Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: *Chronic Venous Ulcers: A Comparative Effectiveness Review of Treatment Modalities*

Draft review available for public comment from September 6, 2012 to October 4, 2012.

Research Review Citation: Zenilman J, Valle MF, Malas MB, Maruthur N, Qazi U, Suh Y, Wilson LM, Haberl EB, Bass EB, Lazarus G. Chronic Venous Ulcers: A Comparative Effectiveness Review of Treatment Modalities. Comparative Effectiveness Review No. 127. (Prepared by Johns Hopkins Evidence-based Practice Center under Contract No. 290-2007-10061-I.) AHRQ Publication No. 13(14)-EHC121-EF. Rockville, MD: Agency for Healthcare Research and Quality. December 2013. Erratum January 2014. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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Comments on draft reviews and the authors' responses to the comments are posted for public viewing on the EHC Program 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
TEP #1	General	Quality of the report: good	Thank you for reviewing our report!
TEP #1	General	The report is clinically meaningful in that it lays bare the lack of evidence used to treat venous ulcers. The implications of which can be interpreted as wasted dollars.	Thank you for your feedback! We felt that it was important to describe the current state of the evidence for the different treatment strategies for chronic venous ulcers. Part of the purpose of this report was to identify areas of weakest evidence and highlight these as potential research gaps.
TEP #1	General	The target population is identified on page iii directly and you may want to consider expanding the sections on Implications for Clinical Practice, Research Gaps and conclusions to include mention of the targets.	Thank you for reviewing the report. As you mention, the target audience includes health care decisionmakers—which is broadly defined to include many different stakeholders. There is actually an accompanying document (a Future Research Needs Document), which presents the gaps that have been prioritized as important by a panel of stakeholders, which is being prepared as part of this project and which will be more specific.
TEP #1	Introduction	Adequate	Thank you for reviewing our report!
TEP #1	Methods	The inclusion/exclusion criteria are justifiable and the fact that only 66 articles out of 10,000 fit inclusion criteria is an indictment of our uncoordinated research efforts.	Thank you for your feedback.
TEP #1	Methods	Yes (search strategies explicitly stated and logical)	Thank you for your feedback.
TEP #1	Methods	Yes (definitions or diagnostic criteria for outcome measures are appropriate)	Thank you for your feedback.
TEP #1	Methods	Yes (statistical methods used are appropriate)	Thank you for your feedback.
TEP #1	Results	It is quite readable and busy clinicians will appreciate its brevity	Thank you for reviewing our report!

Commentator & Affiliation	Section	Comment	Response
TEP #1	Results	The key messages, by the nature of the studies reviewed, are not explicit or very applicable. They are correct but not helpful in either the patient level or the systems level decision making.	We agree that the key messages are limited by the nature of the studies reviewed. We have tried to summarize the results of the studies correctly (which the reviewer acknowledges) while commenting on the limitations of the evidence. Unfortunately, the weakness of the evidence limits the usefulness for decision making at either the patient level or system level.
TEP #1	Results	Yes (characteristics of the studies clearly described)	Thank you for reviewing our report!
TEP #1	Results	Yes (figures, tables, appendices adequate and descriptive)	Thank you for reviewing our report!
TEP #1	Results	No (investigators did not overlook any studies that ought to have been included or included those that ought not to have been)	Thank you for reviewing our report!
TEP #1	Discussion	Yes (are the limitations of the review/studies described adequately)	Thank you for reviewing our report!
TEP #1	Discussion	Not to my knowledge (in the discussion, did the investigators omit any important literature)	Thank you for reviewing our report!
TEP #1	Discussion	The findings are clearly stated but the implications are not articulated as clearly as some will want. That said, I am not sure that they can be stated any better considering the paucity of high and moderate quality evidence.	We agree. We have been limited by the extremely poor quality of the evidence.

Commentator & Affiliation	Section	Comment	Response
TEP #1	Discussion-Research gaps	The research gap portion is much needed and you may want to consider referencing the 1999 American Diabetes Association Consensus Development Conference on Diabetic Foot Wound Care 7-9 April 1999 Boston, Massachusetts Diabetes Care, Volume 22, Number 8, August 1999 as an example of this kind of activity.	We agree. We decided to cite the Center for Medical Technology Policy Methodological Recommendations for Comparative Effectiveness Research on the Treatment of Chronic Wounds.
TEP #1	Executive Summary	Yes, the executive summary is complete and makes the salient points succinctly.	Thank you for reviewing our report!

Commentator & Affiliation	Section	Comment	Response
TEP #1	Discussion	I think that this portion might be expanded to include some systems based suggestions for how to make decisions on the use of products that may have value so that clinicians are allowed to practice the art of medicine. Committees of clinicians and administrators could be suggested to develop local decision trees/algorithms that would drive product use while recognizing the need for continually following the literature for emerging evidence on efficacy and effectiveness. With the focus on cost effective health care and the high cost of many of these advanced wound care products and surgeries, systems of care need to address the needs to provide patient centered care that is cost efficient, timely and clinically effective while ensuring that new and promising products and procedures are considered carefully and systematically.	Our objective was to develop evidence-based conclusions based on the available data. We have now included the following sentence on page ES-22: "We need high quality data on the comparative effectiveness and costs of the treatment options to develop efficient algorithms for guiding therapy to evaluate new therapies, and to better understand which therapeutic interventions have value to ensure appropriate reimbursement in an increasingly constrained health care environment."
Peer Reviewer#1	General- Overall quality	Fair	Thank you for reviewing our report!

