Research Review Disposition of Comments Report

April 2017

Research Review Title: *Treatment Strategies for Patients with Lower Extremity Chronic Venous Disease (LECVD)*

Draft review available for public comment from July 8, 2016 to August 3, 2016.

Research Review Citation: Jones WS, Vemulapalli S, Parikh KS, Coeytaux RR, Crowley MJ, Raitz G, Johnston AL, Hasselbad V, McBroom AJ, Lallinger KR, Sanders-Schmidler GD. Treatment Strategies for Patients with Lower Extremity Chronic Venous Disease (LECVD). Technology Assessment Program. Project ID: DVTT0515. (Prepared by the Duke University Evidence-based Practice Center under Contract No. HHSA290201500004I). Rockville, MD: Agency for Healthcare Research and Quality; April 2017. Available at: http://www.ahrq.gov/research/findings/ta/index.html.

Comments to Research Review

The Effective Health Care (EHC) Program encourages the public to participate in the development of its research projects. Each research review is posted to the EHC Program Web site or AHRQ Web site in draft form for public comment for a 3-4-week period. Comments can be submitted via the Web site, mail or E-mail. At the conclusion of the public comment period, authors use the commentators' submissions and comments to revise the draft research review.

Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the Web site approximately 3 months after the final research review is published. Comments are not edited for spelling, grammar, or other content errors. Each comment is listed with the name and affiliation of the commentator, if this information is provided. Commentators are not required to provide their names or affiliations in order to submit suggestions or comments.

The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

	Commentator & Affiliation	Section	Comment	Response
1.	Peer Reviewer #1	Quality of Report	Superior	No response needed
2.	Peer Reviewer #2	Quality of Report	Fair	No response needed
3.	TEP Reviewer #1	Quality of Report	Good	No response needed
4.	TEP Reviewer #2	Quality of Report	Superior	No response needed
5.	TEP Reviewer #3	Quality of Report	Good	No response needed
6.	TEP Reviewer #4	Quality of Report	Fair	No response needed
7.	TEP Reviewer #5	Quality of Report	Superior	No response needed
8.	Peer Reviewer #1	General Comments	The authors have performed a methodologically rigorous review of lower extremity chronic venous disease (LECVD). It is an important topic, given the morbidity and health care dollars involved. The target population, audience, and key questions are appropriate and clear.	We thank the reviewer for their comment. No response needed.
9.	Peer Reviewer #2	General Comments	This report is useful and timely as a review of the diagnosis and treatment of lower extremity venous disease, with appropriate adult target populations. However, the key questions could have been much better defined and the subsequent analysis therefore would have been more focused and clinically useful.	We thank the reviewer for their comment. The key questions for this report were developed through the AHRQ process with feedback from CMS and Technical Expert Panel members.
10.	Peer Reviewer #2	General Comments	[KQ definitions cont'd] Specifically, for both K2 and K3, although the pathologic differentiation is important between reflux and obstruction, the most important variable in the decision to treat and the aggressiveness/forms of treatment is the clinical presentation. These questions should have been subdivided for the more severe symptoms (patients with C4-C6: skin changes and ulcerations) and those less severe (C1-3: visible veins and edema).	We thank the reviewer for their comment. We did attempt to explore disease severity as a subgroup of interest in KQ 2 and KQ 3, although unfortunately the scarcity of data on these specific subgroups limited these findings.

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11.	Peer Reviewer #2	General Comments	[KQ definitions cont'd] In addition, obstruction and reflux can and do exist concomitantly, especially in patients with more severe disease. Therefore, the separation of the questions based primarily on this etiologic classification, although appealing, is by itself an over-simplification which subsequently limits an understanding of the clinical challenges for these patients. A much more useful process would have started off with the patients' clinical status and then subdivided the analysis into those with different etiologies and combinations thereof.	We thank the reviewer for their comment. The key questions for this report were developed through the AHRQ process with feedback from CMS and Technical Expert Panel members.
12.	TEP Reviewer #1	General Comments	The authors provide a comprehensive systematic review of treatments for lower extremity chronic venous diseases (LECVD). Although the paper is very well done, there are problems that need to be addressed. These can be divided into major and minor concerns.	No response needed
13.	TEP Reviewer #1	General Comments	Although comprehensive, the paper is very long and is difficult to read. Greater use of tables to summarize study results may allow the text to be shortened.	We thank the reviewer for their feedback and understand that this report is both long and perhaps difficult to read. We have attempted to use more summary text and tables to aid in the reading of the report. AHRQ welcomes feedback on specific ways to make the information presented more useful to readers and stakeholders.
14.	TEP Reviewer #1	General Comments	Many of the studies are of poor quality. Is it really necessary to describe these studies? Providing equal coverage for studies of high and low quality coverage distracts the reader from the more important information.	We thank the reviewer for this comment and agree that the good quality studies and their evidence should be highlighted. Although we think it is important to describe the full evidence base, we try to highlight the good quality studies through discussion in the text, emphasizing these findings in the strength of evidence ratings, and through sensitivity analyses when there exists enough evidence for quantitative synthesis.

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15.	TEP Reviewer #1	General Comments	Some of the terms are confusing or overlapping. For example, what is the difference between invasive venography, ascending venography and phlebography? Likewise, imprecise terms such as “thrombophlebitis” are used instead of the more precise “superficial vein thrombosis”.	We thank the reviewer for this suggestion. These terms (invasive venography, ascending venography, and phlebography) are all the same. We have added a statement in the introduction to clarify. We have also modified the text to use superficial thrombophlebitis throughout.
16.	TEP Reviewer #1	General Comments	This paper highlights the need for more high quality studies in this disease area. With the plethora of invasive procedures that are available, the authors need to first provide the evidence that these are better than medical therapy alone. They can then perform comparative effectiveness analyses.	We thank the reviewer for their comment and agree that the comparative effectiveness of the invasive procedures as compare to medical therapy alone is an important first step which precedes the need for evaluation of the comparative effectiveness of invasive procedures against one another. Both of these categories of comparisons are included in our review.
17.	TEP Reviewer #2	General Comments	The report is highly meaningful for a variety of audiences (clinicians, researchers, third-party payers, etc.). The key questions provide an excellent introduction to each topic.	Thank you. No response needed
18.	TEP Reviewer #2	General Comments	I have been involved in writing guidelines and documents of this type over many years. This is one of the best I've ever seen. The authors should be proud. I could nit-pick, but it would involve mostly stylistic issues. This is a strong work.	We thank the reviewer for their comment! No response needed
19.	TEP Reviewer #2	General Comments	Overall, this is a magnificent document!!	No response needed

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20.	TEP Reviewer #2	General Comments	I wonder if anything should be mentioned about the importance of these issues (Dx and Rx of LECVD) on the shifting payment strategies coming in the US. In the future there will be much more of an emphasis on the "value" of tests/treatments. This document (appropriately) does not address things like cost, cost-effectiveness, etc. But I wonder if a paragraph might be appropriate, simply to remind (or emphasize to) the reader that effectiveness and the like may not be the most important end-points. (For example, the document clearly shows that EVLA and RFA are roughly comparable for the treatment of VV. But if one is a lot less expensive, are they really comparable ...?) I believe that it must be the author's intention to simply discuss things like "effectiveness" and let the reader figure out for themselves, in their own setting, which treatments are cheaper.	We agree with the reviewer that these are important issues. However, this review is part of AHRQ's Technology Assessment (TA) Program. This Program uses state-of-the-art methodologies for assessing the clinical utility of medical interventions. Technology assessments are based on a systematic review of the literature, along with appropriate qualitative and quantitative methods of synthesizing data from multiple studies. The main goal of this specific systematic review is to assess the clinical effectiveness and safety of each diagnostic testing modality and treatment modality for LECVD and identify whether specific patient or treatment characteristics are associated with improved outcomes. Cost and cost effectiveness are not within the scope of this review.

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21.	TEP Reviewer #2	General Comments	The only problem is that in many areas (especially diagnostic) the options are not strictly comparable. For example, plethysmography and Duplex ultrasound provide markedly different types of information -- at markedly different intrinsic costs. Saying that "There was insufficient evidence to support or refute the recommendations from current clinical guidelines that DUS be used as the first-line diagnostic test for patients being evaluated for LECVD and/or who are planned for invasive treatment." might be true, but if something like plethysmography will always be cheaper and appears comparable in "effectiveness", it might be the better test? I know an analysis of cost is not only inappropriate for a work of this type, it's also basically impossible. but I would expect some comment/disclaimer to this effect, if only to remind the reader that the practical implications of these findings need to be weighted by other factors like cost.	We agree with the reviewer that these are important issues. However, this review is part of AHRQ's Technology Assessment (TA) Program. This Program uses state-of-the-art methodologies for assessing the clinical utility of medical interventions. Technology assessments are based on a systematic review of the literature, along with appropriate qualitative and quantitative methods of synthesizing data from multiple studies. The main goal of this specific systematic review is to assess the clinical effectiveness and safety of each diagnostic testing modality and treatment modality for LECVD and identify whether specific patient or treatment characteristics are associated with improved outcomes. Cost and cost effectiveness are not within the scope of this review.
22.	TEP Reviewer #3	General Comments	The authors have tackled a very difficult topic, and anyone practicing and managing these patients know that the literature is embryonic, heterogenous, and not helpful in guiding therapy.	No response needed

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23.	TEP Reviewer #3	General Comments	A significant limitation was the inclusion of studies published since 2000, as there is surgical literature before 2000 that demonstrates long-term symptomatic improvement among patients with symptomatic venous varicosities.	We agree that the majority of the literature supporting the use of surgical approaches to treating venous disease predates the year 2000. However, the primary focus of the present report is comparative effectiveness of invasive and non-invasive techniques to treat lower extremity chronic venous disease (LECVD). Given that endovascular techniques to treat LECVD have only been in widespread use since 2000, by necessity, we restricted our literature search to the year 2000 and beyond. Additionally, while surgical techniques for LECVD may not have changed substantially since the 1990s, the increasing adoption of vascular surgery quality initiatives and clinical guideline documents since 2000 may have substantially impacted both surgical outcomes and patient selection. As a result, we argue that surgical outcomes for LECVD post 2000 may be distinct from those prior to this era and have maintained the 2000 cutoff for this report.
24.	TEP Reviewer #4	General Comments	There is a heavy focus on superficial vein treatment when compared to obstructive disease. Superficial vein treatment is not clinically relevant nowadays as most treatments are well known and studied. More focus should have been necessary in obstructive disease and there is plenty of literature.	Superficial venous treatment is responsible for a significant healthcare economic burden. Additionally, our literature review suggests that while most treatments for superficial venous disease have been studied against placebo or compression / usual care, the strength of evidence of these studies is often poor or insufficient due to limitations with study design. Most importantly, since the focus of the present analysis / report is on the *comparative effectiveness* of therapies for LECVD (including superficial disease), we respectfully disagree with the reviewers' comments that comparative effectiveness of superficial disease has been well studied. Our literature review would suggest a relative

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				paucity of direct comparative studies given the magnitude of the economic burden of these procedures. With regard to obstructive disease, we agree that this is a burgeoning area of inquiry and one of both clinical and scientific interest. For these reasons, we devoted an entire key question (KQ 3) to this particular topic. However, based on our literature search, we respectively disagree that there is "plenty of literature" addressing the topic of chronic lower extremity venous obstructive disease. While we did find a significant amount of literature on the treatment of acute lower extremity venous disease, the exploration of such acute disease was outside the scope of this review.
25.	TEP Reviewer #5	General Comments	This systematic review is a very timely and well-written document that is very likely to enhance the care of patients with Lower extremity chronic venous disease. This review will not only be of great interest to the community of physicians and surgeons caring for these patients, but also to the policy makers as well as the payers. In addition the publication of this document could be very useful in generating a timely discussion about the conduct of randomized controlled trials in this challenging patient population. I expect that this document would be a great resource for those planning such trials around the globe.	We thank the reviewer for their comment. No response needed.
26.	TEP Reviewer #5	General Comments	The target population, the audience and the key questions are very well defined and explicitly stated.	No response needed

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27.	Public Reviewer #1 Chandra Branham of AdvaMed	General Comments	The Advanced Medical Technology Association (AdvaMed) is pleased to provide the following comments on the Agency for Healthcare Research and Quality (AHRQ) draft evidence review entitled Treatment Strategies for Patients with Lower Extremity Chronic Venous Disease (LECVD)[Project ID DVTT0515]. The Advanced Medical Technology Association (AdvaMed) is the world's largest trade association representing medical device and diagnostics manufacturers. AdvaMed member companies produce the medical devices, diagnostic products, and health information systems that are transforming health care through earlier disease detection, less invasive procedures, and more effective treatments. AdvaMed members range from the largest to the smallest medical technology innovators and companies. We are committed to ensuring patient access to life-saving and life-enhancing devices and other advanced medical technologies in the most appropriate settings. We greatly appreciate the opportunity to submit scientific evidence in response to the solicitation in order to inform the final report. We encourage AHRQ to continue to seek input and feedback from industry going forward.	No response needed

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28.	Public Reviewer #1 Chandra Branham of AdvaMed	General Comments	In order to improve the process in the future, we would also encourage AHRQ to post its request for scientific evidence earlier in the process, for example, when the protocol was posted. This would allow for interested stakeholders to submit information and provide input earlier in the process, and would afford AHRQ the opportunity to have a fuller picture of the evidence to inform the draft report. AdvaMed supports any efforts to improve the process to ensure that the proposed and final reports are as robust and comprehensive as possible.	We thank the reviewer for this comment. The standard AHRQ process is to issue the request for supplemental evidence at the time that the Final Protocol is posted. Federal Register notices are also posted for Technology Assessment program topics unless deemed unwarranted for the specific project.
29.	Public Reviewer #1 Chandra Branham of AdvaMed	General Comments	The report's conclusions speak to the fact that varied outcomes have been measured within the studies reviewed. We ask that the AHRQ include a discussion around the evolution of outcome measures from surrogate clinical outcomes (reflux free rates and closure rates) to patient-centric quality of life measures.	Thank you for your comment. Based on our literature review, we would suggest that there are three related but distinct issues in the outcome assessments currently used in LECVD: 1) variation of clinical endpoints 2) use of surrogate endpoints and 3) use of physician determined endpoints that do not take into account patient perceptions of quality of life and disease status. We have modified the discussion to address these interrelated but distinct issues separately. As it relates to the use of patient-reported outcomes (PRO) in outcome assessments, we have noted that PROs are being considered for use in venous comparative effectiveness studies and are given a 1B Recommendation for use by the 2011 American Venous Forum Guidelines. Such a grade means that the benefits clearly outweighs the risks, burden, and costs based on medium quality evidence.

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30.	Public Reviewer #1 Chandra Branham of AdvaMed	General Comments	We recommend that AHRQ include an acknowledgement of the in-progress studies, including industry-sponsored studies of diagnostic and interventional devices, and ATTRACT. Within the AdvaMed group, there are currently 10 ongoing studies with more than 2,400 patients included. See the appendix of our MEDCAC presentations for these ongoing studies. (Presentations of Dr. Mark Turco and Dr. Mark Garcia).	We thank the reviewer for this suggestion. Of the ongoing studies mentioned, we have abstracted and included an early publication from the VeClose trial with data on outcomes at 3 months (estimated date for completion of the full study is Sep 2016). Morrison N, Gibson K, McEnroe S, et al. Randomized trial comparing cyanoacrylate embolization and radiofrequency ablation for incompetent great saphenous veins (VeClose). J Vasc Surg. 2015. 61:985-94. We have also added acknowledgement in the Future Research section of the Discussion that there are a number of trials planned, recruiting, ongoing, or pending publication which may provide helpful data to answer current pending questions and advance the field. We have discussed specific areas where we think these trials may be able to provide evidence relevant to existing research gaps.

