PERSPECTIVE ARTICLE

Clinical interventions for venous leg ulcers: Proposals to improve the quality of clinical leg ulcer research

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The present status of clinical leg ulcer healing research was reviewed by 25 experts over 2 days on September 28 and 29, 2015. Multiple clinical effectiveness reviews were presented suggesting that published clinical wound healing research often does not meet present (2015) evidence based standards. Specific areas requiring remediation were highlighted and approaches to overcoming existing challenges were proposed. Participants using anonymous voting technology developed an action plan to resolve perceived deficiencies. Statements were accepted if 75% of participants agreed. Older patients with a high frequency of comorbid conditions posed particular difficulties in designing clinical research protocols and better diagnostic categorization is necessary A standardized model template for collecting information about diagnosis and evaluation of the effect of interventions on healing of all types of leg ulcers was considered a high priority. Such a model template could be modified depending on the specific etiology of the leg ulcers. Generally agreed on quantifiable standards to establish degree of morbidity was considered a high priority. There was universal agreement that sources of funding and conflicts of interest needed to be disclosed in presentations and all publications. All clinical research studies should be registered with appropriate authorities. There was substantial enthusiasm for a clinical research network with quality standards for membership and an advisory research core available to investigators. Such a network should be funded and actively managed to insure long-term viability. The governance of such an entity needs to be established by the wound care community. The present trend to integrate patients into the clinical research process was endorsed and there was enthusiasm to develop patient advocacy for wound healing research.

A number of Clinical Effectiveness Reviews (CER) were recently published that questioned the quality of clinical research articles informing therapy for venous leg ulcers (VLUs).[1–4] For example, an Agency for Health Care Research and Quality (AHRQ) study reviewed 10,066 citations from the world's venous ulcer literature and found that only 60 papers could be analyzed; that means only 0.6% of the articles met 2012 evidence standards. In

another effort to evaluate evidence, the Centers for Medicare and Medicaid Services (CMS), commissioned AHRQ to conduct a CER on the literature justifying the use of outpatient negative pressure wound therapy. This review also found the quality of evidence to be very low[5]; one could easily conclude that payers are increasingly likely to demand high quality evidence to justify payment. This weak quality of evidence echoes similar findings reported earlier by the Center for Medical Technology Policy.[6]

Recently, this generally acknowledged deficit in high quality information stimulated the Society for Vascular Surgery and the American Venous Forum to publish a CER using evidence based methods. This publication suggested there was a need to improve the diagnosis and therapy of VLUs.[7] Driver and Gould[8] describe an ongoing effort in this report by multiple wound healing organizations to assist the Food and Drug Administration (FDA) in developing new evidence based guidelines for approving new interventions. These indecisive CERs do not tell us that wound treatments do not work; rather they highlight the fact that we need to improve published information that meets current standards. Decision makers, including payers, clinicians and patients have a problem when faced with low quality evidence about the most effective treatment for leg ulcers.

A group of concerned clinical investigators and evidence based medicine authorities organized a meeting of wound care leaders to discuss these results and develop an action plan to improve clinical wound healing research. Several grant requests to support such a conference were approved by AHRQ but lacked sufficient priority to obtain funding. The concerned organizing group, not-for-profit Wound Healing Coalition Foundation, and HMP Communications raised funds from: pharmaceutical companies, device manufacturers and wound management companies to support a consensus conference. We acknowledge these generous sponsors for their generous charitable contributions.

A meeting was convened on September 28 and 29, 2015, which aimed to Improve Clinical Research for Leg Ulcers. The goals of the meeting included: analysis of the flaws uncovered in published VLU research, possible methods of remediation, and development of an action plan to improve clinical leg ulcer research.

Invitations were extended to leaders of major wound care organizations and the leadership from the: Association of Advanced Wound Care, the Symposium for Advanced Wound Care, the Wound Healing Society, the American Venous Forum, the Society for Vascular Surgery, the American College of Wound Healing, the Wound Ostomy Continence Nurses Association, American Society of Physical Therapy, the FDA, CMS, pharmaceutical manufacturers, wound care management companies, and distinguished clinical wound care researchers including the Coordinating Editor of Cochrane Wounds.