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer#1	General	The aim of the report to review the effectiveness of advanced wound dressings, systemic antibiotics and surgery for venous ulceration is an important and clinically meaningful area. However there were some areas that the authors need to clarify and provide additional details and justification:	Thank you for your feedback.
Peer Reviewer#1	General	There is an explicit statement regarding assessing the included studies in regard to the target population of people with venous ulcers but the authors do not provide details or descriptions of this target population. The assumption is that it is the elderly but there is also another group who may get venous ulcers—those who have a history of illicit drug use. The authors make no mention of this anywhere in the report even if it is to acknowledge that they are excluding studies who have this population.	In Appendix D, we provided details about the eligibility criteria of the studies (Table 1) and study population characteristics (Table 2), which generally did not say anything about including or excluding patients with a history of illicit drug use. In the "Search Results" section of the Executive Summary, we have added a statement that "in most studies, the mean or median age was greater than 60 years." In the section on "Study Population Characteristics" for Key Question 1, we report that "the median age of patients was between 60 and 70 year years..."
Peer Reviewer#1	General	There is no mention of cost as an outcome within the authors analytic framework or any reason stated for not including this as an outcome.	We added a statement on page ES-5 and in Table 4 of the body of the evidence report to indicate that "we did not include costs as an outcome in this systematic review, but rather we focused on patient-centered outcomes, consistent with the aims of the Effective Health Care Program."
Peer Reviewer#1	General	The authors also exclude topical antibiotics but do not state their justification for this.	Topical antibiotics were considered under dressings.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer#1	Introduction	The authors seem to downplay the level of evidence regarding compression therapy for venous ulcers. There have been a number of reviews including O'Meara et al (1997) that conclude that there is robust evidence that compression increases ulcer healing rates compared with no compression. It is also clear that multi-component systems appear more effective than those composed mainly of inelastic constituents such as the Unna's Boot.	We stated emphatically that the standard of care is compression with at least 2 layers and cite a Cochrane review establishing this. We did not have direct recordings of level of compression which would have been a great addition. In Table 4 of the evidence report, we indicated that the comparisons of interest included studies that compared interventions with conservative care where conservative care included "at least moderate compression..." Furthermore, we were struck that the term Unna boot was used generically and appeared to be applied to multiple modalities.
Peer Reviewer#1	Introduction	The citation of Margolis as a justification of using wound healing as a "surrogate" for complete healing does not seem appropriate as Margolis is referring specifically to this as a predictor of healing for compression therapy and identified that ulcers over 10cm2 and 12 mth duration are lease likely to heal. The authors also do not acknowledge the challenges of wound measurement within the clinical environment.	We agree that wound measurement is difficult. That is why under Research Gaps we highlighted the need for developing a consensus discussion to develop uniform terms and measurements. Wound healing rates as described by Dr. Margolis have been found useful for diabetes as well as venous disease. We wanted to confirm the utility of this intermediate outcome.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer#1	Introduction	In the section on advanced wound dressings the authors need to put more emphasis and acknowledgment regarding the lack of evidence for many of these dressings and explicitly state that there is a particular challenge in showing these dressings are cost-effective.	We agree with this comment. We tried to use a bit of tact in describing our disappointment with the data. We added a statement on page ES-5 and in Table 4 of the body of the evidence report to indicate that "we did not include costs as an outcome in this systematic review, but rather we focused on patient-centered outcomes, consistent with the aims of the Effective Health Care Program.
Peer Reviewer#1	Introduction	When the authors are describing the use of antibiotics they need to explain and distinguish between colonization and infection of venous ulcers.	We added some text to the Antibiotics section of the Introduction chapter describing the difference between colonization and infection.
Peer Reviewer#1	Introduction	The description needs to be clarified regarding the clinical indications and likely numbers of venous ulcer patients who will be having long term antibiotics and how many would be having them administered through a central catheter. They should also explain and comment on the likely cost and practical implications of this.	We added a few sentences to the Antibiotics section of the Introduction chapter to provide more clinical context for the use of antibiotics in chronic venous ulcers.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer#1	Methods	There seems to be a lack of detail and justification in relation to some areas of the methodology: The literature search seemed to be a little restricted in terms of the number and range of databases searched. The authors need to describe why they limited the searches to the specific databases.	We searched four electronic databases, plus conducted a variety of hand searches. We do not feel that this is a "restricted" search. As indicated in the Search Strategy section of the Methods chapter, we also searched for studies in clinicaltrials.gov and by requesting information about relevant studies from manufacturers.
Peer Reviewer#1	Methods	There is no description of whether or not the authors included grey literature. There needs to be a clear statement in regard to why this body was excluded. It is especially important in regard to dressings where there are a large number of papers supported and presented at conferences through the auspices of manufactures. If grey literature was included then the authors need to provide details of database, conference proceeding searched etc.	As indicated in the response to the previous comment, we searched for studies in clinicaltrials.gov and requested information about studies from manufacturers. We did not include conference abstracts in the review. We added this statement to Table 4.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer#1	Methods	The decision to include non-RCTs within the evaluation of surgical treatments is not clearly justified. On what basis was the decision made that the authors would find few comparative studies within this area? There also does not seem to be a clear basis of having 30 participants as the cut-off point for non-RCTs included within the surgical assessment.	We would have liked to have included only comparative studies for the surgical treatments. However, we knew prior to starting the review that the literature on surgical treatments was going to be very limited. We acknowledge that the noncomparative studies are of poor quality, and have downgraded the conclusions drawn from these studies. Similar reviews of surgical literature (see Tenbrook JA, Iafrati MD, O'Donnell TF et al. Systematic review of outcomes after surgical management of venous disease incorporating subfascial endoscopic perforator surgery. Journal of Vascular Surgery. 2004;39(3):583-9.) also include noncomparative studies. The cut-off of 30 participants was chosen to limit studies with very minimal power.
Peer Reviewer#1	Methods	In regard to the decisions about undertaking meta-analysis. The authors do not describe their tests of heterogeneity to justify not doing a meta-analysis. Was this based on clinical or statistical measures of heterogeneity?	We added to the Data Analysis and Synthesis section of the Methods chapter, "We qualitatively assessed the homogeneity of the studies with respect to key variables (population characteristics, study duration, and comparisons)."
Peer Reviewer#1	Methods	Within the description of the data synthesis methods the authors need to justify why they did they not undertake sensitivity analysis regarding subgroups.	We added to the Data Analysis and Synthesis section of the Methods chapter that we lacked sufficient data to conduct these types of analyses.
Peer Reviewer#1	Methods	The inclusion of one patient within the key informants in regard to the methods and scope of the study seems a little tokenistic. The authors need to specify more details about the basis for their recruitment and experience of venous ulceration.	The patient perspective is important to the EPC program, and we tried very hard to recruit patients to serve as Key Informants. A wound care organization recommended this particular patient to us because the patient has had chronic venous ulcers for several years and was very knowledgeable about the condition and treatments. Most importantly, we interviewed the patient in an environment where one could feel comfortable expressing one's thoughts.

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Peer Reviewer#1	Methods	The exclusion of topical and hyperbaric 02 does not acknowledge that although not FDA approved for venous ulcers it is used on the basis of it being “investigational” and maybe in widespread use within the US	We have removed that sentence from Table 4.
Peer Reviewer#1	Results	In detailing the list of studies that were excluded from the review the group of “Other” seems very large (n=531). There needs to be more detail and specifics about this group.	We have reviewed the studies excluded for “other” reasons, and reclassified these when possible.
Peer Reviewer#1	Results	A more clear exclusion criteria than “no patients with chronic venous ulcers” would be that there were ulcers of other aetiology with no reporting of venous separately.	We have changed this to “No separate analysis of chronic venous ulcers.”
Peer Reviewer#1	Results	There seemed to be an inconsistency in terms of the criteria applied for inclusion and exclusion. For example Jull et al (honey dressings) was excluded as “no patients with chronic venous ulcers” but basis this may not be the case. Jull did include mixed and venous (ABPI 07-1) ulcers but so did other studies that were not excluded from the review e.g. Falanga et al.	The reviewer mentions two different papers: (1) Jull A, Walker N, Parag V, et al. Randomized clinical trial of honey-impregnated dressings for venous leg ulcers. British Journal of Surgery. 2008;95:175-82 and (2) Falanga V, Sabolinski M. A bilayerd living skin construct (APLIGRAF®) accelerates complete closure of hard-to-heal venous ulcers. Wound Repair and Regeneration. 1999;7:201-7. The Jull study included patients who had venous ulcers for only 2 weeks. In our review, we considered only studies of patients with chronic venous ulcers, meaning patients must have had an active ulcer for at least 6 weeks. Thus, the Jull study was excluded because it did not meet our definition of chronic venous ulcers. The Falanga article met the inclusion criteria for patients with chronic venous ulcers.

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Peer Reviewer#1	Results	In describing the results of studies examining cellular skin equivalent dressings the authors need to comment on the likely costs and sustainability of the healing reported within the studies found.	We added a statement on page ES-5 and in Table 4 of the body of the evidence report to indicate that "we did not include costs as an outcome in this systematic review, but rather we focused on patient-centered outcomes, consistent with the aims of the Effective Health Care Program." However, we mentioned the expense issue in the Implications for Clinical Practice and Policy of our discussion section.
Peer Reviewer#1	Results	The authors seemed overly positive and uncritical in reporting about cadexomer iodine and human skin equivalent especially in regard to them reporting that there was "moderate" evidence.	Our evidence grading evaluated risk of bias, consistency, directness, and precision of the body of evidence, as described in the Methods chapter. We consistently followed this protocol when grading the evidence for all comparisons.
Peer Reviewer#1	Results	The authors also need to acknowledge the funding of the manufacturing companies within the trials included in the review. It would also have been informative to know which of the included studies had industry sponsorship.	We totally agree! We added a statement about industry support to the Search Results and Limitations of the Evidence Base in the Discussion section of the report.
Peer Reviewer#1	Results	Within the KQ3 the authors need to emphasize that the level of evidence found was low. In addition the key points in KQ3a need to be changed to acknowledge this lack of evidence. The authors state that sclerotherapy may improve healing but then state that there was insufficient evidence this appears to be misleading.	In Key Points we have clearly mentioned the strength of evidence for each intervention type in parentheses. In the case of sclerotherapy, we found only one randomized clinical trial of 40 patients and two cohorts of 188 patients. These studies had high risk of bias and were inconsistent and imprecise making the effect unclear with insufficient strength of evidence.