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31.	Public Reviewer #1 Chandra Branham of AdvaMed	General Comments	We recommend that AHRQ include a more robust acknowledgment of the published literature on vein treatments before the January 2000 cutoff of the review. We recognize the time limits of the review necessitated narrowing the scope of the review, but it is critical that the review acknowledge the evidence published pre-2000.	We agree that the majority of the literature supporting the use of surgical approaches to treating venous disease predates the year 2000. However, the primary focus of the present report is comparative effectiveness of invasive and non-invasive techniques to treat lower extremity chronic venous disease (LECVD). Given that endovascular techniques to treat LECVD have only been in widespread use since 2000, by necessity, we restricted our literature search to the year 2000 and beyond. Additionally, while surgical techniques for LECVD may not have changed substantially since the 1990s, the increasing adoption of vascular surgery quality initiatives and clinical guideline documents since 2000 may have substantially impacted both surgical outcomes and patient selection. As a result, we argue that surgical outcomes for LECVD post 2000 may be distinct from those prior to this era and have maintained the 2000 cutoff for this report.
32.	Public Reviewer #2 Antonio Montecalvo via Amy Ryan with Organogenesis, Inc.	General Comments	Organogenesis, Inc. appreciates this opportunity to submit comments on the Technical Assessment Report on Treatment Strategies for Patients with Lower Extremity Chronic Venous Disease prepared for the Agency for Healthcare Research and Quality (AHRQ). As a leader in the regenerative medicine space, Organogenesis specializes in bioactive wound healing and soft tissue regeneration. Our main products include Apligraf?, which is approved by the Food and Drug Administration (FDA) for the treatment of venous leg ulcers and diabetic foot ulcers, Dermagraft?, which is FDA approved for the treatment of diabetic foot ulcers, and PuraPly and PuraPly Antimicrobial which are FDA cleared for use with a variety of wounds.	No response needed.

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			We appreciate the report's evaluation of the evidence supporting different approaches to diagnosing and treating lower extremity chronic venous disease (LECVD). LECVD is a common condition in the US with the risk of serious complications including amputation. As noted in the report, venous ulcers are one of the signs and symptoms of LECVD. We agree with the findings, that there is not enough evidence in the diagnosing of lower extremity chronic venous disease (LECVD). Ulcers of the lower extremities that fail to heal, or heal extremely slowly, are a serious and widespread health problem. They are the most common chronic wounds, with an estimated prevalence between 1 and 1.3 percent of the world population and 2.5 million people in the U.S. Often leading to osteomyelitis and amputation, ulcers of the lower extremities are a major cause of disability and the annual cost to the healthcare system to treat such wounds runs to billions of dollars. The availability of safe and effective treatments for these wounds is therefore of significant public health concern.	

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33.	Public Reviewer #2 Antonio Montecalvo via Amy Ryan with Organogenesis, Inc	General Comments	As the technical assessment report highlights, clinicians have numerous options for diagnosing and treating LECVD and its complications. We note that the report does not directly address treatment for venous ulcers. Should AHRQ include an assessment of treatment options, we urge the agency to evaluate the role of skin substitutes and to recognize that the products currently being marketed for treatment of venous ulcers and other ulcers of the lower extremities are not interchangeable. Certain products, such as Apligraf and Dermagraft, play a critical role in achieving wound closure, not just wound management as provided by other products. Apligraf is the only product with FDA approval for healing venous leg ulcers. We believe an evidence-based analysis that carefully considers the data on specific products, particularly those items that have been subject to clinical studies and premarket approval by the FDA, will demonstrate the value of our products. However, any such technology assessment should not extrapolate from evidence that is specific to advanced modalities such as Apligraf or Dermagraft and assume that similar results will be achieved by other products that have not been subject to the same level of rigorous review and evaluation.	Thank you for your comment. We agree that treatment venous ulcers are a scientifically, clinically, and economically important subgroup of LECVD. Although we had pre-specified disease severity (as determined by CEAP), including venous ulceration, as subgroups of interest for our analysis, we found very inconsistent reporting of disease severity within the confines of our literature search and thus were unable to report *comparative effectiveness* of therapies by disease severity. As the commenters point out, we did also pre-specify that wound therapy was an intervention of interest, however, we did not find sufficient studies meeting our inclusion criteria (RCTs and observational studies of greater than 500) addressing specific wound therapies or algorithms to include in the present report.

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34.	Public Reviewer #2 Antonio Montecalvo via Amy Ryan with Organogenesis, Inc	General Comments	Of particular value to such assessment are studies that compare the clinical effectiveness of specific products. Below we provide references to studies published in peer-reviewed journals that compare the effectiveness of Apligraf and a commonly used wound management product and to studies specific to healing of venous ulcers that we believe will better inform AHRQ?s understanding of these products and their use in treating venous ulcers. For example, the Marston study (2014) found that wound closure for the bilayered living cellular construct (Apligraf) was significantly greater compared with the porcine collagen product (SIS) and reduced the median time to wound closure by 44 percent. We also provide a reference to the ESCHAR trial. This large study provides the strongest evidence to support the fact that venous surgery may improve VLU recurrence rates ? but does not improve healing rates for VLUs. We urge AHRQ to incorporate this data in any assessment of treatment of symptoms of LECVD and are happy to answer any questions you might have about research or products. [references provided] Barwell JR1, Davies CE, Deacon J, Harvey K, Minor J,et al. Comparison of surgery and compression with compression alone in chronic venous ulceration (ESCHAR study): randomised controlled trial. PubMed.gov June 2004. http://www.ncbi.nlm.nih.gov/pubmed/15183623 Falanga, V, D Margolis, O Alvarez, M Auletta, F Maggiacomo, et al. Rapid Healing of Venous Ulcers and Lack of Clinical Rejection with an Allogeneic Cultured Human Skin Equivalent. Arch Dermatol 1998, 3: 293 - 300. Kirsner, R, M Sabolinski, N Parsons, M Skornicki, and W Marston. Comparative effectiveness of a bioengineered living cellular	We thank the reviewer for the suggested citations and have considered the studies against our inclusion/exclusion criteria in the final report. Specifically: • The study by Barwell was included in our review along with several companion articles • The study by Falanga did not meet the date inclusion criteria for our review • The studies by Kirsner and Marston were both considered during the review but excluded at the abstract stage. .

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35.	Public Reviewer #3 Catherine Ratliff of University of Virginia Health System	General Comments	Lower Extremity Chronic Venous Disease (LECVD) this acronym is much less common in the literature as for example-chronic venous insufficiency (CVI), lower extremity venous disease (LEVD), venous leg ulcer and so it would be nice to mention other search terms that were used.	Appendix A includes the exact search terms that were included in our search strategy covering these suggested terms.
36.	Public Reviewer #5 from the American Academy of Family Physicians	General Comments	Overall, the review outlined the topic and focus well and documented the methodology and findings clearly. The myriad of outcomes and interventions made reading complex. It would be helpful to present Table 38 information earlier.	We thank the reviewer for this suggestion but feel that the discussion is the correct place to summarize the numerous findings which are provided in more detail in the individual results sections. No change made.
37.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	General Comments	The Society for Vascular Surgery (SVS), a professional medical society composed of 5,400 specialty-trained vascular surgeons and other medical professionals who are dedicated to the prevention and cure of vascular disease, and The American Venous Forum (AVF), a professional medical society composed of 800 healthcare professionals dedicated to improving the care of patients with venous and lymphatic disease, offers the following comments: The SVS and AVF appreciates the opportunity to provide comments on the AHRQ Technology Assessment Program's Treatment Strategies for Patients with Lower Extremity Chronic Venous Disease (LECVD) report. If you have any questions or need additional information, please contact Pamela Phillips, SVS Director of the Washington Office at pphillips@vascularsociety.org or 202-787-1220.	No response needed

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38.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	General Comments	The structure is typical of AHRQ reviews using RCTs when available and exclusively if sufficiently numerous but with use of some large observations studies if this is the available data. The general categories are appropriate but sometimes the subdivisions become less appropriate simply because data is lacking to be useful in clinical decision making.	No response needed
39.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	General Comments	Page 4 Scope of Review section/Rationale and Context ? ?In the past ? in the United States.?) While primary care physicians, vascular surgeons, vascular medicine specialists, cardiologists, and/or radiologist are listed, this statement does not reflect the wide scope of other specialties that care for venous disease, some of which receive no specific training in venous disease under ABMS training programs. Because this Technical Assessment does not provide data on specialties providing venous care, this statement should be omitted.	We have amended this statement in the discussion to clarify that some providers without formal training in venous care often diagnose/manage these patients within the United States.
40.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	General Comments	The review includes only a small proportion of all published studies of venous disease (1%), raising concern regarding how representative this document is and generalizability.	We are uncertain of the calculation performed by the commenter to arrive at the noted percentage. The search strategies employed in this review identified 11,624 unique citations published on or after 1/1/2000. We screened these results by applying the set of inclusion and exclusion criteria detailed in the Methods section through two layers of review (title/abstract and then full-text), and included all relevant literature meeting the specified criteria.
41.	Public Reviewer #7 Robert White	General Comments	On behalf of the representatives of the Venous Care Partnership (?Partnership?), we appreciate the opportunity to comment on the June 28, 2016 AHRQ Technology Assessment (TA), ?Treatment Strategies for Patients with Lower Extremity Chronic Venous Disease (LECVD).	Although an expansion of the literature search period to the pre-2000 era would likely yield an increased number of studies assessing the accuracy and precision of non-invasive testing for the diagnosis of chronic venous disease (CVD), the availability, use,

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			The Partnership is comprised of appointed representatives from ten specialty societies and associations representing over 100,000 physicians who care for patients with venous disease. It is these representatives who have contributed to this letter. We want to recognize the authors of the AHRQ technology Assessment as they have put substantial effort into this document. However, we have both general and specific concerns that we would like to bring to your attention. 1. Most importantly, in conducting this review the authors? were restricted to reviewing the literature published since the year 2000. When questioned by the panel, the authors acknowledged this limitation, but did not adequately emphasize that this could lead to misleading conclusions. The diagnosis and treatment of venous diseases has a long history. Much of the evidence supporting the diagnosis and treatment of superficial venous disease was established before the limited time period covered by this review. For example, duplex ultrasound is currently recognized as the standard of care for the diagnosis of acute deep venous thrombosis, yet studies validating its accuracy in comparison to contrast venography were performed well before the year 2000. Given the results of previous rigorously conducted studies, it expected that there is little recent evidence evaluating the accuracy of duplex ultrasound. Similarly, compression therapy has been validated as an effective therapy in the treatment of chronic venous disease. Two systematic Cochrane reviews (?Effects of compression on venous ulcer healing?, O'Meara et al and ?Compression for	and technological advancement of non-invasive testing for CVD has changed significantly since that time. Widespread use of more recent technological innovations such as power Doppler ultrasound, 64 slice computed tomography scanners, and higher field strength / non-contrast magnetic resonance angiography techniques have occurred since 2000. Additionally, widespread participation in quality certification programs, such as IAC Vascular Testing, IAC CT, and IAC MRI have occurred since 2000 as well. Thus, we believe that expansion of the literature search to include studies prior to 2000 would uncover studies of diagnostic devices that have been superseded by current technology and potentially missing techniques required by current accreditation standards. Regarding the specific citations list, O'Meara and Nelson were identified as potentially relevant systematic reviews and as such their component references were reviewed for possible inclusion and so included through that methodology. Rasmussen and Brittenden are both included in our report as companion studies to their main analyses.

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			preventing recurrence of venous ulcers?, Nelson et al.) demonstrated the effectiveness of compression therapy. Unfortunately, both of these were listed in the references of the AHRQ document but not cited in the text. Both sclerotherapy and the surgical removal of the incompetent saphenous veins were established as effective by clinical trials published prior to 2000. Accordingly, as the long term value of superficial venous intervention was well established before 2000, evidence acquisition shifted to focusing on the improved early outcomes in comparison to standard interventions (e.g. high ligation of stripping) rather than comparison to conservative therapy alone. Several well-done randomized clinical trials (Rasmussen et. al, JVS 2010 2, Brittenden et. al, NEJM 2014) have confirmed that the newer technologies have equivalent outcomes in comparison to traditional surgery, but are associated with less post-operative discomfort, improved early quality of life, and more rapid return to productive activity. Limiting the systematic review of the literature to the period after 2000 eliminated the evidence base on which the more recent technology rests. In a comparable example, we no longer test the value of aspirin in acute myocardial infarction when discussing the value of antiplatelet therapy, for it was wellestablished decades ago; now we focus on therapeutic advances. Limiting the conclusions to the literature published after 2000 removes the foundational base upon which this work has been done.	

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42.	Public Reviewer #7 Robert White	General Comments	Another significant concern is that the abstract inclusion criterion for the second question, KQ2, was too rigorous. Randomized controlled trials were preferred and observational trials were only considered if the sample size was greater than 500 subjects, excluding adequately powered but smaller clinical trials. Of the 10,201 abstract reviewed only 88 studies met the inclusion criteria for KQ2. We believe that the strict size criteria resulted in an incomplete appraisal of the evidence. Indeed, the report?s authors noted that the therapies did provide benefit, but that the evidence was insufficient to estimate at what time point, in what population and at what severity that benefit exists. Our position is supported by the panelists who noted that The National Institute for Health and Care Excellence (NICE) guidelines, which were largely based on a randomized trial funded by the NHS Health Technology Assessment Program (Michaels, BR J Surg 2006), may be more representative of the current state of the evidence. We recognize that the authors were given a very specific task with a specific methodology, but we would encourage the authors to acknowledge these limitations of the study design and the effect on the report?s conclusions.	Thank you for your comment. As a point of clarification, our inclusion criteria were randomized controlled trials of >/=20 patients and observational studies of >/=500 patients. While we acknowledge that this excludes a number of smaller observational studies, we respectfully disagree that excluding RCTs of < 20 patients or observational studies < 500 patients necessarily excludes “adequately” powered smaller clinical trials. In general, power calculations were rarely given among the methods section of even the RCTs and unless variance in the primary outcome of an RCT was extremely small and the point estimates of effect significantly different, it seems unlikely that an RCT would be adequately powered at 19 patients. With regards to “adequately powered” observational studies, we did not an observational study that contained an adequate post-hoc analysis of “power”, though we acknowledge the statistical controversy surrounding the calculation of post-hoc power. Additionally, we would note that while observational studies can serve as a valuable source of data regarding therapeutic effectiveness in the “real world,” they have generally been insufficient to establish efficacy. In the case of chronic venous disease (CVD) this systematic review has identified 90 randomized controlled trials evaluating the efficacy and comparative efficacy of a number of medical and interventional therapies. Despite the inclusion of these trials, the overall strength of evidence remained low and a number of clinically important subgroups (subgroups by

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				CEAP disease severity, subgroups by anatomy, and subgroups by patient demographics) could not be analyzed due to a lack of data. While it is possible for observational studies to generate high strength of evidence data, the included observational studies of >/= 500 patients were also of low strength of evidence and lacked important subgroup data. As a result, it seems unlikely that inclusion of observational studies of < 500 patients will result in 1) the generation of high strength of evidence data 2) the addition of adequate data on clinically important subgroups 3) a significant change to the overall conclusions of the report that are currently based primarily on evidence of efficacy and comparative efficacy from randomized controlled trials
43.	Public Reviewer #7 Robert White	General Comments	Similarly, the criteria used to exclude articles that relate to KQ3 on chronic venous obstruction resulted in a partial view of the overall body of evidence. Older compelling studies have demonstrated a strong correlation between iliac venous obstruction and a poor clinical outcome. Additionally, studies have demonstrated the correlation between relief of venous obstruction and improved clinical outcome. Some of this data is derived from RCTs, and the quality and consistency of this information has had a significant influence upon physician decision-making when they approach severely-affected patients with CVD and PTS.	We thank the reviewer for their comment. We do not disagree that chronic venous obstruction due to iliac venous obstruction has been associated with symptoms and poor functional status, however the majority of the treatment studies have been single arm studies with no active comparator (including control or no treatment).

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44.	Public Reviewer #7 Robert White	General Comments	We are concerned that the specificity of the questions posed for the MEDCAC may obscure the larger evidence base. KQ2 divided superficial venous disease into two broad categories; symptomatic and asymptomatic. The panelists seemed to be unclear as to the meaning of this stratification. Is a patient with a leg ulcer and no complaints an asymptomatic patient? Was a patient with spider veins and complaints of heaviness, achiness and throbbing a symptomatic patient? We recognize the difficulty associated with the nomenclature and look forward to helping define more precise definitions to facilitate specific conclusions. For now, we would encourage the authors to acknowledge these limitations and the effect on the report?s conclusions.	We thank the reviewer for their comment and as suggested now acknowledge these limitations in the discussion.