More than 25 attendees gathered on Sept 28 and 29, 2015 to discuss this substantial challenge. Before the meeting, attendees were supplied with multiple CERs, guidelines, draft suggestions to improve clinical wound research, and a full agenda. The meeting was recorded for accuracy and a transcription of the meeting was made available to all attendees. The initial portion of the meeting was devoted to discussing and analyzing the problems observed with clinical venous ulcer research. The remainder of the meeting focused on the development of an action plan. Predominantly dichotomous statements were voted on secretly using hand held modules. Vote totals were collected and declared adopted if 75% of the attendees were in agreement. If that percentage was not met, the statement was either modified by discussion to obtain 75% agreement or was discarded. The statements and exact percentages for approval are listed in this report.

All venous ulcer presenters and action plan section chairs and co-chairs were asked to summarize their presentations and discussions. These statements were then used to prepare this communication, reviewed by the organizing committee, the presenters and discussion chairs, edited, consolidated, and reviewed by all authors before submission for publication.

PRESENT EVIDENCE BASED STANDARDS

Medical practice that utilizes an evidenced based approach uses information from well-designed studies to inform treatment decisions. The design of the studies and the quality of the studies are often hierarchically ranked to prioritize the results to determine "best evidence." Ultimately health care decisions should be based on evidence, the healthcare provider's experience and the patients experience and desires. It is important to realize that the evidence for all treatment decisions cannot always be found in the literature, and at times literature may present conflicting information. It is also possible that not all questions can be answered by conducting studies that are thought to yield the "best" level of evidence.

There are multiple experimental study designs. Randomized clinical trials (RCTs) are considered the highest quality of study because they are most likely to control bias by the use of randomization, that controls treatment selection bias, and by blinding which minimizes opportunities for information bias. RCTs are utilized to determine **efficacy** that measures the extent that an intervention produces a beneficial result under ideal conditions.

Inclusion and exclusion criteria attempt to define a homogeneous population, favoring more predictable and less variable results. These criteria also define comorbid diseases and medications. Sample size to assure adequate statistical power is critical; it is well known that observations in small groups of subjects are often not replicated at all, or to the same extent when larger sample sizes are evaluated. **Internal validity** asks the question whether the instruments or procedures used in the research measured what they were supposed to measure. **External validity** asks the question whether the results can be generalized beyond the immediate study. It is important to realize that the subjects enrolling in an RCT are not randomly selected from the community at large. Not everyone volunteers for an RCT so it is possible that the results of an RCT might not be generalizable to the general population of people with an illness. Evidence is often evaluated using grading systems.

The most common system for grading research evidence is called GRADE[9,10] whereas another popular system is called SORT.[11] However, it is possible to use these techniques poorly making an RCT a very low quality study.[3] Meta-analyses, or the systematic combination of multiple studies, are often conducted in an attempt to create a single estimate of the effect from multiple RCTs. To perform this analysis one must assess the quality of the studies

available for review. The Cochrane Collaboration conducts and maintains systematic reviews of the effects on health care; these may or may not include meta analyses depending on the volume, nature and quality of the primary research evidence. Cochrane reviews including wound reviews are published and maintained in the Cochrane Library. The majority of efficacy trials in wound healing in the USA, are performed for registration (FDA approval) and use strict FDA mandated endpoints.[4]

At the time of writing (February 2016) the Cochrane Wounds Group has published 125 systematic reviews of wounds-related interventions.[12] These reviews are periodically updated as new research is completed. Twenty-six of these reviews address treatments for leg ulcers. Unfortunately most of these reviews are unable to provide a clear message for decision makers due to the poor quality of the primary research. One strength of Cochrane reviews is they use a standardized, systematic approach to assessing the quality of the evidence, including the risk of bias in the primary studies. The Cochrane risk of bias tool was also used in a study of 167 RCTs of wound interventions. These studies were selected from the Cochrane Wounds Group Specialized Register of Trials on the basis that they were RCTs of treatments for foot, leg or pressure ulcers, were published between 2004 and 2011 and reported in English.[13] Focusing on the 63 leg ulcer trials the first notable deficiency was their small sample size (median of 37 participants per treatment arm).[14] Studies with small sample sizes are associated with inflated treatment effects[15] and conversely also raise the risk of a Type II error (not detecting a true difference between two studies when it exists). To give some context to the consideration of sample size, if we want to compare two treatments for VLU healing, and expect 60% complete healing at 3 months' follow up with our standard care group and want to detect an improvement to 75% complete healing at 3 months with our new treatment (at 80% power and a significance level of 0.05) we would need an overall sample size of 330 (with continuity correction). If we wanted to maintain statistical power in the face of possible losses to follow up we would need to inflate this further (e.g., by 10%). If we want to increase our power to 90% we would need a sample size of 432 overall (216 in each group).[16] Obviously we would need an even larger sample size to detect a smaller difference in healing. In summary, there is an abundance of evidence that leg ulcer studies do not meet international benchmarks in terms of sample size, adequate reporting of studies, and internal validity.

