



*Alliance of Wound Care Stakeholders July 16, 2014 Comments on the AHRQ Draft TA on
“Negative Pressure Wound Care Technologies”*

General

The Alliance of Wound Care Stakeholders (“Alliance”) is submitting the following comments in response to the AHRQ draft report entitled, “Negative Pressure Wound Therapy Technologies.” The Alliance is a nonprofit multidisciplinary trade association representing 16 physician and clinical organizations whose mission is to promote quality care and patient access to wound care products and services. These comments were written with the advice of Alliance organizations that not only possess expert knowledge in complex acute and chronic wounds, but also in wound care research. A list of our members can be found on www.woundcarestakeholders.org.

While we appreciate the opportunity to offer our comments, we are very disappointed in the short amount of time that the AHRQ allowed for a deadline to respond to this very dense document that is so critical to wound care stakeholders. It is our understanding that the Technology Assessment Program provides 2 weeks for public review of its draft reports. However, releasing the report on July 1 and then extending the due date one day to July 16th does not take into consideration the holiday during which with many wound care professionals take vacations during this time and thus does not constitute a meaningful public comment period. This is the second time in the past few years during which AHRQ has released its draft during a major holiday—the first was during New Years and Martin Luther King’s birthday in 2011 for “Skin Substitutes for Treating Chronic Wounds. We would respectfully request that in the future that AHRQ and its contractors plan more carefully and not release a draft TA during a holiday.

The Alliance has treated writing our comments to this draft very seriously, and has convened many conference calls, conversations and emails to ensure that all stakeholders’ input will be included. Since we still do not believe there is enough time to give this important document the careful consideration that it needs, we are submitting these comments, but intend to supplement our filing as we receive more information from our members.

While we congratulate the authors on undertaking such a complex assessment, there are many serious issues with this TA that demonstrate a fundamental lack of understanding in regard to NPWT and wound care, the settings in which NPWT is used in regard to study inclusion, and many methodological issues, which we have addressed in the various sections.

Introduction/Background

The authors seem to demonstrate a fundamental lack of understanding of the use of NPWT, as well as its mechanisms of action:

1. In the Introduction the authors state that *“The exact mechanism by which these devices may promote wound healing is not known. Hypotheses for the healing effect include the removal of excess fluid while improving circulation to the wound bed,¹¹ reducing bacterial load on wound surface, or the presence of a mechanical effect that aids wound healing.¹²”* The authors cite amongst other references the original Wake Forest publication (Morykwas, Argenta, Shelton-Brown, & McGuirt, 1997). This seems to imply to a non-specialist reader that the therapy is poorly understood and relatively uninvestigated, whereas on the contrary, there has been rather a lot of progress and understanding developed over the NPWT mechanisms of action: see Glass & Nanchahal for an independent recent review (J Plast Reconstr Aesthet Surg 2012;65(8):989-1001.). In particular the reduction of bacterial bioburden in contaminated clinical wounds under NPWT has been extensively investigated and now widely accepted as not to be a major mechanism of action; hence the increasing interest in the use of antimicrobials, of one sort or another, in combination with NPWT (Siegel HJ, et al., Clin Orthop Relat Res 2014;472(3):830-5; Kim PJ, et al., Plast Reconstr Surg 2013;132(6):1569-79.

It is likely that several mechanisms are responsible for the benefit of NPWT, including: fluid removal, drawing the wound together, micro-deformation, and moist wound healing (Orgill DP, Bayer LR. Plast Reconstr Surg 2011;127 Suppl 1:105S-115S); systemic mobilization of endothelial progenitor cells (EPCs) during NPWT (Seo SG, et al., Exp Mol Med 2013;45:e62); and support [of] (neo-) angiogenesis and transformation of chronic non-healing wounds in a physiological wound healing process when combined with surgical debridement (Malsiner CC. et al., Int Wound J 2013 Sep 13. [Epub ahead of print]). In summary, the authors could have done a much better job of describing the mechanism of action of NPWT by reviewing more recent references in the literature.