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45.	Public Reviewer #7 Robert White	General Comments	We would like to express our concerns regarding potential inaccuracies and assumptions contained within the document. The authors state ?There is substantial variation in how patients with LECVD are diagnosed and treated. In the past, vascular surgeons often diagnosed and treated patients with LECVD; now, however, primary care physicians, cardiologists, vascular medicine specialists, and radiologists also diagnose and manage these patients in the United States. In addition to physician specialty, other reasons for therapeutic variation include: patient characteristics and preferences, reimbursement rates for diagnostic tests and treatment modalities, and the clinical care location of these diagnostic tests and invasive procedures (as this dictates reimbursement, specifically when physicians own the office-based clinics or ambulatory surgery centers where the procedures are performed).? The first portion of this statement is not accurate as ligation and stripping were often performed by general surgeons, sclerotherapy was performed by phlebologists, and endovascular venous procedures were developed and performed by interventional radiologists. Furthermore the paragraph implies that changes in outcomes were affected by a change in who (i.e., the specialty) and where the treatment was provided. We feel that this inference is without evidentiary support and recommend excluding this comment.	We thank the reviewer for their comment. We have now modified the text to read: “In the past in the United States, general surgeons and vascular surgeons often diagnosed and treated patients with LECVD; now, however, primary care physicians, cardiologists, vascular medicine specialists, interventional radiologists, and others with and without formal training in venous care also diagnose and manage these patients. Other reasons for differences in diagnostic and treatment strategies exist and include: patient characteristics and preferences, reimbursement rates for diagnostic tests and treatment modalities, and the clinical care location of these diagnostic tests and invasive procedures (as this dictates reimbursement, specifically when physicians own the office-based clinics or ambulatory surgery centers where the procedures are performed).”
46.	Public Reviewer #7 Robert White	General Comments	In the methods section, the authors describe the complications that are ?typically seen? following venous treatments. We would encourage the word ?typical? be changed as this implies that listed complications are expected or relatively frequent, which the data does not support.	We have removed the word “typically” from the description of the adverse events

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47.	Public Reviewer #7 Robert White	General Comments	Another point of needed clarification relates to a reference to a study by O?Sullivan G et al. in the discussion section for KQ3 on treatment of chronic venous obstruction. The patients reported in this paper were treated for acute thrombosis caused by right iliac artery compression of the left common iliac vein. Although some of the patients may have had a prior thrombosis of this segment, the thrombolytic was used to treat an acute deep venous thrombosis, and therefore the study is not relevant to patients with chronic obstructions.	We thank the reviewer for their comment. The referenced paper does include both acute and chronic patients, but acute patients were not described in this report. As described in the report, chronic patients were treated with lytics and endovascular procedure and then stopped using lytics as outcomes were assessed. While the relevance of this study is low given its use of urokinase, we included it for completeness.
48.	Public Reviewer #7 Robert White	General Comments	Need for patient centered outcomes: We would submit that surrogate endpoints such as CEAP, patency and closure rates are not patient centered outcomes, dilute interpretation of the value of these therapies, and should not be used as a basis for policy decisions. Given that this disease is chronic and predominantly characterized by morbidity rather than mortality, patient centered benefit should be the primary outcomes of interest. This may include assessment of patient-relevant symptoms (e.g. pain, swelling), quality of life, and functional limitations. We would be happy to work with CMS and AHRQ to develop better standards for outcomes measurement. As this document presumably serves to inform policy decisions, we ask the authors to acknowledge this point and remove references to non-patient centered outcomes from the document.	We agree with the commenter's assertion that LECVD is predominantly characterized by morbidity rather than mortality and that patient centered outcomes form an important aspect of assessment of therapies in this setting. Moving forward, we agree that patient-reported outcomes should be the primary endpoint for studies in LECVD. However, given that several studies exist suggesting correlation between clinician reported outcomes and patient-reported outcomes (Kahn et al. Relationship between clinical classification of chronic venous disease and patient-reported quality of life: results from an international cohort study. J Vasc Surgery) and the vast majority of the existing literature validating the efficacy of therapies for LECVD use clinician reported endpoints, we believe that these endpoints do provide useful information about available therapies. As such, they can be regarded as putative surrogate endpoints (in distinction to validated surrogate endpoints per FDA criteria).

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49.	Public Reviewer #7 Robert White	General Comments	In summary, although the authors have conducted an extensive review within the limitations required of them, this document may have hindered interpretation of the totality of the evidence, thus diminishing its ability to effectively inform policy decisions. The exclusion of publications prior to the year 2000, the focus on patient conditions without description, broad and overlapping questions, and stringent study inclusion criteria have provided a subjective portrayal of the scientific evidence upon which modern venous treatment is based. We would be pleased to meet with AHRQ and CMS to discuss our concerns further and to serve as a resource to both entities in future endeavors related to venous disease. Respectfully submitted, August 3, 2016	We thank the reviewer for their comments. We agree with the commenter's assertion that LECVD is predominantly characterized by morbidity rather than mortality and that patient centered outcomes form an important aspect of assessment of therapies in this setting. Moving forward, we agree that patient-reported outcomes should be the primary endpoint for studies in LECVD. However, given that several studies exist suggesting correlation between clinician reported outcomes and patient-reported outcomes (Kahn et al. Relationship between clinical classification of chronic venous disease and patient-reported quality of life: results from an international cohort study. J Vasc Surgery) and the vast majority of the existing literature validating the efficacy of therapies for LECVD use clinician reported endpoints, we believe that these endpoints do provide useful information about available therapies. As such, they can be regarded as putative surrogate endpoints (in distinction to validated surrogate endpoints per FDA criteria)..
50.	Public Reviewer #7 Robert White	General Comments	The listed representatives of the Venous Care Partnership, on behalf of the organizations they were appointed by, have endorsed this letter: Alliance for Wound Care Stakeholders (AWCS) Caroline Fife, MD American College of Cardiology (ACC) Gregory Piazza, MD American College of Phlebology (ACP) Mark Forrestal, MD Neil Khilnani, MD Mark Meissner, MD Melvin Rosenblatt, MD Marlin Schul, MD American College of Radiology (ACR)	No response needed

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			Anne Roberts, MD American Heart Association (AHA) Joshua Beckman, MD Society for Vascular Medicine (SVM) John Bartholomew, MD Suman Rathbun, MD Society of Interventional Radiology (SIR) Neil Khilnani, MD Sanjay Misra, MD Akhilesh Sista, MD Suresh Vedantham, MD The Society for Cardiovascular Angiography and Intervention (SCAI) Kenneth Rosenfield, MD US Compression Alliance Nick Morrison, MD Vascular Interventional Advances (VIVA) Michael R. Jaff, DO John Kaufman, MD Sean Lyden, MD Alliance for Wound Care Stakeholders (AWCS) Supplemental Reviewer Marcia Nusgart, R.Ph. Executive Director Venous Care Partnership Staff Contact: Robert White Society of Interventional Radiology rwhite@sirweb.org	
51.	Public Reviewer #8 Jim Harmon from BTG International Inc.	General Comments	Thank you for a very thorough and well-presented draft Technology Assessment Report on Lower Extremity Chronic Venous Disease (the ?Report?) which was presented at the recent MEDCAC meeting held on July 20, 2016. The comments made here are submitted on behalf of Provensis Ltd. (?Provensis?), a BTG International Group (?BTG?) company, in response to the Report. BTG is a specialty healthcare company that, in relevant part, develops products targeting the treatment of varicose veins.	No response needed

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52.	Public Reviewer #9 Laura Bolton from International Consolidated Guideline Task Force	General Comments	We realize the AHRQ Technical Assessment (TA) was constrained by CMS time requirements, resulting in exclusion of meta-analyses, observational studies of less than 500 subjects and studies pre-dating the year 2000. These exclusions prove a disservice to professionals managing patients with chronic venous insufficiency because much evidence for diagnosing or managing venous insufficiency and venous ulcers is contained in studies and scientific literature which meets one or more of these exclusion criteria. It also undermines the credibility of the AHRQ, CMS and evidence-based practice (EBP) concepts in general when an AHRQ TA counters more thorough Cochrane meta-analyses on the same subject. Studies described below, informing CMS decisions about effectiveness and economic outcomes of evidence-based practice for patients with venous ulcers would have been included in this TA if the AHRQ had not had these limitations. Patients with chronic venous insufficiency and the professionals who serve them would benefit more from including this prior evidence to add perspective and clarity to the AHRQ TA. References cited in these comments are available on request.	We appreciate the reviewer's request to expand the literature search to include observational studies of less than 500 patients. While observational studies can serve as a valuable source of data regarding therapeutic effectiveness in the "real world", they have generally been insufficient to establish efficacy. In the case of chronic venous disease (CVD) this systematic review has identified 90 randomized controlled trials evaluating the efficacy and comparative efficacy of a number of medical and interventional therapies. Despite the inclusion of these trials, the overall strength of evidence remained low and a number of clinically important subgroups (subgroups by CEAP disease severity, subgroups by anatomy, and subgroups by patient demographics) could not be analyzed due to a lack of data. While it is possible for observational studies to generate high strength of evidence data, the included observational studies of >/= 500 patients were also of low strength of evidence and lacked important subgroup data. As a result, it seems unlikely that inclusion of observational studies of < 500 patients will result in 1) the generation of high strength of evidence data 2) the addition of adequate data on clinically important subgroups 3) a significant change to the overall conclusions of the report that are currently based primarily on evidence of efficacy and comparative efficacy in from randomized controlled trials.
53.	Public Reviewer #3 Catherine Ratliff of University of Virginia Health System	Executive Summary	Nicely done	No response needed

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54.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Executive Summary	Under diagnostic, intravascular ultrasonography should be included.	As suggested, we now include intravascular ultrasonography as a diagnostic tool of interest within the abstract text as well as throughout the main text..
55.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Executive Summary	Even though the summary states that duplex imaging cannot be proven as the best first line diagnostic study, the discussion concedes that it has become so commonplace and that prior studies and guidelines support such use. For clarity this should be included.	We have the following statement in the discussion "DUS has supplanted invasive imaging modalities (e.g., ascending and descending phlebography or venography) as the primary choice for diagnostic testing in all adult patients with LECVD."
56.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Executive Summary	When treating May-Thurner Syndrome, the authors fail to separate an acute treatment (thrombolysis) from a chronic condition requiring only venous stenting. This could be made clearer in a review concentrating on chronic disease or it should be made clearer that the former is an acute or chronic process to clarify the situation since none of the other conditions studied fall in this category.	We thank the reviewer for their comment. The referenced paper does include both acute and chronic patients, but acute patients were not described in this report. As described in the report, chronic patients were treated with lytics and endovascular procedure and then stopped using lytics as outcomes were assessed. While the relevance of this study is low given its use of urokinase, we included it for completeness. .

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57.	Public Reviewer #8 Jim Harmon from BTG International Inc.	Executive Summary	BTG (through Provensis) holds an approved New Drug Application (?NDA?) for Varithena? (polidocanol injectable foam) 1% which is a prescription medicine used to treat incompetent great saphenous veins, accessory saphenous veins, and visible varicosities of the great saphenous vein (?GSV?) system above and below the knee. Varithena? is the only FDA approved drug for this indication in the treatment of venous disease in CEAP Classes 2 through 6. Varithena? is effective in small, medium, and large diameter veins and also in tortuous vein anatomies. In support of its regulatory approval, BTG conducted two randomized, blinded, parallel-group, multicenter Phase 3 clinical studies for Varithena?: the VANISH-1 and VANISH-2 studies. These two pivotal studies were included in the Report with a quality rating assigned by the authors of the Report as ?good?.	No response needed
58.	Public Reviewer #8 Jim Harmon from BTG International Inc.	Executive Summary	We have concerns, however, that the methodology employed by the Report?s authors does not make distinctions between Varithena? and physician compounded foam (?PCF?) and that the conclusions made in the Report may lead to denial of access to procedures for many patients suffering from the symptoms of chronic venous disease. We trust that consideration will be given to the comments made during the public comment period and that the Report will be reviewed to ensure that the most current and relevant available literature and evidence are considered in order to provide an accurate assessment of the available treatment options for chronic venous disease. Our primary concerns fall into two categories: (1) distinctions between proprietary endovenous microfoam (Varithena?) and physician compounded foam; (2) patient reported outcomes.	Regarding the discussion of patient-reported outcomes, we agree with the commenter's assertion that LECVD is predominantly characterized by morbidity rather than mortality and that patient centered outcomes form an important aspect of assessment of therapies in this setting. Moving forward, we agree that patient-reported outcomes should be the primary endpoint for studies in LECVD. However, given that several studies exist suggesting correlation between clinician reported outcomes and patient-reported outcomes (Kahn et al. Relationship between clinical classification of chronic venous disease and patient-reported quality of life: results from an international cohort study. J Vasc Surgery) and the vast majority of the existing literature validating the efficacy of therapies for LECVD use clinician reported

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				endpoints, we believe that these endpoints do provide useful information about available therapies. As such, they can be regarded as putative surrogate endpoints (in distinction to validated surrogate endpoints per FDA criteria). Regarding distinctions between proprietary endovenous microfoam and physician compounded foam: We acknowledge that there may be differences between proprietary formulations of certain drugs and physician compounded or generic versions of those drugs. However, to allow for an assessment of *comparative effectiveness* of various interventions / therapies for LECVD, we assumed that intra-class variation in a drug or interventional technique or medical therapy was smaller than inter-class variation in interventions. To assume the opposite would suggest that distinct studies of a specific intervention / technique / drug should not be pooled and the merit of each intervention / technique / drug need be assessed only via a single study (or series of studies targeting a specific formulation). The available evidence did not allow such granular comparisons.

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59.	Public Reviewer #9 Laura Bolton from International Consolidated Guideline Task Force	Executive Summary	Authors of the AHRQ Technology Assessment (TA) on Lower Extremity Chronic Venous Disease (LECVD) devoted much effort to summarizing evidence supporting management of LECVD. Possibly constrained by a misinterpretation of their mandate to exclude all pre-2000 evidence, they omitted important 2012 and 2014 updates of Cochrane systematic reviews (SR) with meta-analyses providing compelling support for beneficial effects of patient-appropriate sustained compression to treat venous ulcers. Protocols of care using this evidence have significantly improved venous ulcer healing outcomes while reducing costs of care compared to historical controls in the US, UK and Canada . Acknowledging this evidence in addition to correcting the tables and analyses related to compression and other interventions described below may reverse the TA conclusions regarding insufficient evidence supporting beneficial effects of compression or other interventions for patients with chronic venous insufficiency or venous ulcers.	We thank the reviewer for their comment. We reviewed the suggested systematic reviews during our process and their included component references. All individual studies which met our inclusion criteria are included in our review.
60.	Peer Reviewer #1	Introduction	Page 4 line 29: would not include the word "typically" -- implies that these are common complications, and it would be useful to include the rates of these complications with references	We have removed the word “typically” from the description of adverse events
61.	Peer Reviewer #1	Introduction	Page 4 line 49: Given the absence of data demonstrating that heterogeneity in treatment is a result of multiple specialties involved in CVD, this statement is too presumptive. If the authors feel this is true, they should include a reference.	We have modified the text to clarify.
62.	Peer Reviewer #2	Introduction	Short but appropriate	No response needed
63.	TEP Reviewer #1	Introduction	The introduction clearly defines the goals of the paper and describes the methodology. There are only a few minor concerns.	No response needed

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64.	TEP Reviewer #1	Introduction	Page VI: Line 31: What is the difference between "invasive venography" and "phlebography"?	For clarity, we have removed the term phlebography in this sentence
65.	TEP Reviewer #1	Introduction	Page VI: Lines 41-55: The authors need to make it clear that these procedures are for treatment of varicose veins.	Unfortunately we do not feel that we can state that these procedures are all for varicose veins. Many times the reason was not completely specified by the individual studies (inclusion criteria was sometimes just reflux / insufficiency without mentioning varicosities). So while clinically these are mostly used for varicosities, we can't always conclude that from the inclusion criteria / population statements of the included studies. We have not modified the text.
66.	TEP Reviewer #1	Introduction	Page VI: Lines 55-57: For what indication was compression used in these studies?	We have provided this detail in the results sections and appendix tables.
67.	TEP Reviewer #2	Introduction	The introduction, like the rest of the manuscript, is concise and well-written. The addition of a table for "definition of terms" is a nice touch and one that's rarely used this effectively in a manuscript of this type.	No response needed
68.	TEP Reviewer #3	Introduction	The authors clearly define the scope of their literature review and objectives.	No response needed
69.	TEP Reviewer #4	Introduction	Fine	No response needed
70.	TEP Reviewer #5	Introduction	The introduction is very well written and the epidemiological data is the most contemporary one for United States. It may be beneficial if some european prevalence data could be added as well, to reflect the worldwide burden of VTE.	We thank the reviewer for their comments. The specific guidance for this report indicated that the interventions in question were to be focused on those available in the United States. As a result, we focused the introduction and epidemiology presented in the report on the United States population as well.
71.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Introduction	Page 1, end of first paragraph, last sentence: Thrombosis is an acute process and is not included in the pathophysiology of chronic disease which included reflux, obstruction or both. Same comment for Table 2 Po definition.	We have modified the sentence and table to clarify that it is "chronic unresolved" thrombosis.