It is important to realize that the subjects enrolling in an RCT are not randomly selected from the community at large. Not everyone volunteers for an RCT so it is possible that the results of an RCT might not generalize to the general population of people with an illness. The extent a clinicians' patients' resemble the study population may help predict whether the same degree of efficacy and safety will be seen in a particular patient.[5] After RCTs are carried out to help show "if an intervention can work" under ideal study conditions, **effectiveness** studies are then performed in "real life" populations to determine whether an intervention works in a broader population. Additional attempts to make RCTs more generalizable include pragmatic study designs, which rely on more relaxed requirements than the conduct of an RCT thereby allowing the study to become very large and more like routine medical practice. **Nonexperimental study designs** are often observational and include studies like cohort studies, case-control studies, and cross sectional studies. These studies tend to be larger than RCTs and less expensive to conduct particularly if they use previously collected data. Observational study designs are not without their problems when used to estimate the relationship between exposure to a treatment (e.g., a wound dressing) and the outcome healing. Such studies are highly susceptible to selection bias (treatment allocation not at random but heavily influenced by the particular patient and their wound) and detection bias (the collection of data on outcomes being influenced by the knowledge of the treatment). Moreover it is likely to be difficult to understand or estimate the influence of these and other biases on the results of the studies and therefore impossible to correct. However, for many diseases and in many circumstances (like understanding the natural history of an illness) they may represent the best evidence available. Because these studies tend to observe patients and healthcare providers in their routine practice settings, the results from observational studies are often thought to be more generalizable or reflect the effect of an intervention under routine conditions. Expert opinion is also a type of evidence that can be used to inform medical decisions.

When choosing an intervention, most commonly a clinician wishes to choose between interventions as opposed to between an intervention and standard care or placebo (which is often studied in efficacy trials). Studies, which compare interventions, are called comparative efficacy or comparative effectiveness studies, depending on design and the population studied.

This provides a direct comparison of existing health care interventions to determine what works best for which patients under which circumstances and which have the greatest harm and risk.

SPECIFIC CONSIDERATIONS IN VENOUS ULCER RESEARCH

Between 1 and 2 percent of the population over the age of 65, have a VLU making it among the most common chronic wound. At this time only one therapy has received FDA approval specifically to treat and heal VLUs.[17] The failure of new products to receive FDA approval was foreshadowed by a study published in 2003 by Bennett et al.[18] that described a series of growth factors that had been shown to enhance wound repair in animal models of chronic wounds but most often failed to show efficacy in human trials. The cause of the failure of these products to gain approval is not known, although many have opined that a reason could be due to inconsistent disease definitions. This concern was documented by a recent review of VLU[3] that noted that there was a lack of standard definitions of VLU in the studies of the treatment of VLU. The definition or diagnosis of VLU varies from guideline to guideline.

These guidance documents tend to define VLU either based on clinical presentation or based on the confirmation of anatomic/structural venous abnormalities. Most clinical trials that have been published on advanced wound care

for the treatment of VLU have based the diagnosis of VLU on clinical findings and location.[4] However, as early as 2006 the Wound Healing Society defined VLU as ulcers of the lower extremity that may be caused by elevation of ambulatory venous pressure, referred to as "venous hypertension," which they defined as a measurable structural alteration in the venous system of the lower extremity.[19,20] A similar definition of a VLU, was recently proposed by the Society of Vascular Surgery and the American Venous Forum.[7] This definition is based on expert opinion alone and there is lack of research demonstrating that an anatomically based definition of VLU is better than a clinical definition with regard to patient outcomes. In all cases, the definition of VLU also includes the caveat that the affected limb(s) has adequate arterial flow.