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Peer Reviewer#1	Results	The authors seem to be stretching the definition of the impacts on quality of life in terms of including "ulcer specific QoL measure" the ones referred to by the authors and reported were often subjective and symptom related rather than validated QoL instruments.	Thank you for your feedback. The Charing Cross Venous Ulcer Questionnaire was validated in "Measuring the quality of life in patients with venous ulcers" published in Journal of Vascular Surgery (2000) by Smith el al. We recognize that the use of inconsistent and unvalidated ulcer-specific quality of life measures is a weakness of the studies reviewed and a limitation in the available literature. Thus we acknowledged our inability to draw conclusions about the effects of advanced wound dressings on quality of life as a key point.
Peer Reviewer#1	Results	In describing the results of pain as an outcome for the included trials it would be informative to have known how this was measured within the trials.	Pain was not measured in a consistent method across all studies. An explanation of how pain was evaluated is included in each study description.
Peer Reviewer#1	Results	There is a lack of consistency in terms of the reporting of 'p' values. Some are reported whilst some are not reported or omitted e.g. p58 CHIVA median time to healing.	This was a matter of inadequate reporting. Frequently, the studies did not report enough information to determine or calculate a p-value.
Peer Reviewer#1	Results	In Appendix D need to check < or > not omitted	We have reviewed the appendix for completeness, adding in the signs where omitted.
Peer Reviewer#1	Results	In the table the authors report the exclusion criteria of the studies but not their inclusion criteria.	We combined the exclusion and inclusion criteria into one column. The inclusion criterion can be inferred by its opposite (e.g., a study that includes only patients with chronic venous ulcers excludes patients without chronic venous ulcers).
Peer Reviewer#1	Results	The authors need to define what "worldwide" means	We provided more specifics about study location.
Peer Reviewer#1	Results	In table 5a they report loss to follow up as a criteria but the authors should also include whether the study undertook ITT analysis	We used the Downs and Black quality assessment tool to assess study quality. This tool does not have a specific question about intention-to-treat analyses. However, we recorded if a study used appropriate statistical tests, which would capture if a randomized controlled trial used an intention-to-treat analysis.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer#1	Results	In table 5b some of the rows regarding support of the studies are blank why is this?	We have added in the data regarding support.
Peer Reviewer#1	Discussion/conclusion	The authors need to specify and cite their justification for the base population with which they are comparing the included citations.	In the Introduction, we presented the rationale for focusing our review on the population of patients that have chronic venous leg ulcers. We decided not to repeat that justification in the Discussion section, although we have tried to be consistent about indicating that our conclusions refer to the treatment of chronic venous leg ulcers.
Peer Reviewer#1	Discussion/conclusion	The authors state that there were difficulties related to blinding for dressings but they also need to comment on how likely this may have influenced the results of the included studies.	We added the following to the Conclusions section of the Discussion chapter: Most studies were not blinded, and the results are therefore subject to reporting and ascertainment bias.
Peer Reviewer#1	Discussion/conclusion	In the discussion the implications for policy of the evidence found for surgical interventions, human skin equivalent seem overly positive based on the level and lack of evidence that the authors found.	These are essentially the only areas where there is good clinical trial data.
Peer Reviewer#1	Discussion/conclusion	The lack of discussion in regard to cost or cost-effectiveness of the interventions seems to be a big omission and the authors also do not highlight these as potential gaps in the research evidence.	We added a statement on page ES-5 and in Table 4 of the body of the evidence report to indicate that “we did not include costs as an outcome in this systematic review, but rather we focused on patient-centered outcomes, consistent with the aims of the Effective Health Care Program.”
Peer Reviewer#1	Discussion/conclusion	In KQ1 the authors state that cadexomer iodine has an advantage in terms of wound healing but this was based on the authors finding one study which had flaws in its design.	Several studies evaluated antimicrobial dressings. We edited the conclusion statement in Table D and the Key Points for KQ1 so that it discusses antimicrobial dressings in general, rather than just dressings with cadexomer iodine.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer#1	Discussion/conclusion	In the discussion on implications the authors need to acknowledge the low evidence for all of the treatments.	At the end of the Executive Summary, we have emphasized the limitations of the evidence, and have stated "that for the majority of commonly used interventions there are little to no efficacy data…"
Peer Reviewer#1	General: Clarity/usability	Overall the report is clear and has a clear and logical structure and organization. The key points are clearly expressed but the authors do need to more clearly highlight the lack of evidence. The conclusions of the report would have more easily informed policy and practice decisions if the authors had included cost as an outcome.	We added a statement on page ES-5 and in Table 4 of the body of the evidence report to indicate that "we did not include costs as an outcome in this systematic review, but rather we focused on patient-centered outcomes, consistent with the aims of the Effective Health Care Program."
TEP #2	General	Quality of the report: superior	Thank you for reviewing our report!
TEP #2	General	The report is clinically meaningful in that with the possible exception of sprayed on living cells on applied tissues simple compression is as good as a wide variety of more expensive therapies.	Thank you for reviewing our report!
TEP #2	Introduction	The striking aspect of this extensive literature search of paucity of well designed and controlled studies. Where these do exist more invasive and expensive approaches are not proven to be clearly more effective	We agree.
TEP #2	Methods	The inclusion and exclusion criteria are explicitly defined and reasonable. Statistical methods are appropriate to the data presented.	Thank you for reviewing our report!

Commentator & Affiliation	Section	Comment	Response
TEP #2	Results	The details presented in 113 pages are exemplary with data reiterated in tables and with individual articles summarized in explicit detail. For the poor quality of the literature the reviewers have been very fair.	Thank you for reviewing our report!
TEP #2	Discussion/conclusion	Most of the conclusions are valid i.e. essentially that one cannot firmly conclude that there are advantages of more invasive or expensive approaches over simpler approaches. To do more large scale studies without rigorously exploring a new promising approach seems a waste of resources and can field little clinical usefulness.	Or--without defining standards. We think this reviewer is agreeing with us, just saying it a bit differently
TEP #2	General- Clarity/usability	The report is exemplary in weeding through large volumes of indecisive and poorly controlled studies with the few exceptions noted by the reviewers. The conclusions in my view should focus on the most promising hypothesis which target the few methods that seemed promising from this extensive review.	We tried to call attention to the few interventions that have the strongest evidence, while emphasizing the evidence gaps that call for more research.
TEP #3	General	Quality of report: Good	Thank you for reviewing our report!
TEP #3	General	Very clinically relevant due to increases of aged, obese, diabetic and others with chronic predisposing conditions.	Thank you for reviewing our report!

Commentator & Affiliation	Section	Comment	Response
TEP #3	General	Target population not clearly stated: explicit inclusion of primary care providers, geriatricians, general and vascular surgeons, dermatologists, (plastic surgeons?), visiting nurses, and nursing home nurses; all of whom routinely are involved in care decisions for this condition	In Table 4 of the evidence report, we provided detailed information about the population of interest.
TEP #3	General	Key questions are appropriate and clear.	Thank you for reviewing our report!
TEP #3	Introduction	ES-1 line 24: may be overstatement; would remove "all types of" (wound dressings) as number is limitless and you excluded some for lack of studies.	We have changed the text in the Antibiotics section of the Introduction to say, "Antibiotic use is widely prevalent in the management of venous ulcers."
TEP #3	Introduction	ES-1 line 28: "carefully" is unnecessary. Comma after dressings should be dropped or "that" changed to "which".	These edits have been made to the Executive Summary, under the Scope and Key Question section.
TEP #3	Introduction	ES-3 last line of adverse effects of surgery: would insert "of" after "recurrence".	We have made this change to the Analytic Frameworks in both the Executive Summary and the Introduction.
TEP #3	General	(As an aside, I often wish that the interventions were in bold in the summary paragraph to quickly take me to what I have interest in....)	We have bolded the interventions in the Results section of the Executive Summary.