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72.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Introduction	Page 2 Adverse Effects of Diagnosis: Inclusion of PAD as a misdiagnosis is confusing. Diagnosis of venous disease is distinct from PAD based on clinical assessment and diagnostic testing. While identification of coexisting PAD is important, venous disease should not be ?misdiagnosed? as PAD.	We thank the reviewer for their comments. We agree that the diagnosis of venous disease is distinct from PAD after the completion of history, exam, and appropriate diagnostic testing. We simply wish to convey, for example, in the presence of a lower extremity ulcer, although history and exam form the mainstay of differentiating arterial/venous/neurologic etiologies, misidentification of all relevant etiologies (particularly in mixed lesions) may lead under or over treatment.
73.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Introduction	Page 4 Adverse Effects of Treatment: While potential adverse effects of treatment of endo-venous and surgical interventions are listed, potential adverse effects of non-treatment are not included.	We have now included the following statement in this section “Adverse effects of undertreatment may include decreased patient quality of life, venous ulceration, failure to heal venous ulceration, superinfection and potentially amputation”

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74.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Introduction	Page 5-6 Key Questions: Concern is that distinctions sought in KQs become blurry. KQ1 is a ?Narrative review of the diagnostic modalities? ? There is not a question posed, yet in the Section on KQ1 there is a conclusion of insufficient data. What is the Key Question? KQ2 addresses ?varicose veins and/or LE chronic venous insufficiency/incompetence/reflux? but that represents a wide spectrum of disease from varicose veins to venous ulcers with different margins of benefit/risk in the evidence, however, in the KQ2 analysis, this distinction is not made. KQ3 addresses ?LE chronic venous thrombosis/obstruction including post-thrombotic syndrome?, but this can also represent a wide spectrum of clinic disease from PTS symptoms to venous ulcer yet no distinction is made in the analysis. Between KQ2 and KQ3, there is no distinction made between interventions performed for superficial venous insufficiency, deep venous insufficiency/obstruction, and/or both. A distinction in analysis is required between severity of disease in KQ2 and KQ3.	We thank the reviewer for their comments. We do recognize that the spectrum of disease included in both KQ 2 and KQ 3 is very broad. As a result, we prespecified analyses based on disease severity (as assessed by CEAP class), symptom status, and venous anatomy. However, due to a combination of a lack of specificity in the inclusion/exclusion criteria in the identified studies, as well as a lack of results presentation within these subgroups, we were unable to perform the analyses suggested by the reviewer.

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75.	Public Reviewer #8 Jim Harmon from BTG International Inc	Introduction	Distinctions between Proprietary Endovenous Microfoam (Varithena?) and Physician Compounded Foam First, it is important to clarify that Varithena? is a fundamentally different therapy from older treatments which have been used for decades and which are broadly referred to as ?sclerotherapy? or ?foam sclerotherapy? in the literature that was referenced in the Report. The Report and the presentation made at the July 20, 2016 MEDCAC meeting included multiple references to ?sclerotherapy? or ?foam sclerotherapy?, yielded from search strategies which included these two terms specifically. As mentioned above, the Report also included two publications resulting from BTG?s VANISH-1 and VANISH-2 studies, and the authors of the Report qualified them as ?good?. Although these studies were qualified as ?good? in the Report, the safety and efficacy profile of Varithena? has been underrepresented in the literature due to its comparatively recent regulatory approval against the decades of study on PCF and the resulting concentration of literature concerning treatment of venous disease with PCF. As a result, PCF studies are heavily represented in the Report, which has strongly and negatively influenced the results as to the availability of a safe and effective therapy for treatment of chronic venous disease. Varithena?, a proprietary endovenous microfoam, is a product that can very easily be differentiated from PCF. As stated above, Varithena? received FDA approval pursuant to a NDA. To the contrary, there is currently no approval in the United States for the creation of PCF using liquid sclerosants. In addition, not only was Varithena? subject to rigorous, highly controlled clinical trials in order to obtain marketing approval from the FDA, the product is manufactured in strict compliance with the FDA?s current Good Manufacturing Practice (cGMP) guidelines, as compared to PCF which is	Regarding the discussion of patient-reported outcomes, we agree with the commenter's assertion that LECVD is predominantly characterized by morbidity rather than mortality and that patient centered outcomes form an important aspect of assessment of therapies in this setting. Moving forward, we agree that patient-reported outcomes should be the primary endpoint for studies in LECVD. However, given that several studies exist suggesting correlation between clinician reported outcomes and patient-reported outcomes (Kahn et al. Relationship between clinical classification of chronic venous disease and patient-reported quality of life: results from an international cohort study. J Vasc Surgery) and the vast majority of the existing literature validating the efficacy of therapies for LECVD use clinician reported endpoints, we believe that these endpoints do provide useful information about available therapies. As such, they can be regarded as putative surrogate endpoints (in distinction to validated surrogate endpoints per FDA criteria). Regarding distinctions between proprietary endovenous microfoam and physician compounded foam: We acknowledge that there may be differences between proprietary formulations of certain drugs and physician compounded or generic versions of those drugs. However, to allow for an assessment of *comparative effectiveness* of various interventions / therapies for LECVD, we assumed that intra-class variation in a drug or interventional technique or medical therapy was smaller than inter-class variation in interventions. To assume the opposite would suggest that distinct studies of a specific intervention / technique / drug should not be pooled and the merit of each intervention / technique / drug need be assessed only via a single study (or series of studies targeting a specific formulation). The

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76.	Public Reviewer #9 Laura Bolton from International Consolidated Guideline Task Force	Introduction	The introduction makes a clear distinction between varicose veins and deep vein thrombosis but should clarify the burden of venous ulcers. Please mention the 600,000 Americans with chronic venous insufficiency (CVI) so severe that they have a venous ulcer (4% of the total population over 65 years of age). Average direct costs of managing a venous ulcer for 6 months in the United States have been reported as $15,732. This does not include indirect costs such as loss of income or buying unreimbursed items or travel related to venous ulcer care or the patient-centered toll on quality of life, pain, function and social isolation.	We thank the reviewer for this comment and have added this information to the introductory section.
77.	Public Reviewer #9 Laura Bolton from International Consolidated Guideline Task Force	Introduction	Please note that a population subgroup of interest for KQ2 and KQ3 with an active or healed lower extremity venous ulcer indicates a greater severity of disease, meriting separate analysis for the following CEAP classes: a) CEAP classification C6 = presence of an active venous ulcer or b) CEAP classification C5: presence of a healed venous ulcer	We thank the reviewer for their comment and agree that these population subgroups would be of interest. We prespecified analyses based disease severity (as assessed by CEAP class), symptom status, and venous anatomy. However, due to a combination of a lack of specificity in the inclusion / exclusion criteria as well as a lack of results presentation by these subgroups, we were unable to perform the analyses suggested by the reviewer.
78.	Peer Reviewer #1	Methods	Page 10: population: asymptomatic should be defined as physical symptoms, given that disfigurement could be considered to have psychological "symptoms", even if pain, paresthesias, heaviness, etc. are not present.	Unfortunately we are limited in this analysis to the information provided by the authors of the included studies and whether they designated the patients to be symptomatic or asymptomatic. We address this limitation in the discussion
79.	Peer Reviewer #1	Methods	Page 10: interventions: Villalta presumes a venous diagnosis, so it is strange to include in KQ1 as an intervention on par with the other diagnostic modalities. I.e., it is not used for diagnosis of venous disease	We thank the reviewer for this suggestion and have removed this specification.

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80.	Peer Reviewer #1	Methods	Page 11: comparators: somewhere it should be noted that large observational data (basically doubling the #of patients in this analysis) were excluded because of a lack of a comparator, and this exclusion should be justified or explained. For example, the series by Raju and Neglen did not have comparators and were excluded, but there is useful data from them such as stent patency and safety data	Given the scope of this review to evaluate the comparative effectiveness of interventions we were limited to those which included active comparators.
81.	Peer Reviewer #2	Methods	Why limit the reviews only since 2000? This may exclude good quality studies from the 1990s which would still be very relevant. This is especially problematic for diagnostic imaging studies as most comparison investigations were performed earlier (Page 31, Line 29). I appreciate the authors' willingness to add recommended studies during the review process but it would have been most helpful to utilize the same rigorous search criteria for the earlier time period. One example is van den Bos RR, Kockaert MA, Neumann HA, et al. Technical review of endovenous laser therapy for varicose veins. Eur J Vasc Endovasc Surg 2008;35(1):88-95. PMID: 17920307	Although an expansion of the literature search period to the pre-2000 era would likely yield an increased number of studies assessing the accuracy and precision of non-invasive testing for the diagnosis of chronic venous disease (CVD), the availability, use, and technological sophistication of non-invasive testing for CVD has changed significantly since that time. Widespread use of more recent technological innovations such as power Doppler ultrasound, 64 slice computed tomography scanners, and higher field strength / non-contrast magnetic resonance angiography techniques have occurred since 2000. Additionally, widespread participation in quality certification programs, such as IAC Vascular Testing, IAC CT, and IAC MRI have occurred since 2000 as well. Thus, we believe that expansion of the literature search to include studies prior to 2000 would uncover studies of diagnostic devices that have been superseded by current technology and potentially missing techniques required by current accreditation standards. We reviewed the suggested citation but it was excluded at the full text level because of not being original data

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82.	Peer Reviewer #2	Methods	Medical treatment methods should have included venoactive agents, such as flavonoids and saponins. Although not approved in the U.S., they are common in Europe and do have reasonable published studies associated with them.	The scope of this review is specific to agents approved within the United States
83.	Peer Reviewer #2	Methods	For KQ2 (Page 23, line 23), a sample size of >500 was required for the study to be included. Perhaps all relevant studies were this big. However, if otherwise appropriate, there is nothing magic about 500. Particularly with the heterogeneity of the published studies in this field, this arbitrary numerical requirement may have been too stringent. What about using 250 as a cutoff?	We understand the concern about eliminating smaller observational studies. The decision to limit the inclusion of these studies was made following discussions with AHRQ, CMS, our technical expert panel, and after looking at the numbers of excluded studies and their potential impact on our findings. While observational studies can serve as a valuable source of data regarding therapeutic effectiveness in the "real world", they have generally been insufficient to establish efficacy. In the case of chronic venous disease (CVD) this systematic review has identified 90 randomized controlled trials evaluating the efficacy and comparative efficacy of a number of medical and interventional therapies. Despite the inclusion of these trials, the overall strength of evidence remained low and a number of clinically important subgroups (subgroups by CEAP disease severity, subgroups by anatomy, and subgroups by patient demographics) could not be analyzed due to a lack of data. While it is possible for observational studies to generate high strength of evidence data, the included observational studies of >/= 500 patients were also of low strength of evidence and lacked important subgroup data. As a result, it seems unlikely that inclusion of observational studies of < 500 patients will result in 1) the generation of high strength of evidence data 2) the addition of adequate

	Commentator & Affiliation	Section	Comment	Response
				data on clinically important subgroups 3) a significant change to the overall conclusions of the report that are currently based primarily on evidence of efficacy and comparative efficacy in from randomized controlled trials.
84.	Peer Reviewer #2	Methods	For mechanical compression [Appendix B] (Page 188, Line 121), there is no listing of compression stockings. This should obviously be an included variable and identified separately.	Although Appendix B lists the data elements and categories used during abstraction, for these data elements, investigators were also given text boxes and so additional information such as what type of compression used was captured if needed.
85.	TEP Reviewer #1	Methods	The methods, search strategies, outcomes and analyses are clearly defined and are appropriate.	No response needed
86.	TEP Reviewer #2	Methods	I'm not a statistician and my assessment is therefore based more on a "lay-sense" than on scientific (statistical) principles. With this disclaimer, the methods seemed exceptionally clear and easy-to-follow. I cannot suggest a better search strategy. Outcome measures are always a problem; the ones used here are "par for the course" and represent a traditional -- and acceptable -- approach. I can't comment on the statistics.	No response needed
87.	TEP Reviewer #2	Methods	See my general comments -- I wonder if there shouldn't be a little more said (disclaimer?) about the potential role of end-points that are not emphasized here (like cost-effectiveness), but are clearly important and may ultimately be the key drivers in the future?	We agree that the cost effectiveness of these interventions may be an important driver in downstream implementation and use. Although beyond the scope of our review we now include mention of this outcome in the discussion.