2. It should be noted that the goal of NPWT is to improve wound healing to the point where application of traditional dressings that maintain a moist wound environment can be applied to finish the process. NPWT is ideal for chronic wounds that are “stuck” and unable to progress. NPWT is cost effective by helping certain wounds progress through the healing process which in turn reduces the hospital readmission rates and overall healthcare expenditures. We believe that this point was missed by the authors.
3. Although NPWT is often initiated in the hospital and patients’ transition to the home, it is not a straight path to home care. Patients can transition to the home, long term care, or long term acute care facilities. Their wounds can also be treated in a hospital affiliated or independent wound clinic, physician office, or visiting nurse association in the home settings. Each of these settings has different standards of care and delivery methods and thus makes it difficult to define control groups and monitor study protocols.
4. The authors discuss the limitation to chronic wounds in the present review and although they acknowledge the extensive use of NPWT on acute and surgical wounds, they seem to imply that use of

NPWT in “surgical” wounds is exclusive to acute care settings and not in the home. This is misleading and misrepresents the true burden of post-surgical wound dehiscence that is treated in the homecare situation with NPWT. Although it is an imprecise term, such wounds are often referred to as “sub-acute” and in a wound after 4 weeks of non-healing the biology of these wounds will quickly approach that of chronic wound with microbial contamination, poor extracellular matrix, edema and exudate (Schultz

GS, et al., *Int Wound J* 2004;1(1):19-32.). A very significant proportion of wounds managed by NPWT in outpatient clinics or in the home setting are dehisced surgical wounds with delayed healing. For example an analysis of Outcomes and Information Set (OASIS) data on outcomes in NPWT-treated Stage III or Stage IV pressure ulcers (N = 98) or surgical wounds (N = 464) found almost five times the number of post-surgical wounds treated at home compared to pressure ulcers (Baharestani MM, et al., *Ostomy Wound Manage* 2008;54(11):48-53.). Significantly, outcomes from early initiation of NPWT in the dehisced surgical wounds were excellent. Similar data are found overseas. In an analysis of NPWT in homecare in the UK (known as Community-based wound care in the UK) 68% of all NPWT episodes were for post-surgical dehisced wounds (Dowsett C, et al., *Int Wound J* 2012;9(5):544-52.). Unless a similar AHRQ review is scheduled to be undertaken shortly on the use of NPWT on dehisced surgical wounds, it seems arbitrary to exclude these wound types when management of these wounds represent a major use of NPWT in the home care setting and moreover that such wounds are considered to respond well to NPWT.

5. Question 2 Part A: what does “similar to Medicare patients” mean? The stated definition (age 65 or older or disabled) does not even begin to really define what this hypothetical population is.

Methods/Results

We found several issues in regard to the methodology of this TA, some of which are very serious flaws:

1. Why aren't hospital/inpatient/LTC studies results applicable to the home setting? There is no delineation between hospital use and home use. Patients are not followed in the inpatient setting long enough to make determinations that hospital-based NPWT is insufficient. Patients are often started inpatient then transferred to LTC or home use. The decision just to look at studies that exclusively had home settings is flawed because the use of NPWT does not change between settings and such a strategy excluded many valuable studies.
2. Patient compliance with wound therapies, nutrition, psychosocial concerns, management of comorbidities and environment are all critical components in wound management. Management of the above can be closely monitored and documented in an acute care setting. The home environment presents greater challenges in ensuring the above variables are appropriately managed. Therefore, the home care environment presents many barriers to obtaining quality study data and it may be unrealistic to expect outcomes of the type proposed in the TA. We believe that having a clinician on the team who is well versed in the practice of NPWT at home would have made this TA much more useful.
3. Whereas the protocol registered at Prospero specified that for RCTs the Cochrane risk of bias tool would be used and the Newcastle-Ottawa tool used for observational trials, it appears that in the actual

assessment a modified Cochrane risk tool was used for all studies; moreover the predefined critical outcomes were somewhat different to the usual Cochrane tool and NOT pre-specified. Use of the Cochrane tool for risk of bias assessment for observational trials is WHOLLY inappropriate.