Commentator & Affiliation	Section	Comment	Response
TEP #3	Methods	Very detailed and justified inclusion and exclusion criteria. Search strategies clear. Definitions and criteria appropriate as reasonably possible, despite the lack of clear definitions as written in the discussion section.	Thank you for reviewing our report!
TEP #3	Results	Detail to sections appropriate and graphics very helpful, as well as tables summarizing the results of relevant studies to each intervention	Thank you for reviewing our report!
TEP #3	Results	As a clinician, I do not think that the inclusion of "Mortality" table 9, p 31 from the limited number of studies added anything useful (as we are aware of unlikelihood of the intervention directly causing the death. The single explanatory paragraph without table would be sufficient.	We have removed this table.
TEP #3	Discussion	Sounds like no reasonable direction can be given for research until consensus can be reached on definitions (I would like to see a definition of "standard" compression therapy, including frequency of dressing changes).	This has been addressed at the end of the Executive Summary in terms of the need to establish consensus definitions, and is also reviewed in the Research Gaps section.

Commentator & Affiliation	Section	Comment	Response
TEP #3	Discussion	Another unanswered question for the practitioners “in the trenches”: Is care at a “wound clinic” (proliferating across the country) superior to that at other locations of care? Is the level of experience with care of the condition more important than the intervention?	While we acknowledge that this is an important question for practitioners, this was outside the scope of our review. We focused on clinical interventions for chronic venous ulcers, and did not systematically review the evidence for the delivery and organization of care.
TEP #3	General-Clarity/usability	From a practitioner standpoint, the conclusions were not stated in such a way to provide guidance towards continuance in use of the “non-inferior” compression for venous ulcers, while awaiting the further studies showing definitive evidence of superiority of other interventions and delineation of specific populations that would benefit from those alternatives.	Although we agree in concept, the evidence was insufficient to provide clearer guidance about specific populations that would benefit from interventions other than just the current standard of compression therapy.
Peer Reviewer #2	General	Quality of the Report: Superior	Thank you for reviewing our report!

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	I think the report is meaningful because of what it reviews, but there are gaps in the information. The issue of patient compliance is not addressed. Studies show that less than 50% of venous ulcer patients will wear their compression devices as prescribed by the provider. How can the failure of therapy be blamed on the treatment, bandage, or device if the patient refuses to use it?	We agree. This is a methodological issue that needs to be addressed in a consensus conference. We sought to collect data on adherence with compression device use, but it was rarely reported. We added a statement about adherence to the Study Population Characteristics section for KQ1 results.
Peer Reviewer #2	General	Under Scope and Key Questions, you mention that compression therapy of at least 20 mm Hg pressure was accepted for the review. That is not accepted as adequate compression for optimal therapy. The standard is 40 mm Hg pressure. It is the opinion of most of us in the field that one of the main problems with compression therapy is being able to obtain "adequate" compression. A recent review article of experienced nurses applying compression bandages showed that the subbandage pressure in >50% of patients was outside of the "effective compression therapy" range. Additional training with feedback was successful in markedly improving the	We agree that this is an important issue. However, the previous Cochrane review established a minimum of 20 mm Hg of pressure. We added the following sentence to page ES-5 where we explained that compression therapy was the comparator of interest: "Although some experts recommend a higher pressure for compression therapy, we did not want to exclude too many studies and therefore used 20 mm Hg as the minimum pressure based on the results of a previous systematic review conducted by the Cochrane Collaboration." We also added the following paragraph to the limitations section of the Discussion chapter: In our review, we included studies only if the participants used at least a moderate level of compression (e.g., at least 20 mm Hg of pressure), excluding studies that either did not report the level of compression used or did not use an adequate level of compression. Although some experts recommend a higher pressure for compression therapy (at least 40 mm Hg), we did not want to exclude too many studies and therefore used 20 mm Hg as the minimum pressure based on the results of a previous systematic review conducted by the Cochrane Collaboration.[3] However, we may have biased our results in favor of the advanced wound dressings and surgical

Commentator & Affiliation	Section	Comment	Response
		situation, but the device used to measure the subbandage pressure and do the training is too expensive for most centers or hospitals to afford. Thus we continue treating patients with suboptimal compression therapy and wonder why the outcomes are not what we expect. This area should be addressed in the manuscript. We, also, need support by someone (government, companies, grants, ?) to help us establish the training programs and improve this issue.	procedures by including studies that allowed a lower level of compression therapy (i.e., between 20 and 40 mm Hg).

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	Many of the treatments reviewed are truly not designed to "heal" venous ulcers. They are designed to modify or improve the wound environment to give the wound a chance to heal. For that reason, many therapies are to be used for a specified period of time to achieve something specific then stopped or changed to another type of therapy to do something else for the wound microenvironment. To say some of these products are ineffective is to admit that we don't know the real role these dressings play in managing the wound and optimizing the wound microenvironment to stimulate healing. This should be considered before we condemn them as ineffective.	We went to great length to make the point that we do not know the effectiveness of these interventions. We carefully stated that there is no proof that they work but that does not mean they are ineffective. In a constrained environment, we were very concerned this lack of proof may penalize effective interventions.
Peer Reviewer #2	Introduction	Seems fine	Thank you for reviewing our report!

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Methods	The inclusion and exclusion criteria seem overly strict since the majority of the work done around the world was not considered. About 70 articles out of 10,000 is not a good representation of what is being done or is considered successful by the majority of the practitioners. Randomized, controlled trials are rarely done in wound care for the reasons you state in the manuscript. A patient and treatment registry would probably be more informative.	Our inclusion and exclusion criteria were developed in collaboration with the Technical Expert Panel and AHRQ. We aimed to include the best possible evidence to address our Key Questions. Not only did we include randomized controlled trials, but we also included observational studies that evaluated wound dressings and antibiotics and noncomparative studies that evaluated surgical dressings. We even included studies published in any language so we could capture the work being conducted around the world. We added the suggestion of a patient registry to the Research Gaps section.
Peer Reviewer #2	Results	Most headings imply some treatment compared to "compression therapy alone." Most of the therapies you reviewed are used "in addition to" compression therapy. I think this point needs to be emphasized in all sections if indeed that is what happened. No therapy (bandages or otherwise) will be successful without additional compression therapy. This is true of the operative therapies as well.	We agree and have added in "Plus Compression" to the titles.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Results	On page 21, Condition of the Wound Bed you say there was no information about this. There are numerous articles referencing the elevated protease and inflammatory cytokine levels in the venous ulcer wound bed and the response to treatment with dressings and topical medications. This should be worth including in this review.	Thank you for this suggestion. Unfortunately, none of these studies met our inclusion criteria for this review.
Peer Reviewer #2	Results	On page 40, table 15, on Definitions of Wound Infection Reported in Included Studies, the definitions of infection in chronic wounds is not compatible with accepted standards today--pain, erythema, edema, heat, and purulence are signs of infection in acute wounds but not chronic wounds. I can supply the references on the accepted definitions of wound infection is chronic wounds if not available to you. It makes a lot of difference when determining infection rates.	We used the definitions of infection that were reported in the articles.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Results	On page 44, in Venous or Arterial Impairment section you say there are no studies available. There is a recent article in Jour Vasc Surgery addressing this issue. There are several articles in the literature from the past few years examining the arterial component of venous ulcer disease and the effect of compression therapy on the wound bed. I really think these should be reviewed and included since the treatment of venous ulcers in the patient with vascular insufficiency is critical.	Thank you for this suggestion. Unfortunately, this study did not meet our inclusion criteria.
Peer Reviewer #2	Results	There are several recent articles addressing the issue of quality of life and venous ulcers. These are important as we look at patient centered therapeutic evaluations.	Thank you for your feedback. We have updated our literature review and have added two new articles, but we did not find new quality of life data to integrate into our report.
Peer Reviewer #2	Discussion/conclusion	The future research needs are outlined. It will not be easy to arrange the "development and implementation of a clinical trial network that would have a broad recruiting base, specialized centers that adhere to case definitions, and a commitment to long-term followup." It is a great idea, but with the lack of financial support for this type of project, it is unlikely to be successful or sustainable.	We agree that this will not be easy and will require resources.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General-Clarity/usability	The report seems organized reasonably well. I would be reluctant to suggest the overall findings are good enough to support policy decisions. There are some practice decisions that can be made from the collected data, but it is not as simple as the review would imply. If it were, you would have not reviewed over 10,000 articles and only used about 70 of them. See my other comments above.	We recognize that the weaknesses of the evidence limit the usefulness to clinical decision makers, but we believe that the report still has important implications for policy makers about the needs for more research. We have tried to emphasize the needs for more research.
TEP #4	General	Quality of the Report: Good	Thank you for reviewing our report!
TEP #4	General	Yes, report should be helpful for clinicians	Thank you for reviewing our report!
TEP #4	Introduction	well done	Thank you for reviewing our report!
TEP #4	Methods	appropriate	Thank you for reviewing our report!
TEP #4	Results	appropriate	Thank you for reviewing our report!
TEP #4	Discussion/conclusion	appropriate	Thank you for reviewing our report!
TEP #4	General-Clarity/usability	well organized	Thank you for reviewing our report!
Public: Advamed	General	The current structure of the CER document does not fully reflect contemporary treatment practices involving the use of compression therapy. Consequently, AdvaMed is concerned that the method of comparison proposed in the draft report will not provide any conclusive evidence regarding the effectiveness of any of the modalities being evaluated.	We agree with the concept that compression is the gold standard and we set up the review to ensure that both active and control groups had at least moderate compression.