	Commentator & Affiliation	Section	Comment	Response
88.	TEP Reviewer #3	Methods	The major concern here is the limitation of data included only after 2000.	We agree that the majority of the literature supporting the use of surgical approaches to treating venous disease predates the year 2000. However, the primary focus of the present report is comparative effectiveness of invasive and non-invasive techniques to treat lower extremity chronic venous disease (LECVD). Given that endovascular techniques to treat LECVD have only been in widespread use since 2000, by necessity, we restricted our literature search to the year 2000 and beyond. Additionally, while surgical techniques for LECVD may not have changed substantially since the 1990s, the increasing adoption of vascular surgery quality initiatives and clinical guideline documents since 2000 may have substantially impacted both surgical outcomes and patient selection. As a result, we argue that surgical outcomes for LECVD post 2000 may be distinct from those prior to this era and have maintained the 2000 cutoff for this report.
89.	TEP Reviewer #4	Methods	Too much focus on comparative studies. other studies may have been missed/not included despite their contributions to the body of evidence.	The scope of the project was on the comparative effectiveness of the available treatments and so this was the focus of the included studies and our discussion.
90.	TEP Reviewer #5	Methods	The methodology of this review is superb. The Inclusion and exclusion criteria using the PICOTS elements are very appropriate. In spite of the challenges of heterogenous outcomes reported in the included studies the authors have done an excellent job outlining and defining these in the document.	We thank the reviewer for their comment. No response needed
91.	TEP Reviewer #5	Methods	Statistical methodology for the relevant sections and particularly Key question 2 seem to be appropriate.	No response needed

	Commentator & Affiliation	Section	Comment	Response
92.	Public Reviewer #1 Chandra Branham of AdvaMed	Methods	As it finalizes the review, we would ask that AHRQ include comparative observational studies with 100 or more patients in its evaluation of treatments for symptomatic CVI patients. There are multiple studies that the report currently excludes because of the 500 patient limit for; these studies meet the rest of AHRQ?s rigorous inclusion/exclusion criteria. The majority of these studies track clinical and quality of life outcomes for one year or more and would help further reinforce the durability of more invasive treatment options for CVI patients.	We appreciate the reviewer's request to expand the literature search to include observational studies of less than 500 patients. We note that observational study sample size requirement of 500 or more patients was only applicable to KQ 2; for KQs 1 and 3 we allowed observational studies with as few as 20 patients. While observational studies can serve as a valuable source of data regarding therapeutic effectiveness in the "real world", they have generally been insufficient to establish efficacy. In the case of chronic venous disease (CVD) this systematic review has identified 90 randomized controlled trials evaluating the efficacy and comparative efficacy of a number of medical and interventional therapies. Despite the inclusion of these trials, the overall strength of evidence remained low and a number of clinically important subgroups (subgroups by CEAP disease severity, subgroups by anatomy, and subgroups by patient demographics) could not be analyzed due to a lack of data. While it is possible for observational studies to generate high strength of evidence data, the included observational studies of >/= 500 patients were also of low strength of evidence and lacked important subgroup data. At the time of the Draft report, we assessed the likely impact to the review findings if we were to consider observational studies for KQ 2 of less than 500 patients. The KQ 2 size criterion impacted 47 studies. The size distribution of these studies was as follows: 3 with 20-49 patients, 15 with 50-99 patients, 28 with 100-499 patients, and one study with

	Commentator & Affiliation	Section	Comment	Response
				an overall population larger than 500 patients that had only approximately 240 patients relevant to KQ 2. The majority of these studies had comparisons that included invasive surgical/ endovascular treatments, which was already the intervention section of the report with the largest amount of evidence. As a result, we conclude it to be unlikely that inclusion of observational studies of < 500 patients would result in 1) the generation of high strength of evidence conclusions, 2) the addition of adequate data on clinically important subgroups, or 3) a significant change to the overall conclusions of the report that are currently based primarily on evidence of efficacy and comparative efficacy in from randomized controlled trials.
93.	Public Reviewer #1 Chandra Branham of AdvaMed	Methods	We recommend that AHRQ include an evaluation of other quality of life measures not included in the draft such as return to work and return to normal activities.	Our review looked for patient-reported quality of life and we included within our report those studies which reported such outcomes.
94.	Public Reviewer #1 Chandra Branham of AdvaMed	Methods	To the point made at the MEDCAC by Dr. Meissner, we also request that AHRQ do a sub-analysis of the endovascular treatment category as a whole.	Given the heterogeneity in treatments, comparison, outcomes, and timing of endpoints we did not feel that such a sub-analysis would modify our findings
95.	Public Reviewer #1 Chandra Branham of AdvaMed	Methods	To the point made at the MEDCAC by panelist, Dr. Lewis, we also request that AHRQ do a metaanalysis of the varying quality of life instruments.	We attempted to include evidence supporting several types of QOL measures, including patient-reported and other validate instruments and considered whether quantitative synthesis of these tools was feasible. Although we still feel that the difference in measurement tools does not allow quantitative synthesis of these findings, we now attempt to clarify the direction and consistency of the benefit for the reader.

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96.	Public Reviewer #4 Martin Schul with ACPPROVein Registry	Methods	Page 96 1st paragraph: Simply noting that a manuscript I published was used to compare foam sclerotherapy to compression shows the lack of critical review em;owed when reviewing the studies. REF #130 is a multi center randomized control trial comparing compression to liquid sclerotherapy for reticular veins and telangiectasia. It addressed symptom response to compression and sclerotherapy and monitored results thru 12 months and amazing patient retention. Its perfectly fine to exclude this study from review for saphenous interventions, but not to use it in compression benefits or to use it for a comparison it did not address are simply sloppy examples of the review.	We thank the reviewer for the clarification. This study is now excluded.
97.	Public Reviewer #4 Martin Schul with ACPPROVein Registry	Methods	Many studies show symptom response, or validated full HRQL forms yet the inconsistency in tool used does not mean that the tools could not have been pulled and compared to the benefit for a given treatment, disease state, or subgroup. Of course there has been little interest in HRQL in the early 2000's, yet over the past ten years, more and more studies incorporate response to pain, edema, heaviness, etc. These studies could have been given better value if pooled for the benefits they offer. Ignoring this feature suggests the effort was simply not put forth, leading the tech assessment to one set for failure.	We thank the reviewer for their suggestion and agree that despite the heterogeneity it is important to note whether the different health related QOL tools show a benefit or not. Although we still feel that the difference in the measurement tools does not allow quantitative synthesis of these findings we have attempted to clarify the direction of benefit for the reader.

	Commentator & Affiliation	Section	Comment	Response
98.	Public Reviewer #5 from the American Academy of Family Physicians	Methods	The lack of significant published research on diagnostic studies since 2000 is troubling. While the rationale for not going back prior to 2000 for KQ1 was noted, there remains concern that important evidence on diagnosis is being missed.	Although an expansion of the literature search period to the pre-2000 era would likely yield an increased number of studies assessing the accuracy and precision of non-invasive testing for the diagnosis of chronic venous disease (CVD), the availability, use, and technological sophistication of non-invasive testing for CVD has changed significantly since that time. Widespread use of more recent technological innovations such as power Doppler ultrasound, 64 slice computed tomography scanners, and higher field strength / non-contrast magnetic resonance angiography techniques have occurred since 2000. Additionally, widespread participation in quality certification programs, such as IAC Vascular Testing, IAC CT, and IAC MRI have occurred since 2000 as well. Thus, we believe that expansion of the literature search to include studies prior to 2000 would uncover studies of diagnostic devices that have been superseded by current technology and potentially missing techniques required by current accreditation standards.

	Commentator & Affiliation	Section	Comment	Response
99.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Methods	Page 9 Search Strategy: Inclusion of studies from January 1, 2000 ? January 6, 2016 based on the key questions is limiting especially for areas for which evidence pre-dating 2000 would be important (examples: diagnostic testing, validation venous Duplex ultrasound as standard, effectiveness of compression). Why is study search strategy limited to this date range?	Although an expansion of the literature search period to the pre-2000 era would likely yield an increased number of studies assessing the accuracy and precision of non-invasive testing for the diagnosis of chronic venous disease (CVD), the availability, use, and technological sophistication of non-invasive testing for CVD has changed significantly since that time. Widespread use of more recent technological innovations such as power Doppler ultrasound, 64 slice computed tomography scanners, and higher field strength / non-contrast magnetic resonance angiography techniques have occurred since 2000. Additionally, widespread participation in quality certification programs, such as IAC Vascular Testing, IAC CT, and IAC MRI have occurred since 2000 as well. Thus, we believe that expansion of the literature search to include studies prior to 2000 would uncover studies of diagnostic devices that have been superseded by current technology and potentially missing techniques required by current accreditation standards.

	Commentator & Affiliation	Section	Comment	Response
100.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Methods	Page 10-12 Inclusion and Exclusion Criterial and Table 4): By excluding observational studies <500 patients some important high quality evidence is missed.	We appreciate the reviewer's request to expand the literature search to include observational studies of less than 500 patients. We note that observational study sample size requirement of 500 or more patients was only applicable to KQ 2; for KQs 1 and 3 we allowed observational studies with as few as 20 patients. While observational studies can serve as a valuable source of data regarding therapeutic effectiveness in the "real world", they have generally been insufficient to establish efficacy. In the case of chronic venous disease (CVD) this systematic review has identified 90 randomized controlled trials evaluating the efficacy and comparative efficacy of a number of medical and interventional therapies. Despite the inclusion of these trials, the overall strength of evidence remained low and a number of clinically important subgroups (subgroups by CEAP disease severity, subgroups by anatomy, and subgroups by patient demographics) could not be analyzed due to a lack of data. While it is possible for observational studies to generate high strength of evidence data, the included observational studies of >/= 500 patients were also of low strength of evidence and lacked important subgroup data. At the time of the Draft report, we assessed the likely impact to the review findings if we were to consider observational studies for KQ 2 of less than 500 patients. The KQ 2 size criterion impacted 47 studies. The size distribution of these studies was as follows: 3 with 20-49 patients, 15 with 50-99 patients, 28 with 100-499 patients, and one study with an overall population larger than 500 patients that had only approximately 240 patients relevant to KQ 2. The majority of these studies had comparisons that included invasive surgical/ endovascular treatments, which was already the intervention section of

	Commentator & Affiliation	Section	Comment	Response
101.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Methods	QoL is an important outcome measure with venous disease and does not appear to be included in this document.	We have included patient related quality of life as one of the outcomes of interest
102.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Methods	Page 12 Study Selection: By limiting to 2 reviewers there is a potential for bias. How is assigning of Strength/Level of Evidence reconciled when there is disagreement between the reviewers?	The EPC methods for systematic review are devised so as to reduce bias and follow IOM standards for systematic review. As described in the methods section, when there is disagreement between reviewers consensus is either determined through discussion of the two reviewers or through participation of a third senior reviewer.
103.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Methods	The report would benefit from a risk/benefit analysis.	We agree with the reviewer that although this report addresses the risks and benefits of the various interventions it does not explore the tradeoffs between these outcomes. Unfortunately this type of analysis is outside of the scope of this report. We believe that such an analysis is important and encourage the performance of such analyses using evidence from our review.
104.	Public Reviewer #9 Laura Bolton from International Consolidated Guideline Task Force	Methods	Strength of Evidence (SOE) criteria (page 15) would be valid if it included pre-2000 evidence, but without being able to weigh all evidence, it is not feasible to judge whether the statement is likely to change. For example, much evidence supporting compression for venous ulcer management(1) and prevention of recurrence (2) pre-dates the year 2000. Exclusion of this evidence from this AHRQ TA precluded adequate perspective to assess SOE on compression and on any issue with substantial clinical evidence prior to the year 2000.	As described in the methods, the strength of evidence rating focuses on the evidence included in the study (and so post 2000). To aid the reader, within the discussion and throughout the text we also attempt to put our findings in to context of what was already known prior to 2000.
105.	Public Reviewer #9 Laura Bolton from International	Methods	Inclusion / exclusion criteria for references omitted important evidence supporting compression effects on healing venous ulcers	We thank the reviewer for their comment. We reviewed the suggested systematic reviews during our process and their included

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	Consolidated Guideline Task Force		while significantly reducing costs of management.(1 3 4 5) and reducing recurrence.2 Perhaps the authors intended to include the O'Meara et al. (2012)(1) and Nelson et al. (2014)(2) metaanalyses supporting efficacy of elastic compression on VU healing and prevention of recurrence. Although these Cochrane reviews were included as references # 26 and #16 in the AHRQ TA, neither was cited in its text. The 2012 meta analyses support conclusions quoted below regarding implications for practice1: ?Forty-eight RCTs reporting 59 comparisons were included (4321 participants in total). Most RCTs were small, and most were at unclear or high risk of bias. Duration of follow-up varied across RCTs. Risk ratio (RR) and other estimates are shown below where RCTs were pooled; otherwise findings refer to a single RCT. There was evidence from eight RCTs (unpooled) that healing outcomes (including time to healing) are better when patients receive compression compared with no compression. Single-component compression bandage systems are less effective than multi-component compression for complete healing at six months (one large RCT). A two-component system containing an elastic bandage healed more ulcers at one year than one without an elastic component (one small RCT). Three-component systems containing an elastic component healed more ulcers than those without elastic at three to four months (two RCTs pooled), RR 1.83 (95% CI 1.26 to 2.67), but another RCT showed no difference between groups at six months. An individual patient data meta-analysis of five RCTs suggested significantly faster healing with the four-layer bandage (4LB) than the short	component references. All individual studies which met our inclusion criteria are included in our review. We reviewed these specific systematic reviews for their relevant component references to see if they met our inclusion/exclusion criteria. Many of the citations which were not included either were published before 2000 or did not have comparisons of interest.

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			stretch bandage (SSB): median days to healing estimated at 90 and 99 respectively; hazard ratio 1.31 (95% CI 1.09 to 1.58). High-compression stockings are associated with better healing outcomes than SSB at two to four months: RR 1.62 (95% CI 1.26 to 2.10), estimate from four pooled RCTs. One RCT suggested better healing outcomes at 16 months with the addition of a tubular device plus single elastic bandage to a base system of gauze and crepe bandages when compared with two added elastic bandages. Another RCT had three arms; when one or two elastic bandages were added to a base threecomponent system that included an outer tubular layer, healing outcomes were better at six months for the two groups receiving elastic bandages?	

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106.	Public Reviewer #9 Laura Bolton from International Consolidated Guideline Task Force	Methods	The 2014 Cochrane review by Nelson and Bell-Sayer(2) supported main results quoted below. This evidence may be important to encourage efficient, cost effective management of chronic venous insufficiency adequate to prevent recurrence of a healed venous ulcer: ?Four trials (979 participants) were eligible for inclusion in this review. One trial in patients with recently healed venous ulcers (n = 153) compared recurrence rates with and without compression and found that compression significantly reduced ulcer recurrence at six months (Risk ratio (RR) 0.46, 95% CI 0.27 to 0.76). Two trials compared high-compression hosiery (equivalent to UK class 3) with moderate-compression hosiery (equivalent to UK class 2). The first study (n=300) found no significant reduction in recurrence at five years follow up with high-compression hosiery compared with moderate-compression (RR 0.82, 95% CI 0.61 to 1.12). The second study (n = 338) assessed ulcer recurrence at three years follow up and found that highcompression hosiery reduced recurrence compared with moderate-compression (RR 0.57, 95% CI 0.39 to 0.81). Statistically significant heterogeneity precluded meta-analysis of the results from these studies. Patientreported compliance rates were reported in both trials; there was significantly higher compliance with mediumcompression than with high-compression hosiery in one and no significant difference in the second. A fourth trial (166 patients) found no statistically significant difference in recurrence between two types of medium (UK class 2) compression hosiery (Medi versus Scholl: RR 0.74, 95% CI 0.45 to 1.2). ?	We thank the reviewer for their comment. The first component reference from the Cochrane review by Vandongen et all was included in our review. Based on feedback from our Technical Expert Panel which recommended not including different compression types or degrees of compression as comparators of interest, the remaining three studies were not considered applicable.

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107.	Peer Reviewer #1	Results	Page 129: safety concerns: the conclusion that urokinase infusion at the time of stenting chronic venous obstructions is associated with a higher rate of complications is dubious. The study that is referenced is a retrospective analysis, in which many of the patients were thought to have at least an acute component to their presentation and thus needed thrombolytic infusion. The implication is to not lyse chronic thrombus because of safety concerns, but the paper reads as a combination of acute and chronic venous disease. There should be some consideration to eliminate this study from analysis (it was included because there was a weak comparison between lytics alone vs. lytics plus stenting)	Although the reviewer is correct that this paper includes both acute and chronic patients – the findings represented in our review focus only on the chronic patients. We now clarify this in the text.
108.	Peer Reviewer #1	Results	page 149, line 24: same point [as above]: would not make this conclusion based on the study -- presumption was that the chronic patients had an acute iliofemoral DVT associated with a chronic lesion, variable use -- strong consideration for removing this analysis from the data, or qualifying this data further by stating that this analysis may not be appropriate for management of chronic venous disease	Although the reviewer is correct that this paper includes both acute and chronic patients – the findings represented in our review focus only on the chronic patients. We now clarified this in the text.
109.	Peer Reviewer #2	Results	The characteristics of the studies are nicely detailed in the Appendices.	No response needed

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110.	Peer Reviewer #2	Results	Please see Comment #1 under Methods in regards to the studies included. *"Why limit the reviews only since 2000? This may exclude good quality studies from the 1990s which would still be very relevant. This is especially problematic for diagnostic imaging studies as most comparison investigations were performed earlier (Page 31, Line 29)."*	Although an expansion of the literature search period to the pre-2000 era would likely yield an increased number of studies assessing the accuracy and precision of non-invasive testing for the diagnosis of chronic venous disease (CVD), the availability, use, and technological sophistication of non-invasive testing for CVD has changed significantly since that time. Widespread use of more recent technological innovations such as power Doppler ultrasound, 64 slice computed tomography scanners, and higher field strength / non-contrast magnetic resonance angiography techniques have occurred since 2000. Additionally, widespread participation in quality certification programs, such as IAC Vascular Testing, IAC CT, and IAC MRI have occurred since 2000 as well. Thus, we believe that expansion of the literature search to include studies prior to 2000 would uncover studies of diagnostic devices that have been superseded by current technology and potentially missing techniques required by current accreditation standards.