4. No inter-rating scores (e.g., kappa values) were published regarding the level of agreement between reviewers (risk of bias) for risk of bias assessment. We cannot tell if the two reviewers agreed most of the time or disagreed on every assessment. This is an unknown source of bias.
5. Some studies were rejected for review based on a sample size of 20 or less. This was not pre-specified and is an ad-hoc approach that might leave out some useful studies. There is not rationale for using a sample size of 20. Moreover, the authors might have been able to perform a meta-analysis of some outcomes had they left these studies in.
6. Evidence was downgraded when “inappropriate control groups” and “surrogate outcomes/endpoints” were utilized in studies. Although in some studies there can be some questions regarding these issues, downgrading the evidence on this basis was overly conservative and not justified.
7. Evidence was also downgraded because complete healing was not defined according to the FDA’s definition of healing. For observational trials and non-pivotal trials this is often inappropriate as most of these studies would not use such a definition in practice or pragmatic trials. Moreover, NPWT is often used to partially close a wound to prepare a wound for further surgery (e.g., flap closure). The authors knew this because one of their planned outcomes was “Time to surgical readiness of the wound bed.” We would submit that then to downgrade evidence just because outcomes did not meet the FDA’s definition of healing is illogical and arbitrary.
8. The level of evidence was cited as insufficient. However, in other systematic reviews higher levels of evidence have been found in a broader context. For example in a recent systematic review conducted by the VA they stated: “For diabetic ulcers ... [T]here was moderate-strength evidence for improved healing with a biological skin equivalent (relative risk [RR], 1.58 [95% CI, 1.20 to 2.08]) and negative pressure wound therapy (RR, 1.49 [CI, 1.11 to 2.01]) compared with standard care... Compared with standard care, some advanced wound care therapies may improve the proportion of ulcers healed and reduce time to healing, although evidence is limited” (Greer N, et al., Ann Intern Med 2013;159(8):532-42.).
9. Studies were excluded if they did not have a comparison group. While we understand this is reasonable for determination of efficacy/effectiveness, less common safety issues are usually reported in large case series. Excluding these can miss valuable data.
10. Sometimes NWPT devices are used in heavily exudating wounds in which the patient is not a surgical candidate due to co-morbidities and attempts at alternative wound care has been attempted and has been unsuccessful. NWPT can allow for fewer dressing changes and decreases nursing utilization. It also increases patient comfort and quality of life. This was not included as an outcome.

11. Table 3. Manufacturer/Company – Mendela is incorrect. It should instead be “Medela.”

Discussion/Conclusion

We disagree with many of the conclusions in this TA:

1. The level of data in the literature (over 5,000 citations) is enough for AHRQ to make some sufficient declarative statement on the efficacy and safety of NPWT. Even the study conducted by Fife et al shows this. For the authors to state that Lavery et al’s 2007 study on DFUs is insufficient, tells us that the authors were too stringent on the guidelines for clinical data.
2. Based on data analysis, to dismiss the observational studies as being too inconclusive is unfair given that carriers have adopted less stringent guidelines for acceptance of data that is in real-time. If observational and retrospective studies are acceptable for cellular and/or tissue-based therapies then they should be acceptable for NPWT. We question whether the authors really understand some of the observational studies: “...larger studies were retrospective and based on administrative databases.” For example, the study conducted by Fife et al (Int Wound J 2008;5 Suppl 2:17-22.) is based on electronic health records and is NOT an administrative database.
3. A further concern is the omission of a number of randomized controlled trials (RCTs) from study inclusion because they were not entirely conducted in the home setting (Armstrong DG & Lavery LA, Lancet 2005;366(9498):1704-10.; Blume PA, et al., Diabetes Care 2008;31(4):631-6.). The study by Armstrong and Lavery was subjected to an economic analysis published by Apelquist et al in 2008 (Am J Surg 2008;195(6):782-8), which details where care was given: A total of 24.4% of all dressing changes were performed in the hospital, 18.3% in the outpatient clinic, and 42.1% during home care. In terms of the 10,908 days of total therapy, 9,719 (89.1%) and 1,189 (10.9%) were in the home care and inpatient settings respectively. Similarly, in the randomized study in 342 diabetic foot ulcer patients conducted by Blume et al., which was carried out in 37 centers, the proportion of home care therapy days to total therapy days was 9,471 of 10,579 (89.5%) for NPWT and 12,210 of 12,810 (95.3%) for AMWT (the controls). Given that this is a population consisting of diabetic foot ulcers or patients receiving amputations for foot ulcers, some inpatient care is absolutely necessary (i.e., this is “real life.”). Moreover, in regard to inpatient vs. outpatient NPWT, the data are quite clear that this has evolved to a "bridge to outpatient" technology. Thus, we question the decision to exclude such studies as not being “sufficiently” homecare based. Could the authors have not conducted an analysis of these kinds of trials in terms of subpopulations?
4. The AHRQ TA included the issues related to the 2011 FDA safety communication regarding serious complications associated with NPWT devices used in the home. The Agency expressed concern that, although these devices can be used safely and effectively in that setting, greater risk mitigation is required to prevent patients using these devices from experiencing serious health problems. As stakeholders in the wound care community, the Alliance of Wound Care Stakeholders agreed with the FDA. The Alliance also took this very seriously and partnered in 2011 with the FDA staff to help them with their MedSun Program which was dedicated to developing a relationship with the clinical community to learn about, understand, and solve problems with the use of medical devices as they are

used in the health care environment AND to provide useful safety information back to health professionals to improve patient safety. We helped them with questions in their MedSun NPWT survey and gave them lists of Alliance members who were clinicians that they could send the survey to complete. We invited FDA staff who had responsibility for these issues to speak at our meetings and to the largest wound care conference about the MedSun program and NPWT survey.