Commentator & Affiliation	Section	Comment	Response
Public: Advamed	General	Moreover, AdvaMed is concerned that the objective guiding the report may not be adequate to fully evaluate the range of modalities available to treat chronic venous ulcers. The objective identified in the Structured Abstract section of the paper (see page vi) states that AHRQ will conduct a systematic review of whether "advanced wound dressings, systemic antibiotics, or venous surgery" enhance the healing of venous ulcers *over* the use of adequate venous compression. However, for many years the clinician, provider, and manufacturer communities have recognized the application of some type of compression therapy, either prior to or in conjunction with the other treatments identified in the report, in treating venous ulcers. For example, an article in Wound Repair and Regeneration stated that, "Wound dressings, including advanced dressings, should always be administered to chronic venous leg ulcers as part of a protocol of care that includes effective compression therapy." 1	We agree with the concept that compression is the gold standard and we set up the review to ensure that both active and control groups had at least moderate compression.
Public: Advamed	Data and results	AdvaMed is concerned with the draft reports reliance on HCPCS code descriptors as	Dressings were classified according to function and specific dressing characteristics. The Healthcare Common Procedures System codes were used only as a reference

Commentator & Affiliation	Section	Comment	Response
		the basis for classifying and identifying the characteristics associated with the use of the various technologies that were evaluated. HCPCS codes are broad groupings of products with similar ingredients or components, but not necessarily products with similar function or uses. Choice of secondary ingredients/components, material quality and construction, manufacturing methods, and clinical performance are among the factors that contribute to differences in performance and clinical indications of products within each HCPCS category. While HCPCS categories provide a framework for payment, they are not reflective of the use or performance of the various devices that may be grouped together nor are they intended for use in scientific research. Lia Van Rijswijk wrote about this problem in 2006 stating that, "Wound dressings are classified according to their ingredients, but in many cases dressings within the same group have different recommended uses and even ingredients. Should future classifications be based on	and not to categorize dressings.

Commentator & Affiliation	Section	Comment	Response
		dressing functions?”2 It is not appropriate to use reimbursement categories to describe results that measure efficacy.	
Public: Advamed	Data and results	AdvaMed also believes that the methods and published literature selected by AHRQ for inclusion in their review may have resulted in the omission of a large body of evidence related to the use of compression therapy in the treatment of chronic venous ulcers. Because the use of some type of compression therapy in the treatment of venous ulcers has been the standard for many years, it is difficult to find studies that do not include use of compression. Additionally, it is not always clear based on an analysis of the results whether the compression products used in a study were standardized.	We totally agree with the concept that compression is the gold standard and we set up the review to ensure that both active and control groups had at least moderate compression.

Commentator & Affiliation	Section	Comment	Response
Public: Advamed	Data and results	Finally, AdvaMed has concerns regarding the draft report's reliance on Randomized Controlled Trial (RCT) data in reaching its conclusion. The low number of RCTs related to the use of compression therapy in chronic venous ulcer management does not adequately represent the lives of actual patients living with this condition. Compliance with treatment recommendations is a major problem within this patient population. Additionally, the rates of compliance associated with patients in an RCT setting can skew the effectiveness results for some of these therapies. To address this concern, AdvaMed recommends that the draft report also consider data from observational studies.	In Table 4, we explicitly stated that we included both randomized controlled trials and observational studies with a comparison group for all interventions and that we included observational studies without a comparison group for surgical interventions. Compliance with compression therapy was rarely reported in the studies.
Public: Advamed	General	We are pleased to provide AHRQ with our input on the draft comparative effectiveness review and encourage the organization to continue to seek stakeholder input and feedback, as similar documents are drafted in the future.	Thank you for reviewing our report!

Commentator & Affiliation	Section	Comment	Response
Public: Peter Steve/Sunny wipes	Executive Summary	New topical skin antisepses formulations now exist in Australia. The skin rejects synthetics and toxins can add to the problems not help. The technology has been designed as a natural alternative to hazardous harmful chemical formulations and is very effective against bacteria and fungal skin diseases. www.sunnywipes.com.au	Thank you for this information. Unfortunately, it is outside the scope of our review because it is not an intervention for treating chronic venous ulcers. While we acknowledge other interventions that could be potentially used for chronic venous ulcer healing, we constrained our review to those that are included in this systematic review. As with most systematic reviews, we balanced the comprehensive and depth of a systematic review, considerations of stakeholder input, and the feasibility of completing a timely systematic review. As a part of usual processes in development of an AHRQ systematic review, we engage relevant stakeholders to provide input on the most relevant key questions, interventions, comparators, and outcomes, as well as details of the systematic review protocol. Input from stakeholders identified the current set of interventions as those that presented greater uncertainty in clinical care.
Public: Peter Steve/Sunny wipes	Introduction	Alcohol is recognised by the World Health Organisation as being an effective killing agent against gram positive and gram negative harmful bacteria and other microbes. SunnyWipes uses a natural based alcohol and adds eucalyptus oil to render the formulation unpalatable (meaning it cannot be ingested by humans and therefore is safe for use in the community and around children). This is unlike the majority of denatured alcohol based products on the market which contain toxic added chemicals and petro based alcohols (commonly isopropanol) to render the formulation toxic if consumed.	Thank you for this information. Unfortunately, it is outside the scope of our review because it is not an intervention for treating chronic venous ulcers.

Commentator & Affiliation	Section	Comment	Response
		In addition, they mask the smell of the petro chemicals or toxic chemicals, by using fragrances or odour substitutes. Most of these agents are not good for your skin or health as they are synthetic chemicals and are recognised as contact irritants. Eucalyptus oil has been used for centuries as a natural antimicrobial agent. Therefore the SunnyWipes products provide 2 powerful microbe killing agents. Unfortunately, there is not enough scientific data to prove Eucalyptus oil is an antimicrobial agent on its own, and as such it is not allowed to be labelled as an active agent according to government healthcare regulators FDA & TGA.	
Public: Peter Steve/Sunny wipes	Methods	EN 12791 EN 1500 TGO 54 OPTION D topical skin study TIME KILL STUDIES TEWA STUDY CORNEOMTRE STUDY BROAD SPECTRUM BACTERIAL STUDY viral SUSPENSION TEST STUDIES Fungal studies MRSA & VRE studies Type 1 ECO certified tender process acceptance and adoption for hand hygiene and hard surface disinfecting	Thank you for this information. Unfortunately, it is outside the scope of our review because it is not an intervention for treating chronic venous ulcers.

