes. Angiography alone is the comparator for KQs 1–3. For KQ 4, the comparator is a different IVDx technique from the index IVDx technique of interest (head-to-head comparisons of IVDx techniques).

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

We will use the eligibility criteria for populations, interventions, comparators, outcomes, timing, study designs, and settings (PICOTS) as enumerated above. We do not expect to contact authors for additional data. We will add data from grey literature sources such as Scientific Information Packages from manufacturers, Transcatheter Cardiovascular Therapeutics, the American Heart Association, and the American College of Cardiology and its i2 (Innovation in Intervention) summit conferences. We will eliminate duplicates of published reports. We will extract relevant data and assess methodological quality. If all these studies are of poor methodological quality, then we will conduct sensitivity analyses with and without unpublished studies.

Although the distinction between studies that apply to decisionmaking (KQ 1) versus PCI technical guidance (KQs 2 and 3) is expected to be straightforward, we anticipate that inadequate reporting on the actual timing of the performance of IVDx techniques in certain studies (immediately prior to versus after PCI) may not always render feasible drawing the distinction

between studies that belong to KQ2 or KQ3. For example, a study that reports that IVUS-guided stenting was compared to angiography-guided stenting without specifying the timing that IVUS was performed with regards to stent deployment may fall within the scope of both KQ2 and KQ3. Based on clinical consultation with experts, we will assign such studies to the scope of KQ3, since application of IVDx techniques for PCI technical guidance is mostly applied in clinical practice at the “immediately after PCI” time point to evaluate stent deployment results.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

Appendix Table 1 at the end of this document contains the proposed literature search strategy. We will conduct the search in MEDLINE[®] and in the Cochrane Central Register of Controlled Trials. We will manually screen all abstracts available in English according to the eligibility criteria, and exclusions will be cross-checked by a second member of the team. The full-text articles of all eligible abstracts will then be reviewed for eligibility. We will tabulate the reasons for excluding any full text articles. For those articles not available in English, we will review the article in its native language, providing someone who has adequate expertise can be identified. A list of articles excluded because of language will be included in the final report. We will ask the internal domain experts to inform us of any potentially missing articles. All suggested articles will be screened for eligibility according to the same criteria used for the original articles. If necessary, we will revise the literature search to find articles similar to those missed. Additional articles will be retrieved from existing guidelines, as well as narrative and systematic reviews. Following submission of the draft report, we will run an updated literature search (using the same search strategy) and will add any relevant articles we find to the final report.

C. Data Abstraction and Data Management

Each study extraction will be conducted by one experienced methodologist and reviewed by at least one other methodologist. Any disagreements will be resolved by discussion in team meetings. Data will be extracted into standard forms in Microsoft[®] Word. The basic elements and design of these forms will be the same as those we have used for other comparative effectiveness reviews and will include fields that address population characteristics, sample size, study design, analytic details, and outcomes. We will also extract basic demographic data such as age, sex, race, type of index disease (chronic vs. acute CAD), comorbidities, and any other factors that may have a role in modifying the association between the application of IVDx and outcomes. Prior to use, the form will be customized to capture all such elements relevant to the KQs. We will test the extraction form on several studies and revise the form as necessary before full data extraction of all articles is performed.

D. Assessment of Methodological Quality of Individual Studies

We will use methods for evaluating study quality that are standard within the Evidence-based Practice Center (EPC) Program and are recommended by the Agency for Healthcare Research and Quality in the *Methods Guide for Effectiveness and Comparative Effectiveness Review*, hereafter referred to as the *AHRQ Methods Guide*.¹⁶ Briefly, we will rate each study as being of

good, fair, or poor quality based on their adherence to well-accepted standard methodologies. The grading will be outcome specific such that a given study that analyzes its primary outcome well but did an incomplete analysis of a secondary outcome would be assigned a different quality grade for each of the two outcomes. Studies of different designs will be graded within the context of their respective designs. Thus, RCTs will be graded good, fair, or poor, and observational studies will separately be graded good, fair, or poor. However, we expect retrospective studies will likely be of fair or poor quality due to the increased risk of bias inherent in retrospective study designs.

E. Data Synthesis

All included studies will be summarized in narrative form and in summary tables that tabulate the important features of the study populations, design, intervention, outcomes, and results. We will consider performing meta-analyses where there are at least three nonoverlapping studies that are deemed to have sufficiently similar populations, compare the same interventions (i.e., specific type of IVDx technique vs. angiography) and assess the same outcomes. Further analyses will be stratified based on patient- and lesion-level characteristics (diabetes, length of lesion, etc.). We expect to require input from the clinical experts (cardiologists or radiologists) in our team to assess whether studies are too clinically heterogeneous for meta-analysis to be appropriate. We will perform random effects model meta-analyses of continuous, binary, and time-to-event outcomes, as deemed appropriate. The findings of the report will be presented according to the order of the KQs. Within each KQ, findings will be presented separately for diagnostic thinking and therapeutic decisionmaking, as well as for short-term, intermediate, and long-term outcomes. They will be further categorized to specific epochs: in hospital, discharge to 30 days, >30 days to 1 year, and >1 year. Outcome data of interest will include periprocedural complications and process, stent-related, surrogate, and clinical outcomes. Outcome data will be presented in detailed evidence tables and will be summarized in the full text and the executive summary of the report.

F. Grading the Evidence for Each Key Question

We will follow the *AHRQ Methods Guide* to grade the strength of the body of evidence for each KQ with respect to four domains: risk of bias, consistency, directness, and precision.