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111.	Peer Reviewer #2	Results	The diagnostic portion, KQ1, is particularly weak. The self-imposed restriction not to evaluate studies before 2000 severely and un-necessarily limited the available data. As a consequence, the review is superficial and conclusions are non-substantive. In fact, as mentioned, duplex ultrasound is the present and universal gold standard for infrainguinal disesase. There is really no clinical debate here but the review's conclusion that "evidence was insufficient for any specific diagnostic test method" reflects more the limitation of this review as opposed to the actual data. I would strongly recommend extending the literature review back to at least 1990 for this question.	Although an expansion of the literature search period to the pre-2000 era would likely yield an increased number of studies assessing the accuracy and precision of non-invasive testing for the diagnosis of chronic venous disease (CVD), the availability, use, and technological sophistication of non-invasive testing for CVD has changed significantly since that time. Widespread use of more recent technological innovations such as power Doppler ultrasound, 64 slice computed tomography scanners, and higher field strength / non-contrast magnetic resonance angiography techniques have occurred since 2000. Additionally, widespread participation in quality certification programs, such as IAC Vascular Testing, IAC CT, and IAC MRI have occurred since 2000 as well. Thus, we believe that expansion of the literature search to include studies prior to 2000 would uncover studies of diagnostic devices that have been superseded by current technology and potentially missing techniques required by current accreditation standards.
112.	Peer Reviewer #2	Results	The authors are to be congratulated for having looked at essentially every possible combination of therapies for comparisons.	No response needed
113.	Peer Reviewer #2	Results	For KQ3, the review appropriately notes that the strength of the evidence in insufficient for all topics, underlining the continued need for randomized trials.	No response needed
114.	TEP Reviewer #1	Results	As noted above, this section is overly long. Greater focus on the high quality studies and better use of tables would streamline this section. Specific concerns are outlined below.	We thank the reviewer for their comment and have highlighted the good quality studies throughout the text and used tables and shading to indicate those outcomes where the strength of evidence were not insufficient.

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115.	TEP Reviewer #1	Results	Page 4: Several of the abbreviations have already been defined and do not need to be repeated (i.e., CEAP and DUS).	We have verified that the abbreviations are defined initially and not repeated unnecessarily
116.	TEP Reviewer #1	Results	Page 4: Line 22: It may be better to say “need for repeat intervention”.	We have made the suggested change.
117.	TEP Reviewer #1	Results	Page 7: Figure 1: In the section on “adverse effects of treatment”, the differences among “thrombophlebitis”, “venous thrombosis”, and “venous thromboembolic events” are not clear.	We have made the needed change in Figure 1.
118.	TEP Reviewer #1	Results	Page 10: Under interventions, D-dimer is measured in plasma or whole blood but not in serum. This needs to be corrected.	We have corrected the text.
119.	TEP Reviewer #1	Results	Page 12: Top box: Once again, the differences among “thrombophlebitis”, “venous thrombosis”, and “venous thromboembolic events” are not clear.	We have clarified within the box.
120.	TEP Reviewer #1	Results	Page 12: Lines 47-48: Was there discussion among the reviewers or investigators? If there were only 2 reviewers, how was consensus achieved?	As described in the methods section, consensus was achieved through discussion of the 2 reviewers for any disagreements. If consensus was not possible a third senior investigator was consulted.
121.	TEP Reviewer #1	Results	Page 21: Lines 39-40: For patients with a prior history of DVT, it also is important to know whether the event was provoked or unprovoked.	We have added in this clarification.
122.	TEP Reviewer #1	Results	Page 22: Duplex ultrasound is the test used most often for initial evaluation of patients with LECVD. Therefore, it would be more logical to place the section on this test before that on plethysmography.	We thank the reviewer for their suggestion but included the diagnostic tools in the order specified in our protocol.
123.	TEP Reviewer #1	Results	Page 25: Conclusions: Although the lack of comparative studies is a limitation, is it not reasonable to recommend DUS as the initial test for evaluation of LECVD? It is widely available, relatively inexpensive, non-invasive, and associated with no harms; features that distinguish it from most of the other tests listed in this section.	The AHRQ systematic reviews are not tasked with providing recommendations. No action needed.

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124.	TEP Reviewer #1	Results	Page 27: Line 41: The title "Comparisons between surgical interventions and surgical interventions" does not make sense.	We now clarify that the comparisons evaluated in this section are between different invasive surgical approaches.
125.	TEP Reviewer #1	Results	Page 28: Line 40: Would it not make more sense to label it "varicose vein recurrence" rather than "vein recurrence" in the title and throughout this section?	We have made this suggested change throughout the report.
126.	TEP Reviewer #1	Results	Page 28: Line 51: The text should read "recurrence" rather than "recurrent".	We have fixed this typo.
127.	TEP Reviewer #1	Results	Page 29: Line 23: "On postoperative day 1" is more grammatically correct than "on day 1 postoperative".	We have made the suggested change.
128.	TEP Reviewer #1	Results	Page 29: Lines 33 and 42: The text should read "2 years follow-up".	We have fixed this typo.
129.	TEP Reviewer #1	Results	Page 29: Line 53: The text should read "3 years".	We have fixed this typo.
130.	TEP Reviewer #1	Results	Page 30: Lines 40, 42, 45 and 50: Does the term "thrombophlebitis" refer to superficial vein thrombosis? If so, the latter is a more precise term. In fact, this is the term used in line 51. The authors need to be consistent throughout the paper.	We now clarify that we are referring to superficial thrombophlebitis.
131.	TEP Reviewer #1	Results	Page 31: Lines 27-29: The last sentence is poorly worded.	We have modified the sentence.
132.	TEP Reviewer #1	Results	Page 36: Line 34: The text should read "lowers".	We have fixed this typo.
133.	TEP Reviewer #1	Results	Page 38: Line 42: The text should read "months".	This text has been corrected.
134.	TEP Reviewer #1	Results	Page 41: Line 54: Does "phlebitis" refer to superficial vein thrombosis or DVT? This needs to be specified.	We have corrected this text to clarify that this refers to superficial thrombophlebitis.
135.	TEP Reviewer #1	Results	Page 48: Line 8: It should be "±" rather than "+/-".	We have made the requested change.

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136.	TEP Reviewer #1	Results	Page 48: Line 39: The text should read “A higher percentage of patients who underwent microfoam sclerotherapy had DVT”.	We have corrected this text.
137.	TEP Reviewer #1	Results	Page 50: Again “thrombophlebitis” should be defined as superficial vein thrombosis.	We have made the suggested correction throughout.
138.	TEP Reviewer #1	Results	Page 56: Line 25: It would be better to say that “After 1 week, there was no DVT in either group”.	We have modified this text as suggested.
139.	TEP Reviewer #1	Results	Page 58: The title does not make sense.	We have modified the title to clarify it is comparing different endovascular approaches.
140.	TEP Reviewer #1	Results	Pages 93-99: Would it not make more sense to start with the sections comparing endovascular procedures with placebo or with medical therapy such as compression to highlight the potential value of invasive procedures?	We have maintained our existing structure to mimic the order of comparisons listed in our protocol.
141.	TEP Reviewer #1	Results	Pages 121-127: The authors need to make it clear in the headings that these sections deal with venous ulcers	We respectfully disagree with the reviewer. While the majority of the studies in this section involve patients with venous leg ulcers, there are studies that involve a heterogeneous population of patients included patients with varicose veins and therefore we feel that highlighting venous ulcers would de-emphasize that we studied a larger population.
142.	TEP Reviewer #2	Results	The results are clear and logical. The format used is effective.	No response needed

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143.	TEP Reviewer #3	Results	I find it difficult to accept that there remains question about the primary role of duplex ultrasonography in the diagnosis of patients with venous insufficiency. Compared to what? Ascending contrast venography is invasive, uncomfortable to patients, requires exposure to iodinated contrast (with all known risks, including allergy/anaphylaxis, renal injury, etc) and ionizing radiation, and it has been reported that venography precipitates venous thrombosis. None of these complications and risks exist with US. Finally, cost is dramatically higher with venography. CT and MR are more expensive and have limited applicability for infrainguinal venous reflux assessment.	We appreciate the reviewer's comments, however there is limited evidence found in this comparative effectiveness review to support or refute DUS as the primary mode of diagnostic testing We therefore did not feel that the systematic review should emphasize duplex ultrasonography's primary role. We have, however, added text regarding the risks of these other tests to the conclusions of KQ 1
144.	TEP Reviewer #4	Results	QoL meaurements, although very relevant are not the only important measures to describe. Reinterventions, patency in the case of obstructive lesion revascularization, etc, should have been slightly better represented.	The scope of the review has attempted to focus on those outcomes most critical to decision making by patients, providers, and policymakers. This includes many outcomes in addition to quality of life measures and these are detailed within the methods section of our report.
145.	TEP Reviewer #5	Results	The authors have presented the results in a very concise and with a pragmatic approach. The Key messages are clear and accompanying figures, tables and appendices are adequately descriptive.	No response needed

	Commentator & Affiliation	Section	Comment	Response
146.	TEP Reviewer #5	Results	I do think that the following reference may be a useful addition in reference to Key question 3. Endovascular therapy for advanced post-thrombotic syndrome: Proceedings from a multidisciplinary consensus panel Suresh Vedantham, Susan R Kahn, Samuel Z Goldhaber, Anthony J Comerota, Sameer Parpia, Sreelatha Meleth, Diane Earp, Rick Williams, Akhilesh K Sista, William Marston, Suman Rathbun, Elizabeth A Magnuson, Mahmood K Razavi, Michael R Jaff, and Clive Kearon Vasc Med, August 2016; vol. 21, 4: pp. 400-407., first published on May 30, 2016	We thank the reviewer for the suggested citations and have considered the studies against our inclusion/exclusion criteria in the final report. For this specific citation it was excluded at our full text level for not being original data.
147.	Public Reviewer #3 Catherine Ratliff of University of Virginia Health System	Results	Would have hoped for more discussion on the types of compression therapies and the amount (mmHg) of compression. Compression is the corner stone for this disease and sorry that there is not more research to support compression regarding prevention, treatment, and prevention of recurrence of CVI.	We agree with the reviewer that this is an important topic, however there is limited evidence available and we have highlighted the need for future research to answer this important question.
148.	Public Reviewer #4 Martin Schul with ACPPROVein Registry	Results	Page 153: KQ1: It is a tragedy that duplex ultrasonography was not clearly stated the most appropriate, sensitive, and cost effective method to address limbs with leg pain/swelling/symptoms suggestive of chronic venous disorders.	Unfortunately there is no enough data to support or refute DUS as the primary diagnostic test.

	Commentator & Affiliation	Section	Comment	Response
149.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Results	Page 18 Figure 2: 103 abstracted studies with only 7 articles for KQ1 and 8 studies for KQ3 raises concerns that the inclusion criteria are too restrictive, missing reports prior to 2000 and those with less than 500 subjects.	We agree that the majority of the literature supporting the use of surgical approaches to treating venous disease predates the year 2000. However, the primary focus of the present report is comparative effectiveness of invasive and non-invasive techniques to treat lower extremity chronic venous disease (LECVD). Given that endovascular techniques to treat LECVD have only been in widespread use since 2000, by necessity, we restricted our literature search to the year 2000 and beyond. Additionally, while surgical techniques for LECVD may not have changed substantially since the 1990s, the increasing adoption of vascular surgery quality initiatives and clinical guideline documents since 2000 may have substantially impacted both surgical outcomes and patient selection. As a result, we argue that surgical outcomes for LECVD post 2000 may be distinct from those prior to this era and have maintained the 2000 cutoff for this report. Although an expansion of the literature search period to the pre-2000 era would likely yield an increased number of studies assessing the accuracy and precision of non-invasive testing for the diagnosis of chronic venous disease (CVD), the availability, use, and technological sophistication of non-invasive testing for CVD has changed significantly since that time. Widespread use of more recent technological innovations such as power Doppler ultrasound, 64 slice computed tomography scanners, and higher field strength / non-contrast magnetic resonance angiography techniques have occurred since 2000. Additionally, widespread participation in quality certification programs, such as IAC Vascular Testing, IAC CT, and IAC MRI have occurred since 2000 as well. Thus, we believe that expansion of the literature search to include studies prior to 2000 would uncover studies

	Commentator & Affiliation	Section	Comment	Response
150.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Results	Page 21 General Concepts and Methods of Diagnosis for LECVD: Reference is made to SVS/AVF varicose vein guidelines (#53), ACP guidelines (#54). Need to add reference to NICE guidelines (#55) here, which is discussed later. Omitted are SVS/AVF Venous Ulcer guidelines which should be added to the document.	We thank the reviewer and have added in the suggested reference.
151.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Results	Page 25 Conclusion: IVUS is mentioned, but there is no description of IVUS in the preceding section. Section should be added on IVUS, along with other venous diagnostic modalities.	IVUS is discussed in the prior paragraph before the conclusion. No change needed.

	Commentator & Affiliation	Section	Comment	Response
152.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Results	Page 25 Conclusion: ?Very few comparative studies?.outcomes studies.? Many validation studies, especially for DUS, were published prior to 2000, and were excluded from this analysis because of the time frame of included studies (post 2000).	We agree that the majority of the literature supporting the use of surgical approaches to treating venous disease predates the year 2000. However, the primary focus of the present report is comparative effectiveness of invasive and non-invasive techniques to treat lower extremity chronic venous disease (LECVD). Given that endovascular techniques to treat LECVD have only been in widespread use since 2000, by necessity, we restricted our literature search to the year 2000 and beyond. Additionally, while surgical techniques for LECVD may not have changed substantially since the 1990s, the increasing adoption of vascular surgery quality initiatives and clinical guideline documents since 2000 may have substantially impacted both surgical outcomes and patient selection. As a result, we argue that surgical outcomes for LECVD post 2000 may be distinct from those prior to this era and have maintained the 2000 cutoff for this report. Although an expansion of the literature search period to the pre-2000 era would likely yield an increased number of studies assessing the accuracy and precision of non-invasive testing for the diagnosis of chronic venous disease (CVD), the availability, use, and technological sophistication of non-invasive testing for CVD has changed significantly since that time. Widespread use of more recent technological innovations such as power Doppler ultrasound, 64 slice computed tomography scanners, and higher field strength / non-contrast magnetic resonance angiography techniques have occurred since 2000. Additionally, widespread participation in quality certification programs, such as IAC Vascular Testing, IAC CT, and IAC MRI have occurred since 2000 as well. Thus, we believe that expansion of the literature search to include studies prior to 2000 would uncover studies

	Commentator & Affiliation	Section	Comment	Response
153.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Results	Page 25-26: ??.and 6 studies where the diagnostic criteria was uncertain.? Studies with uncertain diagnostic criteria, or diagnosis, should be omitted from further analysis due to lack of clarity. This is an example of the concern that some studies with unclear reporting were included but more robust observational studies were excluded (specifically for KQ1 & KQ3).	Our process requires the reviewers to conform to the determined inclusion/exclusion criteria which in this case allowed some variation in diagnostic criteria. Specifically for KQ 1, there was rarely information present within the published studies to fully describe the diagnostic criteria used – mainly because duplex ultrasound has become so widely used and accepted as the gold standard. This meant that the diagnostic criteria for this narrative review KQ was sometimes uncertain.
154.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Results	There is significant discussion on plethysmography, yet it is rarely used in clinical practice since it does not provide sufficient data to be useful. It is encouraging that the SVS/AVF guidelines are mentioned but it might have equally useful to explore the references used to provide the guidelines.	We appreciate the reviewer's comments, however since this was discussed in guidelines (albeit briefly), we believe it warrants discussion in the narrative review/KQ 1 section of the comparative effectiveness review report. No change needed.
155.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Results	Duplex was studied more extensively prior to 2000, it appears as though it is judged too lightly as our diagnostic mainstay and so this analysis misses real world practice.	As prior comments have emphasized, this comparative effectiveness review is limited to the available evidence and highlights the findings since 2000.
156.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Results	Regarding pentoxifylline in the treatment of venous ulcers, several articles of importance were not considered because of the inclusion/exclusion criteria.	It is correct that pentoxifylline is an intervention of interest for KQ 2. We identified two studies of this intervention that met our date range and screening inclusion/ exclusion criteria. Per these findings, we noted in the report that there is limited evidence published since 2000 to suggest that pentoxifylline is effective relative to placebo for reducing venous ulcers (SOE=low).