The Alliance went a step further-by developing and endorsing a set of proposed standards specifically for NPWT suppliers. Although physicians, nurses, physical therapists and other health professionals have primary responsibility for managing and overseeing care of NPWT patients, suppliers of these products play a vital role in ensuring the safe and effective use of these devices in the home. The training and 24/7 support that suppliers provide to professional and caregivers is critically important and requires a different set of competencies than those required for simple functional products. For that reason, the Alliance believed that the competency of all NPWT suppliers, including those participating in the DMEPOS competitive bidding program, should be validated through the external accreditation program already established by CMS, much like the product-specific accreditation required for suppliers of prosthetics, orthotics, rehabilitation products and respiratory products. Validating the competency of suppliers to provide support NPWT patients and caregivers is no less important.

In support of the FDA's recommendations and to assist CMS in the development of NPWT quality and accreditation standards, the Alliance developed and endorsed a set of proposed standards specifically for NPWT suppliers. On the Alliance's website (under comments) is a 2011 letter to CMS Administrator Tavenner stating the need for these standards and that the accreditation process would ensure that NPWT suppliers have the expertise required for support of the clinicians and patients using these devices. We met with the Administrator and her staff to emphasize that CMS adopt these standards.

Since then, CMS used the standards to create interpretative guidelines which were incorporated into standards now used by accrediting bodies. Suppliers who want to furnish NPWT into the home must be accredited.

5. The authors are rather dismissive of the retrospective nature of the study that (Fife et al. performed in 2007 (published in 2008) which evaluated adverse events for the VAC. A point overlooked in the analysis in the TA is that every *prospective* RCT of NPWT *a priori* excluded patients on anticoagulants so as to reduce the risk of bleeding. All prospective trials of NPWT have also excluded patients with most major comorbidities (Carter MJ, et al. Adv Skin Wound Care 2009; 22:316-24.) What was unique about the 2008 Fife study is that it specifically looked for patients treated with NPWT in the home setting who were on coumadin, heparin or other medications associated with an increased risk of bleeding. Since patients taking these medications had been excluded from the prospective trials, the only way to analyze the safety of NPWT in the home setting for patients on these medications was via retrospective analysis of the data which had been prospectively obtained.

The published study referenced in this AHRQ TA was a subset of a much larger analysis performed at the request of the FDA. The FDA requested that KCI provide data on the safety of the VAC in the home setting in relation to moist wound care. Nearly 10,000 wound care patients were analyzed,

approximately 10% of whom underwent NPWT treatment with the VAC. We think that the FDA report is informative and that AHRQ would find it useful. In that analysis, 200 patients on anticoagulants were found among the roughly 900 patients undergoing treatment with the VAC, none of whom had bleeding. Only one patient had VAC treatment discontinued due to blood-tinged drainage (not frank hemorrhage). That patient was on clopidogrel bisulfate and his wound was in the 99th percentile for size within this dataset.

The average number of major co-morbidities among patients treated with NPWT in this large data set was 8. As the 2009 Carter et al study showed, prospective trials have excluded patients with any serious diseases. So, while the AHRQ report is critical of studies utilizing retrospective data, *we submit that analysis of registry data is the ONLY way to assess the safety of NPWT. This is because prospective trials a priori exclude patients with significant co-morbid diseases and patients on medications which increase the risk of bleeding.*

In summary, it appears there is much bias against using registries as the best way to follow adverse events in the real world. For example, AHRQ would not even mention The U.S. Wound Registry in their upcoming edition of the AHRQ book on registries. It appears to us that AHRQ is unsupportive of efforts of the wound care industry to collect this type of data and make clinicians aware of its availability despite our efforts at education. This registry is now expanding its abilities to receive data as a result of the QCDR process.

6. Another key point is that these technologies require better operational definitions regarding when to start and stop. NPWT appears to be most helpful in reducing depth/complexity of wounds. It should then, generally speaking, be stopped in favor of less per-device expensive devices or just split thickness skin grafts when a suitable end point has been reached (Isaac et al, In: The Diabetic Foot: New York: Elsevier, 2013, 899-909).
7. Given that U.S. government agencies are unwilling to fund NPWT clinical studies, most of the cost of these trials must fall on the manufacturers. Adopting an unnecessarily narrow view point of the comparative clinical evidence does not encourage greater industry investment in clinical studies supporting innovations such as antimicrobials, instillation, or disposable NPWT devices. As all stakeholders have at heart the objectives of improving patient outcomes with the most cost efficient treatment protocols, we believe the conclusions of this TA, as it stands, does not serve patients.
8. Finally, we welcome the “characteristics of an ideal study” as outlined in Table 11.