ALLIANCE OF
Wound
Care
Stakeholders

July 21, 2011

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Submitted Electronically

Re: ***Methods Guide for Effectiveness and Comparative Effectiveness Review:*** **"Avoiding Bias in Selecting Studies"**

To Whom This May Concern:

On behalf of the Alliance of Wound Care Stakeholders ("Alliance"), I am submitting the following comments in response to the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Review chapter on "Avoiding Bias in Selecting Studies". I serve as the Executive Director of the Alliance, a 501 (c)(6) multidisciplinary trade association consisting of over 15 physician, clinical, provider, and patient 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. We appreciate the opportunity to offer our comments.

In reviewing the draft chapter, the Alliance generally agrees with the information presented in it. However, we believe that AHRQ is missing fundamental issues that should be addressed when dealing with issues of bias in selecting studies. For example, a form of bias is overly restricting inclusion/exclusion criteria to exclude high risk patients. Many of these patients are women, minorities and older adults.

The Alliance believes that these patient populations should be studied – they are also the patient population that Alliance physicians and clinicians are treating. The underrepresentation of women, minorities and older adults in randomized controlled studies (RCTs) is common. While RCTs are the strongest method for proving clinical efficacy, observational studies can be better at proving effectiveness – specifically in real world practice. As such, the Alliance asks, what does statistical significance mean when one is studying the wrong population?

The Center for Medicare and Medicaid Services (CMS) has acknowledged that there is benefit to analysis of "real world" data if information from large numbers of patients can

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be collected in a uniform fashion (March 29, 2005 Medicare Coverage Advisory Meeting [MCAC]). Part of the need for such studies is that the nature of the RCT design often precludes collecting certain kinds of data because its focus is so narrow. Moreover, in small sample RCTs, certain kinds of events, such as adverse events, will be undercounted or absent if such events are not common.

Wound care patients represent a "priority population" as defined by the Federal Coordinating Council for Comparative Effectiveness (FCCCER). Priority or high risk populations specifically include racial and ethnic minorities, persons with disabilities, the elderly, and patients with multiple chronic conditions or who need chronic care or end-of-life (palliative) health care. These groups have been traditionally under-represented in medical research and wound care, especially in the selection of patients for RCTs.

RCTs can be difficult to properly execute in wound care research because of lack of funding, difficult or complex study designs, narrow focus, extensive inclusion/exclusion criteria, and the problem with endpoints. While testing under controlled conditions is desirable to initially ascertain efficacy, the results may not be generalizable to "real world" wound care patients because a high proportion have many comorbidities or come from highly vulnerable populations that are typically excluded from controlled trials.

Currently there is more exclusion/inclusion criteria but less generalizable research. With the incredible amount of exclusion/inclusion criteria, research is becoming more restrictive. In the article, *Estimating the Applicability of Wound Care Randomized Controlled Trials to General Wound-Care Populations by Estimating the Percentage of Individuals Excluded from a Typical Wound-Care Population is Such Trials*, the author states: "The restrictions of inclusion/exclusion criteria might limit the generalizability of RCTs to the usual wound care patient, and single intervention designs are often poorly applicable to modern wound care practice." [1]

The Alliance believes that this lack of generalizability to real patients is a form of bias as is the exclusion or underrepresentation of a priority or high risk patient population and should be addressed by AHRQ, yet this chapter is strangely silent on this issue. The Alliance encourages AHRQ to generalize data with real patients in order to include more high risk patients in studies therefore lessening the degree of bias.

The Alliance has already identified exclusion/inclusion with respect to research as an issue. As we mentioned in previous comments to AHRQ - Developing strong wound care research principles have been a driving force in the Alliance's workplan. In fact, we created a multidisciplinary panel of 11 wound care experts entitled, "Panel On Wound Care Evidence-based Research" (POWER™), from our participating organizations who

[1] Carter MJ, Fife CE, Thomson B, Walker D. Estimating the applicability of wound care randomized controlled trials to general wound-care populations by estimating the percentage of individuals excluded from a typical wound-care population in such trials. *Adv Skin Wound Care*. 2009;22(7):316-324.

defined a set of guidelines in the form of principles to provide direction to all stakeholders involved in clinical or comparative effectiveness research in wound care.

The POWER™ guidelines identify two principles which underscore the issue:

- Because vulnerable populations are over-represented in clinical wound care practice, they should be included in wound care research
- The rationale for inclusion and exclusion criteria in wound care research should be justified and transparent.

The inclusion/exclusion criteria for many wound care studies are often overly restrictive, and therefore results can be limited in terms of generalizability to "real world" wound care populations, especially vulnerable or priority populations. [2]

These two principles show that although all wound care populations are vulnerable in a sense, some populations are highly vulnerable, and include females, the elderly (various definitions exist: Medicare population ≥ 65 y; ≥ 70 yr; and ≥ 85 y), racial and ethnic minorities, patients with disabilities, patient with multiple comorbidities, and those requiring palliative care.[3][4][5]

For example, patients with renal failure or frail patients under long-term care could be considered highly vulnerable. While highly vulnerable populations are almost never represented in RCTs that test new interventions, products, or strategies, this is often acceptable if the first RCT is used to demonstrate whether the new intervention, product, or strategy, works at all. However, subsequent RCTs should include highly vulnerable populations where feasible. In addition, for other types of studies, whether biobehavioral, observational, or basic science, investigators should also consider including highly vulnerable populations to acquire additional data where relevant.

The Alliance is happy to provide you with more information on these principles and would like to recommend that AHRQ address high risk patients as well as a lack of generalizability in research in this chapter – as both are forms of bias.

CONCLUSION

The Alliance appreciates the opportunity to provide AHRQ with our comments on the draft report. As stated earlier in our comments, due to our members' heavy research

[2] Ibid

[3] Pieper B. Vulnerable populations: considerations for wound care. *Ostomy Wound Manage*. 2009;55(5):24-37.

[4] LeBlanc TW, Wheeler JL, Abernethy AP. Research in end-of-life settings: an ethical inquiry. *J Pain Palliat Care Pharmacother*. 2010;24(3):244-250.

[5] Kilbourne AM, Switzer G, Hyman K, Crowley-Matoka M, Fine MJ. Advancing health disparities research within the health care system: a conceptual framework. *Am J Public Health*. 2006;96(12):2113-2121.

interest and activities, we would be pleased to serve as a resource to you now or in the future. If you have any questions, or would like further additional information, please feel free to contact me.

Sincerely,

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Executive Director

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