	Commentator & Affiliation	Section	Comment	Response
157.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Results	Prevention of recurrence should be an outcome measure with venous ulcers.	Recurrent ulceration is an outcome of interest for KQ 2 and KQ 3.
158.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Results	Consider looking at the differences between foam and regular sclerotherapy which can dictate outcomes.	Per the inclusion/exclusion criteria established for this review (report Table 4), we did not consider same treatment comparisons (such as types of sclerotherapy). We have described comparisons of sclerotherapy and combination strategies including sclerotherapy to other treatments, and where these comparisons are described we have detailed the type of sclerotherapy performed.
159.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Results	The analysis does report a statistically significant difference in recurrent ulceration with surgery vs. compression, yet it is unclear to us why this is not a more prominent finding in the ultimate summary. Under the meta-analysis of any surgery vs. compression, why wasn?t ulcer recurrence analyzed since this seems as important as initial wound healing in the final analysis?	We agree that ulcer recurrence is an important outcome of interest. Our meta analyses, however, are limited to those outcomes where there are 3 or more studies evaluating the effect of similar interventions on specific outcomes of interest.
160.	Public Reviewer #9 Laura Bolton from International Consolidated Guideline Task Force	Results	Please clarify that varicose veins and venous ulcers are heterogeneous conditions with differing expected outcomes. Though both are listed as descriptive of LECVD on the CEAP scale, a varicose vein differs greatly from a venous ulcer. Varicose veins have no open wound, unless managed surgically, in which case there is a surgical wound, not a venous ulcer. If the surgical site becomes infected, it is a surgical site infection, not an infected venous ulcer. A venous ulcer is an open wound, with possible outcomes including partial or complete ulcer healing, ulcer recurrence after healing and adverse events such as pain or ulcer infection.	The reviewer is correct and we did abstract the data according to the construct described. No change made.

	Commentator & Affiliation	Section	Comment	Response
161.	Public Reviewer #9 Laura Bolton from International Consolidated Guideline Task Force	Results	Table 26. Strength of evidence for major outcomes?KQ 2?mechanical compression therapies vs. placebo or usual care. This Table omitted a ?good quality study (321 patients) conducted in Hong Kong? from the evidence supporting both ?Venous wound healing? and ?Patient-reported QOL? with results clearly described on page 121: ?The 3-arm RCT conducted in Hong Kong assessed quality-of-life aspects, ulcer-related pain, and patients? functional status at baseline and after 24 weeks of treatment with a four-layer compression bandaging, short-stretch compression bandaging, or usual care without bandaging.126 Relative to usual care, both compression bandaging interventions significantly reduced ulcer-related pain and improved functional status as measured by the Frenchay Activities Index, and quality of life (QoL) as measured by the Short Form 12-item Health Survey (SF-12) and the CCVUQ at 24 weeks. The mean time to ulcer healing was 10.4 weeks (SD 0.8) for the four-layer bandaging, 9.8 weeks (SD 0.77) for the short-stretch compression bandaging, and 18.3 weeks (SD 0.86) for usual care ($p<0.001$ for comparisons between either compression group with usual care).?	We thank the reviewer for their careful review – we have now corrected Table 26.
162.	Public Reviewer #9 Laura Bolton from International Consolidated Guideline Task Force	Results	Inclusion of these results from a, well-conducted trial of 321 patients in Hong Kong, plus support by the O?Meara et al.1 Cochrane review of 2012, clearly defining parameters of sustained compression adequate to improve venous ulcer healing outcomes may reverse the ?Insufficient? descriptor of evidence supporting efficacy of patient-appropriate compression for venous ulcer healing and its effects on patient-reported quality of life.	The final report included updates of the literature to include the most recent new evidence. Specifically the cited Hong Kong study was included in KQ 2. The O'Meara Cochrane review was looked at for component references per our methods.

	Commentator & Affiliation	Section	Comment	Response
163.	Public Reviewer #9 Laura Bolton from International Consolidated Guideline Task Force	Results	Table 26 omits 6-month significant results described in the TA on LECVD text citing reference #171 as reporting significantly reduced ulcer recurrence. Nelson et al.2 report this same result at 6 months as statistically significant: 15 of 72 (21%) venous ulcers recurred in the compression group, compared to 37 of 81 (46%) in the group without compression (p = 0.0025). Table 26 omits this significant 6-month data on page 124, noting ?No significant differences in recurrent ulceration? at 1-4 months and at 12 months, but omitting the 6-month results. Would this change the ?Insufficient? judgment about ulcer recurrence, as it did in the Cochrane review? Discrepancies between systematic reviews confuse care providers and reduce the credibility of the source.	We thank the reviewer for their careful review – we have now corrected Table 26.

	Commentator & Affiliation	Section	Comment	Response
164.	Public Reviewer #9 Laura Bolton from International Consolidated Guideline Task Force	Results	AHRQ TA Page 28: Comparisons between Surgical Interventions and Compression ? Although some studies favored surgical approaches over compression with regard to wound healing and QoL, there were no consistent differences in the comparative effectiveness of surgical approaches (HL/stripping, HL/stripping/SEPS, CHIVA) versus compression for most available outcomes (QoL, wound healing, hemodynamic outcomes). A meta-analysis of surgical approaches versus compression on intermediate-term wound healing showed a trend toward better outcomes with surgery, but this difference was not statistically significant. (SOE = insufficient) a. Response: Surgical Intervention and Compression are not mutually exclusive. It is inappropriate to compare compression to surgery as compression is an essential complementary intervention. Adequate sustained compression therapy aids return of venous blood to the heart of a patient with chronic venous insufficiency. Guidelines11-14 and systematic reviews recommend surgical treatments in addition to standard compression therapy to aid in venous leg ulcer healing and to prevent recurrence.	We agree with the reviewer that compression and surgical interventions are often used in combination and are therefore difficult to compare to one another. While many studies including a surgical arm specified co-therapy with compression, we did find some studies which did not specify the use of compression pre- or post-surgery and we believe our descriptions of this evidence, the comparisons, and the findings are valid and useful to decisionmakers.

	Commentator & Affiliation	Section	Comment	Response
165.	Public Reviewer #9 Laura Bolton from International Consolidated Guideline Task Force	Results	AHRQ statement Page154 KQ2 Research Gaps: ??while mechanical compression therapies are routinely used postoperatively as an adjunct to invasive interventions for the treatment of LE chronic venous insufficiency/incompetence/reflux and for treatment of venous ulceration, there is little evidence to inform decisions about which of the many types of compression therapies to prescribe or the optimal dosing and duration of compression therapy for chronic venous insufficiency with or without venous ulcers.? a. Response: Compression is supported by the highest level of evidence in multidisciplinary evidence-based clinical practice guidelines of the Association for the Advancement of Wound Care, Society for Vascular Surgery/American Venous Forum, Wound Healing Society and Wound Ostomy Continence Nurses. 11-14 Omitting this evidence and evidence from the Cochrane review by O?Meara et al.1 supporting increased healing rates compared to no compression, particularly with use of the multi-component systems (supported by 39 RCTs) confuses and disserves professionals who choose to follow evidence-based wound care principles.	We agree with the reviewer that compression is supported for use, however the sentence states that little evidence is present to inform decisions about specific types of compression. The review did not however focus on different types of compression and therefore the evidence of this comparison was outside of the scope of the review.
166.	Public Reviewer #9 Laura Bolton from International Consolidated Guideline Task Force	Results	Please separate all analyses that combine interventions addressing varicose veins and venous ulcers. These are heterogeneous indications, with widely differing severity and definitions of efficacy. Combining analyses of the two reduces clarity and clinical relevance of findings.	We agree with the reviewer that these indications are very different. Unfortunately this analysis is not feasible given our abstracted data. We have added in a sentence to comment on this limitation.

	Commentator & Affiliation	Section	Comment	Response
167.	Public Reviewer #9 Laura Bolton from International Consolidated Guideline Task Force	Results	The AHRQ TA states that pentoxifylline is not effective, countering a 2012 Cochrane review of 12 RCTs on 864 patients supporting its efficacy compared to placebo when used with adequate sustained compression.(10) Such discrepancies among reviews undermine the credibility of evidence-based practice.	We thank the reviewer for their comment and now clarify the lack of evidence for pentoxifylline was in the post-2000 published evidence.
168.	Peer Reviewer #1	Discussion/ Conclusion	Page 152 line 44: it is not true that the use of thrombolytics has increased in the chronic obstructive population unless there is a perceived acute component. A single arm trial (ACCESS PTS, sponsor: EKOS/BTG) is looking at the utility of thrombolytic infusion for chronic post-thrombotic obstructive venous disease, but it is not currently a common practice. Would modify this language	We now clarify that it has increased in use for patients with iliofemoral DVT with or without proximal venous obstruction.
169.	Peer Reviewer #2	Discussion/ Conclusion	The Conclusions for KQ1 on imaging is not very helpful, principally because studies before 2000 were not included and therefore there was insufficient data to analyze. This portion will not be helpful to policymakers as, in addition, there is no recommendation made for further studies (appropriately) but the commentary may be misinterpreted by some to not support payment for clinical ultrasound imaging.	We want to clarify that AHRQ-TA and systematic reviews are not for providing a recommendation but rather summarizing the existing data and evidence gaps.
170.	Peer Reviewer #2	Discussion/ Conclusion	For KQ3, the conclusion on Page 160 Line 22 concerning thrombolysis with urokinase is very outdated and should be deleted. Urokinase has not been available for such use for many years and no one uses it for this purpose.	Urokinase was used in an included study. We agree that it is no longer available in the United States – however the findings can most likely be extrapolated to tPA, which is available and used in the United States.

	Commentator & Affiliation	Section	Comment	Response
171.	Peer Reviewer #2	Discussion/ Conclusion	The repeated Conclusions are that more research is needed. Although this is all fine and good, no substantive recommendations are made that can be used for policy decisions. These decisions, however, are being made repeatedly across the country by insurers and CMS (example: compression requirements before approval of interventions for symptomatic varicose veins). They will not wait for additional research before such policies are instituted. Therefore, it would have been very useful to them to have some clinically applicable recommendations on the basis of the data that is available.	The purpose of the systematic review is to summarize the available evidence (and any evidence gaps). Policymakers or guideline organizations who they use this review are tasked with determining recommendations.
172.	TEP Reviewer #1	Discussion/ Conclusion	The discussion is comprehensive, the conclusions are reasonable and the research groups are clearly identified.	No response needed
173.	TEP Reviewer #2	Discussion/ Conclusion	Findings and implications are clear. Limitations are clear, but especially so when the entire document has been read. Questions regarding future research are clear.	No response needed
174.	TEP Reviewer #3	Discussion/ Conclusion	This is well done.	No response needed
175.	TEP Reviewer #4	Discussion/ Conclusion	Fine but too heavy on superficial vein treatment. There is barely any mention to mechanical/pharmaco-mechanical thrombus removal. I am aware that this is predominantly performed for acute/subacute presentation but also for chronic.	We agree with the reviewer that mechanical and pharmaco-mechanical thrombus removal is mainly used for acute or subacute venous disease, and very scant literature is available for the treatment of chronic venous disease.
176.	TEP Reviewer #5	Discussion/ Conclusion	The discussion and conclusions are very appropriate. The limitations of the review are well stated.	No response needed

	Commentator & Affiliation	Section	Comment	Response
177.	TEP Reviewer #5	Discussion/ Conclusion	Again for future research the following paper would be good for KQ3. Endovascular therapy for advanced post-thrombotic syndrome: Proceedings from a multidisciplinary consensus panel Suresh Vedantham, Susan R Kahn, Samuel Z Goldhaber, Anthony J Comerota, Sameer Parpia, Sreelatha Meleth, Diane Earp, Rick Williams, Akhilesh K Sista, William Marston, Suman Rathbun, Elizabeth A Magnuson, Mahmood K Razavi, Michael R Jaff, and Clive Kearon Vasc Med, August 2016; vol. 21, 4: pp. 400-407., first published on May 30, 2016	We thank the reviewer for the suggested citations and have considered the studies against our inclusion/exclusion criteria in the final report. For this specific citation it was excluded at our full text level for not being original data.
178.	Public Reviewer #3 Catherine Ratliff of University of Virginia Health System	Discussion/ Conclusion	Eleven RCTs (1522 patients) compared mechanical compression with either placebo compression or no compression. All of these studies were performed outside of the United States. This should highlight the need for US funded studies	We agree that this is an important characteristics of the 11 RCTs and we highlight this in the description of included studies for this section.
179.	Public Reviewer #4 Martin Schul with ACPPROVein Registry	Discussion/ Conclusion	Page 154: Randomized controlled trials of substantial size to assess subgroups are not feasible. The technologies of thermal ablation, chemical ablation, and compression have long track records and and benefits should not be overlooked. Registries offer the best opportunity when every patient of a practice is captured. Each demographic feature and subgroup grows. As patients of like vein patterns have treatment and surrogate results providers document are paired with the patient's voice through generic quality of life queries, cost effectiveness and comparative effectiveness studies become possible.	We appreciate the reviewer's perspective, however, clinical practice should be guided when possible by well conducted, valid RCTs and can be supplemented by additional data from other sources such as registries or observational studies.

	Commentator & Affiliation	Section	Comment	Response
180.	Public Reviewer #4 Martin Schul with ACPPROVein Registry	Discussion/ Conclusion	One major concern in all of the technologies and mere nature of the studies is the focus was on efficacy of vein closure alone. Subgroup analysis was of little value as the numbers are too small to make a meaningful determination. This is where registries have a role. What is also limited in the trials is the spectrum of disease reported and treated. There are a number of vein reflux patterns that do not involve the great saphenous, or small saphenous veins. Registries capture duplex findings as patients move through treatment of X, Y, Z and patient populations/subgroups may be effectively compared when critical N is achieved.	We thank the reviewer for their comment and agree that registry studies are important. We decided not to include registry studies in this comparative effectiveness study due to the fact that the registry studies that we reviewed often did not have active comparators or comparators at all. RCTs that are completed within registries however will be useful to explore treatment strategies with multiple strata.
181.	Public Reviewer #4 Martin Schul with ACPPROVein Registry	Discussion/ Conclusion	The most effective means to address population differences are through sophisticated registries capturing routine documentation of providers and coupling with quality of life scores. We have employed this in our office for over 2 years and using a patient portal or offering an iPad to complete a generic SF6D and a symptom specific query VVSYM-Quick. These take little time to complete and do not disrupt work flow. The impetus on providers to incorporate quality of life forms in their offices are limited without a altruistic vision of what is needed for the field, the high cost of building a process with their EMR vendor, the lack of incentive to participate from regulating bodies.	We appreciate the reviewer's perspective and agree that the use of QOL measures within clinical practice and office-based care is imperative. Unfortunately, results from comparative effectiveness studies using this methodology are lacking. Hopefully in the future, well conducted, valid RCTs can be completed using EHR records within health systems or registries. No change needed.

	Commentator & Affiliation	Section	Comment	Response
182.	Public Reviewer #4 Martin Schul with ACPPROVein Registry	Discussion/ Conclusion	Page 150: When challenges are addressed, one must understand that there are no standards to follow patients over time. Registries that include all patients help to establish best practices as we see what works best for what patient groups etc. Population differences are important as different cultures perceive their symptoms and burden differently. Registries are the most effective way to capture the large N needed to show whether benefit truly exists when treating patients with venous conditions. The American College of Phlebology's Patient Reported Outcome Registry is the ideal tool and data is beginning to be analyzed as total N exceeds ten thousand unique patients.	We appreciate the reviewer's perspective, and have added the following sentence to the Discussion: Specifically, measuring outcomes that are (A) important to patients (e.g. quality of life, patient perception) and (B) able to be collected within the context of clinical care (e.g. office practice) will be imperative to improve the clinical care of these patients.
183.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Discussion/ Conclusion	Page 149-150 Findings in Relation to What is Already Known: Reference is made to SVS/AVF varicose vein guidelines (#53), ACP guidelines (#54) and NICE guidelines (#55). Omitted are SVS/AVF Venous Ulcer guidelines which should be added to the document. Also, there are other meta-analysis and systemic reviews that are not discussed or compared to the findings here. Need to compare this Technology Assessment to other meta-analysis which may ask the same questions, but have slightly different Methodology and conclusions. (Example: Mayo group analysis in SVS/AVF Venous Ulcer guidelines)	We now include reference to the SVS/AVF venous ulcer guidelines as suggested.
184.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Discussion/ Conclusion	Page 150-153: Challenges and Limitations addressed, but there is no acknowledgement of limitations of Methodology and general overall observations of insufficient to low strength of evidence. How do limitations in methodology impact the observation of lack of sufficient evidence?	The reviewer is correct that underlying methodological limitations of the available evidence can impact the strength of evidence. We now clarify this in the discussion.