While these definitions appear to be similar they are not. It is known that not all individuals who have clinical findings of a VLU also have anatomic abnormalities.[21,22] Since most natural history studies and most clinical trials of VLU have used the clinical definition, the results of these studies may not generalize to the anatomic based definition. Furthermore, it is likely that most practitioners use the clinical definition and it is not clear that it is even possible to conduct anatomic testing of the venous system in all health care settings. This does not mean the VLU definition should not be anatomically based, but before we change, we must realize that it will cause downstream changes to much of what we currently claim to know about VLU.

At this time it might be prudent to define leg ulcers as the following: a VLU is a wound of the lower extremity in an individual with adequate lower extremity arterial flow.

The wound should be located in the gaiter area with clinical signs of venous disease; and a *VLU with confirmed anatomic venous disease* is a wound in an individual with anatomic or structural defect confirmed by several modalities. These modalities include but are not limited to duplex ultrasound or plethysmography.

These issues of experimental design and obtaining the best data will be increasingly critical to health care providers because clinical decisions have direct financial impact. These data determine value of an intervention to health systems and place health systems at risk in the context of effectiveness and risk. At the University of North Carolina, algorithms based on evidence such as The American Venous Forum VLU guidelines are currently serving to help direct decision making. The ultimate utility of clinical interventions is the clinical outcome; recent publications call for standardized outcomes measures as the most effective means of judging the utility of clinical interventions.[23]

SPECIFIC DEFICIENCIES IN VENOUS ULCER RESEARCH

As has been conclusively demonstrated the quality of clinical research on VLUs often do not meet current evidence based standards. In addition to a controversial definition of VLU there are multiple specific shortcomings.[1–4] Wound measurements are imprecise. Individual investigators use a variety of parameters including manual linear measurements, planimetry and volume based assessments. There may be variation in measurement between investigators and between centers and observational bias by interested observers. Clinical descriptions of the ulcers may be incomplete. Adequate photo documentation is not universal.

Outcomes of Wound Healing or Wound Healing Rates are defined differently among trials, and the duration of trials varies significantly. There is consensus that the currently used FDA definition of 100% healing by 24 weeks may be too restrictive. Similarly, there is no consistent definition of what constitutes a wound recurrence for clinical trials purposes. There needs to be a consistent definition of what constitutes wound healing in a clinical trial, or in clinical practice in general.

Quality of Life Measures often lacked metrics for pain and morbidity. There was inconsistency among studies regarding measures utilized to quantify these parameters. With the increased realization that venous ulcers impact direct and indirect costs and family ecosystems, standardized and quantifiable measures are critically needed as outcomes.

Methodological Issues. The clinical trials reviewed have been beset by multiple methodological challenges, including: randomization methods that were not present or minimally described; comparisons between experimental groups were highly biased; lack of sample size calculations resulted in underpowered study designs; poor blinding of patients and/or evaluators; high or unreported attrition rate; lack of stated funding source in manuscripts which might have compounded the risk of bias; inadequate methods to study sequential treatments; insufficient models to study combinations of interventions; lack of description of methods to recruit patients and appropriate control groups; non standardization of duration of observation and unsophisticated methods of statistical analysis.

Among presenters and attendees at our meeting, these challenges were felt to be generally applicable criticisms to clinical wound healing research independent of pathophysiological cause.

IMPROVING CLINICAL ENDPOINTS; COOPERATION WITH THE FDA

The concept of refining and expanding clinical endpoints for wound care research and device/drug approvals was readdressed in October of 2012, when the Association for the Advancement of Wound Care (AAWC) became aware of a newly formed FDA Inter-Center Wound Healing Working Group [ICWHWG] that was charged with updating the content of their 2006 "*Guidance for Industry Chronic Cutaneous Ulcers and Burn Wounds—Developing Products for Treatment*."