Commentator & Affiliation	Section	Comment	Response
Public: Peter Steve/Sunny wipes	Results	Passed all studies above or completed studies with positive outcomes	Thank you for this information. Unfortunately, it is outside the scope of our review because it is not an intervention for treating chronic venous ulcers.
Public: Peter Steve/Sunny wipes	Discussion	A recent hand hygiene product evaluation was conducted by NSW State Ambulance infection control management and procurement, which saw them select the SunnyWipes handgel as their number one preference for hand hygiene, with overwhelming positive responses. Also, several small end user product acceptance trial sites in hospitals have provided feedback and indicated the gel provided relief on itchy sore red hands. Some eczema suffers stated that after using the handgel, it had helped sooth their skin. Others have stated that the handgel had helped relieve sore dry cracked hands of some healthcare staff (ambulance officers). As a result some workplaces have now adopted the hand gel as their staff wanted to use it, over and above the current products they were using. In light of these results and trials, SunnyWipes is now looking for more healthcare workplace sites and participants to conduct more clinical trials to garner end user feedback and	Thank you for this information. Unfortunately, it is outside the scope of our review because it is not an intervention for treating chronic venous ulcers.

Commentator & Affiliation	Section	Comment	Response
		to measure any skin healing positive effects. The objective of the trials is to garner information that can measure its positive impacts, which in turn can help improve hand hygiene adherence, with the aim to reduce healthcare acquired infections. Further, it is hoped that by offering a more natural alternative with less health and environmental risks, adherence will increase and therefore healthcare acquired infections will decrease. Meaning that healthcare workers improve their adherence to the patient care program and the “WHO 5 Moments - clean care saves lives” program. In addition to increased adherence it is expected that the end users skin condition will improve because the reported current range of products have a tendency to compromise their skin, leaving it dry and cracked and requiring the application of additional moisturisers. This technology also has shown very strong anti toxic behaviour and fast acting behavioural [seen but not clinically validated yet] healing and infectious healing Looking for guidance and help?	

Commentator & Affiliation	Section	Comment	Response
Public: Association for the Advancement of Wound Care	Executive Summary-2	KQ2b.Please change here and at all places where this issue or comparison is described in the CER to: For patients with chronic venous leg ulcers *managed with adequate sustained graduated compression* that do not have clinical signs of cellulitis that are being treated with dressings that ~~regulate~~ *retain* wound moisture ~~with or without active chemical, enzymatic, biologic, or antimicrobial components,~~ what are the benefits and harms of using systemic antibiotics when compared with using dressings alone?	Thank you for your suggestion, but we have decided not to change the wording of our Key Questions at this stage. We had finalized the wording of our Key Questions based on input from the Key Informants, Technical Experts, representatives from AHRQ, and members of the public.
Public: Association for the Advancement of Wound Care	Results	In Adverse Events section, first graph: Delete "infection" from sentence beginning with: "Evidence was lacking on the effects of advanced wound dressings on maceration…"	This edit has been made.
Public: Association for the Advancement of Wound Care	Results- KQ	For patients with chronic venous leg ulcers managed with adequate sustained graduated compression what are the benefits and harms of moisture-retentive hydrocolloid dressings as compared to gauze or impregnated gauze primary dressings?	Thank you for your suggestion, but we have decided not to change the wording of our Key Questions at this stage. We had finalized the wording of our Key Questions based on input from the Key Informants, Technical Experts, representatives from AHRQ, and members of the public.

Commentator & Affiliation	Section	Comment	Response
Public: Association for the Advancement of Wound Care	Results- KQ1	Please also correct all statements in the CER suggesting that VU primary dressings do not affect any patient or ulcer outcomes. This counters evidence supporting differences between gauze and occlusive hydrocolloid dressings cited at right. The term “moisture regulating dressings” fails to distinguish dressings that absorb wound fluid from “occlusive” hydrocolloid dressings that seal in wound moisture and have evidence of healing, pain or infection benefits compared to gauze.	We focused our review on the treatment of chronic venous leg ulcers only and did not evaluate evidence on ulcers present for less than 6 weeks. The report summarized that “most interventions used in the management of chronic venous leg ulcers lack supporting evidence that they add any benefits to compression therapy alone. This negative finding does not necessarily mean that the interventions are ineffective, but rather that better studies are needed to demonstrate their clinical impact.”(ES-18) Our review evaluated the effect of advanced wound dressings on healing, pain, and infection compared with gauze, compared with like dressings, and compared with other types of dressings.
Public: Association for the Advancement of Wound Care	Results- General: add KQ	For patients with chronic venous leg ulcers managed with adequate sustained graduated compression that have wound surface necrotic tissue, what are the benefits and harms (including healing, pain and cost) of bedside surgical debridement as compared with autolytic debridement using a hydrocolloid dressing .	Thank you for your suggestion, but we have decided not to change the wording of our Key Questions at this stage. We had finalized the wording of our Key Questions based on input from the Key Informants, Technical Experts, representatives from AHRQ, and members of the public. In our review, we considered debridement as part of conservative care.

Commentator & Affiliation	Section	Comment	Response
Public: Organogenesis	Introduction-Structured abstract	The structured abstract states: "cellular human skin equivalents facilitated the healing of venous ulcers (moderate strength of evidence)". In other sections, products are called out by brand name. To remain consistent, and to minimize confusion, it should be clear that Apligraf is the only product in this category with clinical evidence supporting efficacy in healing VLUs, and Apligraf should be referred to by brand name in the appropriate sections throughout the document.	Our general policy was to use generic names rather than brand names, although we have used some brand names in this report when they refer to unique products. Other products that are currently in development show promise in promoting wound healing as well (see Kirsner RS, Marston WA, Snyder RJ, et al. Spray-applied cell therapy with human allogeneic fibroblasts and keratinocytes for the treatment of chronic venous leg ulcers: a phase 2, multicentre, double-blind, randomised, placebo-controlled trial. Lancet. 2012;380(9846):977-85).
Public: Organogenesis	Introduction-Structured abstract	The conclusions section of the structured abstract states: 'These findings do not mean that the interventions failed to have value. Rather, that the risk of bias and lack of adequate sample size prevented us from establishing statistically valid conclusions of therapeutic efficacy.' While this may be an accurate statement for the majority of the products/interventions reviewed, it may not accurately reflect all interventions, which should be noted.	Thank you for comments. Specific mention is made that Apligraf was specially effective in chronic long-term venous ulcers.

Commentator & Affiliation	Section	Comment	Response
Public: Organogenesis	Executive Summary	Table A on ES-6 and Table 1 page 9 list Oasis in the acellular section of the human skin equivalents and extracellular matrixes category. Oasis is comprised of porcine collagen and would be more appropriately placed in the collagen dressings section.	We revised Tables A and 1 to re-categorize Oasis as a collagen dressing.

Commentator & Affiliation	Section	Comment	Response
Public: Organogenesis	Executive Summary-SOE	Regarding the strength of evidence for Apligraf, as a Class III medical device, the clinical study was conducted under a FDA-approved investigational device exemption (IDE) and pre-market approval (PMA) was required. As part of this process, the FDA conducted a rigorous, prospective review of the pivotal study protocol to ensure that statistically valid conclusions related to product safety and efficacy could be made at the study conclusion (such determinations also include ensuring that appropriate measures are taken to minimize bias). As well, at the conclusion of the study, the data must demonstrate both safety and efficacy to merit support for PMA approval. Based on the results of this randomized, controlled clinical trial, Apligraf received PMA approval from the FDA, and therefore the level of evidence should be changed to "high."	Our evidence grading evaluated risk of bias, consistency, directness, and precision of the body of evidence (not single studies), as described in the Methods chapter. We consistently followed this protocol when grading the evidence for all comparisons. For further information about EPC Program strength of evidence grading, please see the methods chapter on the Effective Health Care website www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayProduct&productID=1163

Commentator & Affiliation	Section	Comment	Response
Public: Organogenesis	Executive Summary	Regarding Apligraf, the FDA required an IDE filing and PMA. In the executive summary, Table A and in page 2, living cellular constructs, such as Apligraf are categorized as a "wound dressing." The text states "Since dressings have been classified as devices and not drugs, the U.S. Food and Drug Administration (FDA) has not required that pre-marketing testing for safety and efficacy be as rigorous as it has been for approval of new drugs." This statement is inaccurate, since the FDA required PMA approval for Apligraf. As well, since Apligraf went through the IDE/PMA process, it is categorized as a "wound or burn dressing, interactive" (product code MGR). Products that go through the 510k pathway are categorized as "dressing, wound, collagen" (product code KGN).	In the Executive Summary in the Introduction section under Advanced Wound Dressings, we now state, "The United States Food and Drug Administration classifies dressings as devices and has had a mixed approach to their regulation. Living cellular constructs have had extensive premarket evaluation and study protocol evaluation; however, pre-marketing testing for safety and efficacy is not as rigorous as it is for the approval of new drugs. This has clearly impacted the quality of potential efficacy data."