	Commentator & Affiliation	Section	Comment	Response
185.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Discussion/ Conclusion	Therapy for May-Thurner might not fit in this analysis due to exclusion criteria. The authors consider the SVS/AVF guidelines in their discussion and note that their analysis may add little further. Despite the lack of RCTs, duplex imaging is considered the diagnostic tool initially required to establish the diagnosis and plan therapy and the disconnect from current practice is possibly most evident here. The analyses as presented are standard and give the statistical validity reported, although this is but just one area are good data is lacking with venous disease.	We agree with the reviewer that little comparative effectiveness evidence exists to guide treatment for May-Thurner syndrome. No change required.

	Commentator & Affiliation	Section	Comment	Response
186.	Public Reviewer #8 Jim Harmon from BTG International Inc	Discussion/ Conclusion	As set forth above, we trust that due consideration will be given to the comments made during the public comment period and that the Report will be reviewed to ensure that the literature and evidence are evaluated in the proper context in order to provide an accurate assessment of the available treatment strategies for chronic venous disease. We respectfully ask that the authors of the Report consider the points we have made in these public comments and include considering the following in its final technology assessment report: ? When assessing evidence supporting the treatment of chronic venous disease, place appropriate significance on the level of robustness of BTG?s VANISH-1 and VANISH-2 studies and consider them independently of the scores of varied, older publications on ?foam sclerotherapy? which is an inconsistently created and studied treatment that is not FDA approved and which is clinically inferior to the standardized FDA approved treatment using proprietary endovenous microfoam; and ? Ensure that the final technology assessment report includes an understanding of VVSymQ? as a PRO tool developed in compliance with FDA guidelines and the value the FDA places on patient reported outcome tools like VVSymQ? as direct measures of patient benefit.	The VANISH studies are included in our report – as well as the most recent publications from this group. Prior to performing the literature review, we discussed the use of validated tools with our Technical Expert Panel, and the VVSymQ (introduced in late 2015) was not included as a tool within our protocol.

	Commentator & Affiliation	Section	Comment	Response
187.	Public Reviewer #8 Jim Harmon from BTG International Inc	Discussion/ Conclusion	We appreciate the opportunity to comment on the Report and we offer these suggestions in the interest of ensuring that patients suffering from chronic venous disease are not denied treatments that are effective and provide symptom relief. We also stand ready to answer any questions or to clarify any of our comments should the panel wish to discuss them further. Please do not hesitate to contact us if we can provide any additional information that would be helpful to you in your review of these comments or as you finalize the technology assessment report.	No response needed
188.	Public Reviewer #9 Laura Bolton from International Consolidated Guideline Task Force	Discussion/ Conclusion	Please reword the term ?chronic venous obstruction? e.g. paragraph 4 of Discussion page 140, and all terms describing ?chronic obstruction? throughout this report. It seems to suggest that the etiology of chronic venous insufficiency is mainly one of venous obstruction. For venous ulcers, the most severe results of chronic venous insufficiency, etiology often involves failure of the veins to return venous blood to the heart, resulting from faulty, not necessarily obstructed, venous valves.	As highlighted in Table 1, we state that chronic venous obstruction and chronic venous insufficiently are separate entities and are treated as such throughout our review.

	Commentator & Affiliation	Section	Comment	Response
189.	Public Reviewer #9 Laura Bolton from International Consolidated Guideline Task Force	Discussion/ Conclusion	All studies cited in the Cochrane reviews or references added below used adequate standards for diagnosing, preventing or managing venous ulcers. The inclusion/exclusion criteria imposed on the AHRQ TA decreased its relevance by omitting many RCTs that support adequate sustained compression as essential in managing venous ulcers. This omission of evidence can confuse multidisciplinary wound care professionals who use evidence-based venous ulcer guidelines recommending appropriate sustained compression as an essential complement to any form of venous ulcer prevention or therapy. Using the principles of evidencebased practice in such guidelines reduces costs of care while improving healing and patient-centered outcomes.(3-5,7,8)	We have reviewed the suggested citations.
190.	Peer Reviewer #1	Clarity and Usability	The report is ambitious and clearly written by methodological experts. It will serve as a good reference. The limitations include: 1) not having a clear endovenous expert amongst the authors; 2) strictness of the inclusion, as much single-arm observational data that may inform the public about treatments for CVD were excluded	We believe that it is important to include investigators with limited risk of bias on our EPC investigator teams. We do however include two vascular specialists as key investigators. We describe (2) in our limitations section.
191.	Peer Reviewer #2	Clarity and Usability	The report is well-organized and the analyses appropriate.	No response needed
192.	Peer Reviewer #2	Clarity and Usability	The Conclusions to KQ2 is essentially a tabular re-statement of prior studies but lacks a succinct summary that would be helpful for policy or practice decisions.	Within the discussion we attempt to place within the context of existing policy our findings. AHRQ systematic reviews summarize the evidence and do not make recommendations. –Recommendations based on our findings are instead left to the policy makers which is consistent with the objective of the EPC systematic review process.

	Commentator & Affiliation	Section	Comment	Response
193.	Peer Reviewer #2	Clarity and Usability	Although this Report is exhaustive in its review, no conclusions or recommendations are made that will be relevant for policy or practice decisions.	Within the discussion we attempt to place within the context of existing policy our findings. AHRQ systematic reviews summarize the evidence and do not make recommendations. Recommendations based on our findings are left to the policy makers which is consistent with the objective of the EPC systematic review process.
194.	Peer Reviewer #2	Clarity and Usability	Acknowledging the limitations of the available clinical data, I would recommend that the report add some specific clinical and policy-relevant recommendations at the end of this Report.	Within the discussion we attempt to place within the context of existing policy our findings. AHRQ systematic reviews summarize the evidence and do not make recommendations. Recommendations based on our findings are left to the policy makers which is consistent with the objective of the EPC systematic review process.
195.	TEP Reviewer #1	Clarity and Usability	Overall the report is well structured and the main points are clearly presented. The conclusions are reasonable and the knowledge groups are identified.	No response needed
196.	TEP Reviewer #2	Clarity and Usability	Clarity and usability are a definite strength of this document.	No response needed
197.	TEP Reviewer #3	Clarity and Usability	The authors have written a clear document, and should be congratulated.	No response needed
198.	TEP Reviewer #4	Clarity and Usability	The report is well structured but not easy to read at times. Too much focus on superficial vein therapies and not enough on obstructive disease. I am afraid the conclusions are not very useful for policy decisions.	We understand that this is a complex report and we have attempted to use tables to highlight our main findings.
199.	TEP Reviewer #5	Clarity and Usability	This is a huge step in the right direction, to improve the care of these patients. This report is very well structured, even though it is long and exhaustive review. The new information presented in the review is very helpful to all stakeholders.	No response needed

	Commentator & Affiliation	Section	Comment	Response
200.	Public Reviewer #5 from the American Academy of Family Physicians	Figures/ Tables	In the Strength of Evidence Tables (8-28, 37, 38), it would be helpful to more clearly highlight the Strength of Evidence (i.e., it was easy to miss as it was a second line in a table that otherwise that was item deep across the rest of the table). A few outcomes (such as in Table 12) are presented as different (in a clinically important way) between groups (Improvement in LE venous hemodynamics/reflux severity (LT), Repeat Intervention (Intermediate Term), Repeat Intervention (Long Term)), yet are SOE Insufficient. Either the SOE should be more clearly highlighted, or positive findings more clearly identified as suspect.	To help highlight the outcomes with SOE which is not insufficient – we now shade those rows in Table 8-28.
201.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Figures/ Tables	Page 3, Table 3: There are several therapies that could be added, including venous angioplasty/stent (which is addressed later in the document), operative venous bypass, valvuloplasty, valve transplantation, SEPS, PAPs (which has been omitted from technology assessment)	We feel that the appropriate therapies are listed later in the document where needed.
202.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Figures/ Tables	Clear and provide structure and background for the report.	No response needed
203.	Public Reviewer #9 Laura Bolton from International Consolidated Guideline Task Force	Figures/ Tables	Please correct Table 26 for the missing data mentioned above under Results section.	We have corrected Table 26.
204.	Public Reviewer #9 Laura Bolton from International Consolidated Guideline Task Force	Figures/ Tables	Please correct Table 38 per above corrections described in the Results section. It appears that the same omissions have not been corrected here. This is difficult to verify as no references are cited in Table 38.	Changes made throughout the results section are reflected in the revised tables

	Commentator & Affiliation	Section	Comment	Response
205.	Public Reviewer #9 Laura Bolton from International Consolidated Guideline Task Force	Figures/ Tables	Please cite all references at appropriate places in all tables.	The specific references are cited in the tables in the “findings” column.
206.	Public Reviewer #9 Laura Bolton from International Consolidated Guideline Task Force	Figures/ Tables	Sustained, adequate compression is complementary to surgery not an appropriate comparison to it. It is an essential adjunct to any treatment to manage or prevent venous ulcers or manage chronic venous insufficiency.	We agree with the reviewer that compression therapy is an important component in the management of patients with chronic venous disease. This has been emphasized in the report. No change is needed..
207.	Public Reviewer #9 Laura Bolton from International Consolidated Guideline Task Force	Figures/ Tables	Please apply all above comments to all appropriate figures.	No response needed to this comment –we have addressed the individual comments/concerns for the appropriate figures.

	Commentator & Affiliation	Section	Comment	Response
208.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	References	The reference list is extensive, but by restricting the inclusion criteria to publications between 2000-2015, important studies are missed predating this time period, specifically in the area of diagnostic testing and compression therapy.	We agree that the majority of the literature supporting the use of surgical approaches to treating venous disease predates the year 2000. However, the primary focus of the present report is comparative effectiveness of invasive and non-invasive techniques to treat lower extremity chronic venous disease (LECVD). Given that endovascular techniques to treat LECVD have only been in widespread use since 2000, by necessity, we restricted our literature search to the year 2000 and beyond. Additionally, while surgical techniques for LECVD may not have changed substantially since the 1990s, the increasing adoption of vascular surgery quality initiatives and clinical guideline documents since 2000 may have substantially impacted both surgical outcomes and patient selection. As a result, we argue that surgical outcomes for LECVD post 2000 may be distinct from those prior to this era and have maintained the 2000 cutoff for this report. Although an expansion of the literature search period to the pre-2000 era would likely yield an increased number of studies assessing the accuracy and precision of non-invasive testing for the diagnosis of chronic venous disease (CVD), the availability, use, and technological sophistication of non-invasive testing for CVD has changed significantly since that time. Widespread use of more recent technological innovations such as power Doppler ultrasound, 64 slice computed tomography scanners, and higher field strength / non-contrast magnetic resonance angiography techniques have occurred since 2000. Additionally, widespread participation in quality certification programs, such as IAC Vascular Testing, IAC CT, and IAC MRI have occurred since 2000 as well. Thus, we believe that expansion of the literature search to include studies prior to 2000 would uncover studies

	Commentator & Affiliation	Section	Comment	Response
225.	Public Reviewer #8 Jim Harmon from BTG International Inc	References	1 Carugo D, Ankrett DN, Zhao X et al. Benefits of polidocanol endovenous microfoam (Varithena?) compared with physician-compounded foams [published online ahead of print June 1, 2015]. Phlebology. 2015. doi: 10.1177/0268355515589063 2 Eckmann DM. Polidocanol for endovenous microfoam sclerosant therapy. Expert Opinion Investigational Drugs. 2009; 18(12): 1919-1927. 3 Varithena? US [Prescribing Information]. London, UK: Provensis Ltd, a BTG International group company; Jun 2014. 4 U.S. Department of Health and Human Services, FDA, CDER, CBER, CDRH. Guidance for Industry ? Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009. 5 Varithena? [prescribing information]. Provensis Ltd, a BTG International group company. December 2013. 6 Kenneth L Todd III, DI Wright and the VANISH-2 Investigator Group. Phlebology. 2014 Oct;29(9):608-18. 7 Gloviczki P, et al. J Vasc Surg. 2011;53(suppl 5):2S-48S. 8 Labropoulos N, Leon L, Kwon S, et al. Study of the (C3 ? C6) venous reflux progression. J Vasc Surg. 2005;41(2):291-295. 2004;40(6):1248-1252. 9 Callam MJ, et al. Chronic ulcer of the leg: clinical history. Brit Med J. 1987;294:1389-1391.	We thank the reviewer for the suggested citations and have considered the studies against our inclusion/exclusion criteria in the final report. Note that for these specific citation #1, 2, 7, 8 were excluded at the abstract level, #3-5 were not peer-reviewed publications, #6 is included in our report, #9 did not meet our date limits.

	Commentator & Affiliation	Section	Comment	Response
226.	Public Reviewer #9 Laura Bolton from International Consolidated Guideline Task Force	References	1. Please add the updated 20121,10 and 20142 Cochrane Reviews to the references. 2. Please add references supporting clinical, patient-centered and economic venous ulcer outcomes cited below3-9, , 3. Please remove the year 2000 as a restriction on this literature search as it omits substantial pertinent literature, exposing the AHRQ TA to a time bias unparalleled by other respected systematic reviews and evidence-based guidelines. References cited in this AHRQ LECVD TA Response are numbered below: 1. O?Meara S, CullumN,Nelson EA,Dumville JC. Compression for venous leg ulcers. Cochrane Database of Systematic Reviews2012, Issue 11. Art. No.: CD000265. DOI: 10.1002/14651858.CD000265.pub3. 2. Nelson EA, Bell-Syer SEM. Compression for preventing recurrence of venous ulcers. Cochrane Database of Systematic Reviews 2014, Issue 9. Art. No.: CD002303. DOI: 10.1002/14651858.CD002303.pub3. 3. McGuckin M, Waterman R, Brooks J, Cherry G, Porten L, Hurley S, Kerstein M. Validation of venous leg ulcer guidelines in the United States and United Kingdom. Amer J Surgery 2002; 183:132-137. 4. Kobza L, Scheurich A. The impact of telemedicine on outcomes of chronic wounds in the home-care setting. Ostomy/Wound Management 2000; 45(10):48-53. 5. McIsaac C. Managing wound care outcomes.Ostomy Wound Manage. 2005 Apr;51(4):54-6, 58, 59 passim. 6. Lal BK. Venous ulcers of the lower extremity: Definition, epidemiology, and economic and social burdens. Semin Vasc Surg. 2015;28(1):3-5. 7. Ma H, O'Donnell TF Jr, Rosen NA, Iafrati MD. The real cost of treating venous ulcers in a contemporary vascular practice. J Vasc Surg Venous Lymphat Disord. 2014;2(4):355-61. 8. Kerstein MD, Gemmen E, vanRijswijk L, Lyder CH, Phillips T, Xakellis G, Golden K, Harrington C. Cost and cost effectiveness of venous and pressure ulcer protocols of care. Disease Management and Health Outcomes 2001;9(11):651-636.	We thank the reviewer for these suggestions and have reviewed them for possible inclusion in the final report. The systematic reviews (#1-3, 10, 11, 12, 13, 14, 15) were identified for the draft report and the component references checked for relevant articles of relevant review. #4, 5, 6, 7, 8, 9, and 16 were identified in our original search and excluded at the abstract level

	Commentator & Affiliation	Section	Comment	Response
227.	Public Reviewer #6 from the Society for Vascular Surgery and American Venous Forum	Appendix	Extensive and informative.	No response needed