Briefly, we will define the risk of bias (low, medium, or high) based on the study design and the methodological quality of eligible studies. We will label the consistency of the data as either “no inconsistency” or “inconsistency present” (or “not applicable” if there is only one study). We do not plan to use rigid counts of studies (e.g., 4 of 5 agree, therefore consistent); instead, we will evaluate the direction, magnitude, and statistical significance of effects across all studies and make a determination. We will describe our logic where studies are in conflict.

We will assess the precision (precise or imprecise) of the evidence based on the degree of certainty surrounding an effect estimate. A precise estimate is an estimate that would allow a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions—for example, both clinically important superiority and inferiority (i.e., the direction of effect is unknown), a circumstance that will preclude a conclusion.

We will assess the directness (direct or indirect) of the evidence, whether there is a single, direct link between the intervention(s) of interest and the health outcome under consideration. If the studies do not directly compare the tests of interest, we will use network analysis to estimate the comparative effect.

As directed by the *AHRQ Methods Guide*, we will assign four possible grades for strength of evidence levels: high, moderate, low, and insufficient. These assignments will be based on our level of confidence that the evidence reflects the true effect for the major comparisons of interest.

G. Assessing Applicability

The following factors will be evaluated to assess applicability of study results: age, center characteristics (tertiary vs. community, patient volume, single center vs. multicenter), operator characteristics (e.g., experience), and evaluation of populations with comorbid conditions.

V. References

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VI. Definition of Terms

All terms requiring definition have been addressed in the background and objectives.

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

Date	Section	Original Protocol	Revised Protocol	Rationale
3/1/2012	Key Question 1	For patients undergoing diagnostic coronary angiography to evaluate the presence/extent of CAD in order to decide on the necessity for coronary intervention, what is the impact of	In patients with CAD, what is the impact of using an IVDx technique and angiography in deciding whether a coronary lesion requires intervention—when compared to angiography alone—on outcomes?	To improve clarity of the Key Question.

		using an IVDx technique—when compared to angiography alone—on outcomes?		
5/1/2012	Outcome presentation of Analytical Framework, Methods, and Results section	Diagnostic thinking, therapeutic decisionmaking, and short- and long-term outcomes	Therapeutic decisionmaking, intermediate outcomes, and patient-centered outcomes	To improve clarity of the presentation
5/1/2012	All sections	IVDx	Intravascular Diagnostic techniques	Avoid use of unconventional abbreviation

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and do not have the opportunity to review the report, until the public review period.

Technical Experts must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than \$10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism. It is our policy not to release the name of the Peer reviewers of TEP panel members until the report is published so that they can maintain their objectivity during the review process.

Appendix Table 1. Search strategy (updated and run on June 2011)

#	Searches	Results
1	intravascular.af.	38,643
2	intra-vascular.af.	214
3	endovascular.af.	25,071
4	endo-vascular.af.	19
5	endocoronary.af.	39
6	endo-coronary.af.	4
7	intra-coronary.af.	185
8	intracoronary.af.	9,142
9	endoluminal.af.	3,133
10	endo-luminal.af.	12
11	transluminal.af.	14,433
12	trans-luminal.af.	26
13	intraluminal.af.	12,938
14	intra-luminal.af.	232
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	9,8862
16	magnetic resonance imaging.af.	266,900
17	magnetic resonance angiography.af.	15,166
18	exp magnetic resonance imaging/	247,897
19	exp magnetic resonance angiography/	13,548
20	elastography.af.	1,307
21	thermography.af.	6,794
22	microcirculatory resistance.af.	32
23	vascular resistance.af.	52,884
24	thermodilution.af.	4604
25	exp Thermodilution/	2209
26	hemodynamics.af.	137,391
27	exp Hemodynamics/	557,384
28	exp endosonography/	7,125
29	physiologic measurement*.af.	316
30	doppler ultrasound.af.	9,280
31	coronary pressure.af.	474
32	doppler velocimetry.af.	1,916
33	ultraso*.af.	345,127
34	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33	1,134,074
35	15 and 34	25,039

#	Searches	Results
36	exp coronary angiography/	43,276
37	ultraso\$.af.	345,127
38	ffr.af.	739
39	fractional flow reserve.af.	563
40	coronary flow reserve.af.	1,705
41	coronary flow velocity reserve.af.	301
42	angioscop\$.af.	1,642
43	optical coherence tomography.af.	7,755
44	exp Tomography, Optical Coherence/	7,570
45	blood flow velocity.af.	50,905
46	exp Blood Flow Velocity/	48,793
47	doppler flow wire.af.	138
48	pressure wire.af.	120
49	coronary pressure measurement.af.	24
50	exp endosonography/	7,125
51	37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50	390,940
52	36 and 51	6,029
53	exp Ultrasonography, Interventional/	11,033
54	exp Fractional Flow Reserve, Myocardial/	215
55	fractional flow reserve.af.	563
56	intravascular ultrasound.af.	4451
57	IVUS.af.	2405
58	53 or 54 or 55 or 56 or 57	13,349
59	35 or 52 or 58	36,060
60	exp myocardial ischemia/	333,632
61	exp Angioplasty, Transluminal, Percutaneous Coronary/	28,041
62	exp stents/	42,961
63	exp Angioplasty, Balloon, Coronary/	28,040
64	exp Myocardial Revascularization/	74,441
65	exp drug-eluting stents/	3,317
66	61 or 62 or 63 or 64 or 65	106,646
67	60 and 66	54,147
68	59 and 67	4,131
69	remove duplicates from 68	3811
70	exp animals/ not humans.sh.	3,582,822
71	69 not 70	3,721