This provided a unique opportunity to improve the quality of clinical research on leg ulcers. Previous work by Drs. Kirsner, Eaglestein, and Robson identified the number of wound healing endpoints as contrasted with common cancers; their publication demonstrated that wound healing device approvals have only one accepted clinical endpoint while cancer has many.[24]

AAWC, working with these authors prepared a presentation of their research and shared this data with the FDA-ICWHWG in early 2013. Subsequently, the Wound-care

Experts/FDA-Clinical Endpoints Project [WEF-CEP], was formalized. In April of 2014, the official WEF-CEP initiative, after multiple meeting with the FDA, was broadened when President Driver of the AAWC, invited President Gould of the Wound Healing Society (WHS) to collaborate on this project. The project remains a collaborative effort between the FDA, the CMS and multiple societies and associations in the wound healing community. The goal being to identify and recommend additional meaningful endpoints to be used in research studies for approval of medical devices, technologies and drugs to improve clinical decision making.

This project hopes to: clearly define primary vs. secondary endpoints, determine appropriate power for studies that will support the primary and secondary endpoints, and identify validated tools to measure the proposed endpoints. Additional challenges include educating clinicians about the FDA regulatory processes, promoting acceptance of "alternative" endpoints generated by the wound-healing community, and advocating for patient-centered outcomes.

The FDA guidance document for industry drafted in 2006, stated approval for wound and burn devices, drugs and biologics was based on complete healing as the primary endpoint. The guidance document however, does discuss accelerated wound closure, facilitation of surgical wound closure and quality of healing in terms of appearance and function, but the emphasis is on complete wound closure as the unitary outcome. The document does not address products that are not intended to achieve full wound closure, e.g., debriding devices or agents, antimicrobials or diagnostics. Furthermore, the guidance document reflects the state of science prior to 2006. New research, focused on specific phases of healing with targeted therapies, will require endpoints that are responsive to new technologies and reflect the advances in understanding the cellular mechanisms involved in wound healing. There are a number of challenges including: new endpoints need to be clearly defined that are operational, measurable, reliable, and reproducible with relevance to wound type and phase of healing/or complete healing. Endpoints should reflect patient issues and concerns while remaining malleable enough to reflect advances in technology. To that end, the WEF-CEP initiative developed an extensive multiprofessional clinical survey to identify endpoints that are meaningful to wound care clinicians and their patients. There have been four surveys with multidisciplinary wound care providers. To date 642 completed surveys have been analyzed and two different lists of endpoints have been assembled; those that are important for measuring the success of a new treatment and those that make a significant difference in the lives of patients.[8] It is interesting that the lists do not fully overlap.

THE ROLE OF PATIENTS IN CLINICAL RESEARCH

Leg ulcer treatment presents a number of substantial challenges to patients and providers. Management is: costly in terms of resources, occurs over prolonged periods of time, has high recurrence rates and often provides little help to patients in support of social problems or substantive advice and management on prevention of recurrence of leg ulcers.[25,26] Many patients have lived with open wounds for many years and endured endless cycles of healing and breakdown. These factors can contribute to depression, loss of esteem and self-neglect.

The trend today, especially in the United Kingdom, is for public involvement in research being carried out "with" or "by" members of the public rather than "to," "about," or "for" them.[27–29] This trend began in 1995 when the *BMJ* argued "patients should help to decide which research is conducted, help to plan the research and interpret the data, and hear the results before anybody else."

The issue was addressed more recently in recommendations of the (UK) NHS National Institute for Health Research[30] to bring together researchers, patients, clinicians, charities and voluntary organizations, careers, and the public to make participation in research an option for every NHS patient.

In the UK this has resulted in patients working with research funders to prioritize research, offering advice as members of a project steering group, commenting on and developing research materials, and undertaking interviews with research participants. Researchers should be challenged and reassured by the prospect of developing new ways to deliver evidence-based practice in partnership with their patient/client group. There is now the view that patients are, in their own way, experts in the experience of living with a wound and have the potential to provide a rich source of information based on their personal experience to help enrich the usability of research methodologies and provide feedback on outcome measures. Their thoughts and perceptions can contribute to a robust protocol, as they will have a good idea of which research questions are worth asking, and when a question should be framed differently. The FDA agrees with this approach in their published opinion in JAMA in November 2015.[31]