Commentator & Affiliation	Section	Comment	Response
Public: Organogenesis	Introduction- Abstract	In the conclusions section of the structured abstract, the text states “the risk of bias and lack of adequate sample size prevented us from establishing statistically valid conclusions of therapeutic efficacy.” Analyses of study quality tend to focus on the lack of blinding in studies with living cellular constructs (Apligraf) as evidence of low study quality and risk of bias. As treatment blinding is not possible in studies with living cellular constructs, other methods are frequently used to minimize any potential for bias in evaluating treatment outcomes. These include: use of clinical photographs for a blinded evaluation, and corroborating the Investigator’s assessment of wound healing by comparison with wound tracing data. In fact, such methods were used in the Veves, 2000, and Falanga ‘98 trials/publications from the Apligraf pivotal studies. Thus, the risk of bias in the Apligraf studies was low, and this should be reflected in the text.	We acknowledge the difficulties with blinding in all studies of dressings, including those studying Apligraf. Although difficult, blinding could still be possible in these trials. For instance, Apligraf could use controls with collagen dressings without fibroblasts or epithelial cells. Blinding was not the only factor we considered in the quality assessment. We used over 20 items from a standardized quality assessment tool to assess study quality (see Appendix D, Table 5).

Commentator & Affiliation	Section	Comment	Response
Public: Organogenesis	Executive Summary	On page ES13, KQ1, paragraph 4, the text states: "One study of autologous living keratinocyte showed improvement in wound healing, especially in patients with long-standing ulcers (over 1 year) that were treated with ACE™ bandages and compression." This text seems to refer to Apligraf, which is living cellular construct comprised of *allogeneic keratinocytes and fibroblasts seeded in a bovine collagen matrix*. It should be made clear that the reference is to Apligraf, and the composition of Apligraf should be accurately represented as stated above. Per the discussion below, Apligraf showed improvement in wound healing in patients with VLUs greater than 1 month duration that had not adequately responded to conventional treatment.	We have made the suggested edits to the Results section for KQ1 of the Executive Summary.

Commentator & Affiliation	Section	Comment	Response
Public: Organogenesis	Executive Summary	On page ES17, KQ1, the text states: "For cellular equivalents, benefit was limited to patients with long-standing ulcers". Similar comments are present in Table D, page ES14, and in the discussion on page 72, KQ1. This text refers to the Apligraf FDA pivotal VLU study. The Apligraf pivotal study design went through the rigorous FDA prospective review process required for IDE studies. The primary endpoint in the study was incidence of and time to complete ulcer healing by 6 months relative to standard of care. The study was designed and powered to test hypotheses related to these primary endpoints, in patients with ulcers greater than *1 month* duration. The study was *not* designed and powered to determine if Apligraf was more effective than the standard of care in healing patients with long-standing ulcers. The text should be changed to reflect the study population: patients with VLUs greater than 1 month duration that had not adequately responded to conventional care.	We feel that what we have stated is correct and did not make any changes to the report.

Commentator & Affiliation	Section	Comment	Response
Public: Organogenesis	Results	The evidence from this study (Falanga '98) indicates that for the primary endpoints (incidence of and time to complete healing by 6 months) 63% of Apligraf treated patients completely healed their ulcer vs. 49% in the control group. The median time to complete wound closure was 61 days for Apligraf vs. 181 days for control (Falanga '98). The data demonstrated safety and efficacy in healing patients with VLUs in ulcers greater than 1 month. If AHRQ is presenting the highest level evidence from this study, the highest level of evidence demonstrated increased healing with Apligraf and decreased median time to healing in ulcers greater than *1 month* duration that had not adequately responded to conventional care. (i.e., the overall study population).	We noted this in the results section.

Commentator & Affiliation	Section	Comment	Response
Public: Organogenesis	Results	On page 20, the text states: "Cellular human skin equivalent dressings provided as much as three times more rapid complete healing of chronic venous ulcers than compression alone, especially for ulcers that had failed therapy and were present for over 1 year. (Moderate strength of evidence)". As stated previously, the Apligraf pivotal study was only designed to test safety and efficacy in patients with ulcers greater than 1 month duration. The text should be changed to ulcers greater than 1 month duration that have not adequately responded to conventional treatment. Additionally this statement should more specifically indicate that it was only Apligraf that yielded these results (not all products in the cellular human skin equivalent dressing category).	In the text on page 20, we were referring to the subgroup analysis of patients with ulcers of > 1 year's duration reported by Falanga in the 1999 publication.

Commentator & Affiliation	Section	Comment	Response
Public: Organogenesis	Results	Regarding the level of evidence: the level of evidence for Apligraf is listed as “moderate” throughout the document (Results, vi; ES13, paragraph 4; Table D, ES14; Wound Healing, Page 20; Table 8, page 30). As mentioned above, the Apligraf VLU pivotal study design went through rigorous prospective IND review, and after the study, went through the rigorous PMA approval process. The Apligraf pivotal study was powered to .8 (n=240), with an alpha of .05, as required by the FDA, which is adequate to generate Level 1 Evidence (High). As mentioned above, efforts were taken to minimize bias. Given these facts, the level of evidence should be changed to “High.”	We graded the strength of the evidence based on the entire body of evidence, not just individual trials. We used 4 domains to grade the strength of evidence: risk of bias, consistency, directness, and precision. We provide details of how we graded the evidence in our methods chapter.

Commentator & Affiliation	Section	Comment	Response
Public: American Physical Therapy Association	General	We suggest that the definition of “adequate compression” be clarified. Compression levels greater than 20 mmHg were discussed but a standard acceptable level was not described in the working definitions. Compression at 20 mmHg or slightly above is known to be inadequate. At least 35 mmHg is required for most individuals without concomitant arterial disease. This definition may be wholly inadequate. As a result, study inclusion may have been inappropriate in comparison to accepted levels of standard of care.	We agree. The literature did not report direct measurement of pressure. We chose the bare minimum of pressure. The suggestions are good ones but our results reflected the state of the publications. We absolutely agree that appropriate measurements should be included in future literature. Furthermore, we acknowledge how the inclusion of studies that use lower levels of compression is a limitation in our review in the Discussion chapter.

Commentator & Affiliation	Section	Comment	Response
Public: American Physical Therapy Association	Results	There appeared to be a lower standard of comparison for surgical studies as they were analyzed without a concurrent comparison group. Conclusions may then indicate a possible bias for surgical approaches. Evidence for surgical intervention was of the lowest level (mainly case series). A different level of evidence should not be permitted for surgical practice because of a historical lack of controlled comparisons. Surgical approaches should have to meet the same level of rigor as other practice interventions such as dressings, exercise or modalities especially in light of the invasive and potentially risky nature of surgical options. We recommend re-statement of no evidence in place of minimal evidence in this instance.	Because so few randomized controlled trials have been done on the surgical interventions, we thought it was important to include observational studies. We wanted to be as comprehensive as possible, so we allowed case series. By including this body of evidence and assessing the quality, we hope to inform decisionmakers about the type of evidence available and to guide future research. We applied the same criteria for rating the strength of evidence. Since observational studies generally have a high risk of bias, the resulting strength of evidence was generally low or insufficient for the surgical interventions.
Public: American Physical Therapy Association	Results	Under the statement of the benefit of cadexomer iodine containing dressings the research indicated improved healing. We recommend this information be included in the conclusion.	This is noted in the discussion section (p 72) and has been added to the conclusion paragraph.

Commentator & Affiliation	Section	Comment	Response
Public: American Physical Therapy Association	Results	The potential benefit of hydrocolloid and biofilm powder and biofilm dressings compared to standard dressings in preventing infection appeared to be minimized. We would suggest this be reconsidered, especially in light of the role of biofilms in the prevention of healing.	The statistically significant proportion of ulcers healed among ulcers > 4 cm is discussed in the results section. This data was also added to the table
Public: American Physical Therapy Association	Results	There also appears to be a potential bias for cellular therapies. This is an expensive therapy that requires as many as five applications in order to produce healing effects. The therapy did not modify recurrence. We also suggest that the use of pentoxiphylline to enhance arterial flow to the venous wound be added.	Pentoxifylline is outside of the scope of this review because it was not an intervention of interest. While we acknowledge other interventions that could be potentially used for chronic venous ulcer healing, we constrained our review to those that are included in this systematic review. As with most systematic reviews, we balanced the comprehensive and depth of a systematic review, considerations of stakeholder input, and the feasibility of completing a timely systematic review. As a part of usual processes in development of an AHRQ systematic review, we engage relevant stakeholders to provide input on the most relevant key questions, interventions, comparators, and outcomes, as well as details of the systematic review protocol. Input from stakeholders identified the current set of interventions as those that presented greater uncertainty in clinical care.

Commentator & Affiliation	Section	Comment	Response
Public: American Physical Therapy Association	Results	We recommend fuller inclusion of the effects of ultrasound on venous ulcers and suggest that KHz and MHz be considered separately. There are at least two studies with 30 subjects or greater that meet the criteria for inclusion in this review. We are aware of two KHz ultrasound studies1 2 and three MHz studies3 4 5 that are positive. The recent study by Taradaj 6 included in the report used a poor study design by mixing surgery plus compression but not including compression with ultrasound or other physical agents as a standard of care thereby biasing the results.	Ultrasound is outside the scope of this review because it was not an intervention of interest. While we acknowledge other interventions that could be potentially used for chronic venous ulcer healing, we constrained our review to those that are included in this systematic review. As with most systematic reviews, we balanced the comprehensive and depth of a systematic review, considerations of stakeholder input, and the feasibility of completing a timely systematic review. As a part of usual processes in development of an AHRQ systematic review, we engage relevant stakeholders to provide input on the most relevant key questions, interventions, comparators, and outcomes, as well as details of the systematic review protocol. Input from stakeholders identified the current set of interventions as those that presented greater uncertainty in clinical care.

Commentator & Affiliation	Section	Comment	Response
Public: American Physical Therapy Association	Results	Although some "interventions" and "adjunctive" therapies were discussed in the draft report, we did not feel that list was fully inclusive. For example, treatment strategies employed by physical therapists such as the use of exercise and gait training to increase the efficiency of the venous pump in helping to reduce edema and the use of Velcro strap compression garments (e.g., Circaid and Farrow bandages) to help with edema management were not included and we recommended they be considered for inclusion.	These modalities were not included in the review because they were not interventions of interest. While we acknowledge other interventions that could be potentially used for chronic venous ulcer healing, we constrained our review to those that are included in this systematic review. As with most systematic reviews, we balanced the comprehensive and depth of a systematic review, considerations of stakeholder input, and the feasibility of completing a timely systematic review. As a part of usual processes in development of an AHRQ systematic review, we engage relevant stakeholders to provide input on the most relevant key questions, interventions, comparators, and outcomes, as well as details of the systematic review protocol. Input from stakeholders identified the current set of interventions as those that presented greater uncertainty in clinical care.
Peer Reviewer #3	Executive Summary-1	Qualify the statement about "resulting in production of growth factors" to read that that occurs in a relatively healthy individual and stable wound environment.	This wording has been edited.
Peer Reviewer #3	Executive Summary-1	add that advanced wound dressings also donate moisture.	We have made this edit.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Executive Summary-Table A	Table A: I would say that Transparent Films and Hydrocolloids Enhance Moisture (to differentiate from those that add moisture) Add hydrofiber dressings to exudate management for completeness. Also, add glycerin and otter performance enhancing (e.g. Na Alginate) additives.	This edit has been made.
Peer Reviewer #3	Executive Summary-Table A	Table A: For completeness under Antimicrobial , the spelling of Manuka Honey should be corrected, add Cadexomer to the Iodine, the PVA dressing has 2 pigments (crystal violet and methylene blue) and there is a new one that has DACC (diakylcarbonochloride), trade name Sorbact.	These edits have been made to Table A and Table 1.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Executive Summary-Table D	There was clearly a lot of work that went into creating these tables, but it is mind boggling to read. Where I'm curious, is in the Cellular Human Skin Equivalent vs. other dressings, to say there is insufficient evidence, while true perhaps today, one must keep in mind that these were trials done almost 18 years ago. Comparators were what they were, and in the Apligraf trials at least they used I believe, adaptic and moist gauze. At least a moist environment. Also, I think it should be noted that in the venous ulcer trials, the time to healing was 85 days faster, there was statistically significant fewer amputations and diagnoses of osteolyelitis in the diabetic ulcer trial. To me that data is meaningful.	Our evidence grading evaluated risk of bias, consistency, directness, and precision of the body of evidence, as described in the Methods chapter. We followed this protocol when grading the evidence for all comparisons.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Executive Summary-Table D	While I do understand the need for clear analysis of the studies that are out there, I don't think this bodes well for clinical wound care. I do wish that the authors would listen to the tape from the SAWC on Wound Care Clinical Trials: Is the FDA Expecting Too Much? Speakers were Rob Kirsner, Bill Eglestein and Marty Robson. It was wonderful, and clearly pointed out the position that the FDA puts wound care in looking at complete healing as the only primary endpoint. Nowhere in wound care is one going to use the same therapy for 12, 16 or 20 weeks. This paper is a perfect avenue for putting that message out there. If it is there, I apologize; this was a difficult read.	We see this as somewhat expected as we would identify evidence gaps in an area and field where rigorous standards have not been previously applied. We agree with this reviewer, but our review was not related to the FDA requirements and was an assessment of wound care interventions (using a number of different outcome measures).
Peer Reviewer #3	General	I have spent 4-5 hours reading this over time and I apologize that I don't have more to offer, but it is a tough read on a computer screen. I applaud the authors.	Thank you for reviewing our report!
Peer Reviewer #4	General	The report is meaningful and helpful for clinicians and the questions are answered	Thank you very much!
Peer Reviewer #4	Introduction	well written	Thank you very much!
Peer Reviewer #4	Methods	Appropriate; unable to comment on statistical methods	Thank you very much for taking the time to review the methods!

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	Enough detail?: Yes some could have offered more details	Throughout the results section of the report, we have added in tables detailing the results of the study.
Peer Reviewer #4	General-Clarity/usability	The literature review is thorough and follows the stated format. The conclusions appear reasonable given the quality of the publications and trials available	Thank you very much!
Peer Reviewer #4	General	The authors should define "adequate compression therapy"	In the Study Selection section of the Executive Summary, we added that adequate compression therapy is at least 2 layers of compression.
Peer Reviewer #4	General	What was the treatment locale of the patients in the various studies? Home vs. hospital	We provided an overview of the study design characteristics, including the setting, in the section "Study Design Characteristics" for each Key Question.
Peer Reviewer #4	General	They should comment upon the role of elevation and if at all measured or controlled for in the various studies. Some of the studies mention percent healing; do any use surface area measurements?	None of the studies reported on elevation.