Research design should accommodate different ethnographic, societal, temporal, and financial realities toward chronic leg ulcers. This joint patient/researcher partnership approach could help the investigator to discover how patients comprehend and interpret the treatment they receive. Research methods should consider: observations, interviews, demographic analysis, and investigation of life-histories in face-to-face interactions in appropriate and hospitable settings. Charities and patient groups across the UK play vital roles in supporting and informing those affected by a given disease or condition and broaching the subject of involvement in a research study or clinical trials (www.patientsinresearch.org). The term "research" to an individual requiring health care intervention can invoke images of complex, expensive solutions, yet the reality is often very different. In all cases, an approach that combines patient centered research and dialogue has the greatest chance of succeeding. Researchers must be sensitive to perceived conflicts between the patient and the academic team and these differences should be resolved at the outset. Also, it must be acknowledged there will inevitably be resistance on the part of some researchers to the prospect of changing culture and clinical research practice by involving patients from the outset of a study design. Nevertheless, that time has come and todays investigators need to increase awareness of the need of the patients they are studying. In the United States the recent creation of the US Agency, Patient-Centered Outcomes Research Institute

(PICORI) was established to enhance translational research and encourage patient involvement in clinical research.

DEVELOPMENT OF AN ACTION PLAN TO IMPROVE CLINICAL RESEARCH IN LEG ULCER HEALING

The organizing group, after extensive debate, formulated a series of proposals and distributed them in advance, to the entire group of meeting attendees. In the second half of the meeting these, predominantly dichotomous statements, were voted on by the participants anonymously, using personal hand held modules (CLiKAPAD). Statements were quantified and declared adopted if 75% of the attendees were in agreement. If the percentage in agreement did not reach 75% acceptance, the statement was modified and revised to obtain 75% agreement. If after multiple revisions 75% could not be obtained the statement was discarded. The final statements and exact percentages for approval are listed in this report. If there was extensive discussion of the statement the essence of the conversations is summarized after presentation of the result.

1. Are the present diagnostic and assessment tools sufficient for clinical investigation in wound care? %Yes 31% No 69%. Rejected. This statement was modified repeatedly but the participants felt the statement was imprecise because of: variability in the skill of the investigator(s), the effectiveness of the clinical measurements, and the variation in the accessibility and quality of specific tests. Statements 2 and 3 were substituted.
2. Are there adequate parameters to segregate wounds into common clinical types in an older population (greater than 65 years of age) that may have multiple comorbidities? Yes 21% No 79%. This question speaks to the need for improvement in diagnostic and clinical assessment tools in the older population.
3. Would clinical trials in wound care benefit from improved diagnostic assessment tools? Yes 100% No 0%.
4. Should there be a standard data template for collecting clinical research information for the major types of leg ulcers which are modifiable for particular types of wounds Yes 96% No 4%.
5. Should the Wound Healing community adopt and if necessary validate existing tools for Quality of Life, Mobility etc. for patients with leg ulcers to assess changes in morbidity? Yes 100% No 0%. There was extensive discussion regarding this statement. Some in the audience thought present methods were inadequate while others suggested that there were useful data base protocols; regrettably, all agreed there was no consistent utilization of existing protocols. Some participants suggested that cultural and international values effect quality of life assessments. It was agreed on that wound-healing researchers should validate and modify presently available protocols to insure they are appropriate for leg ulcers, or if necessary, introduce new parameters. Furthermore, it is appropriate to modify such tools to recognize national and cultural perspectives.
6. Surgical interventions for chronic leg ulcers pose unique investigative challenges; should wound-healing researchers consider evaluating clinical research approaches for surgical interventions? Yes 85% No 15%. This statement generated extensive discussion regarding the specificity of the term surgical interventions. Consequently, the following 2 statements were introduced.
7. Device interventions for chronic leg ulcers pose unique investigative challenges should we define the clinical research approaches for these interventions? Yes 96% No 4%.
8. Procedural interventions for chronic leg ulcers pose unique investigative challenges should we define the clinical research approaches for these interventions? Yes 86% No 14%.
9. Should the Wound Healing Community require the reporting of funding source and conflicts of interest for presentations and publications on wound healing? Yes 100% No 0% Extensive comments were made from the audience that studies performed in major university settings always required statements of conflict of interest and registration in research registries; such actions are not universal. Furthermore, in a number of CERs, numerous papers were discarded because the source of funding was not listed.
10. Should the Wound Healing Community require prospective registration of trials on national or international registries? Yes 100% No 0%.
11. Should the Wound Healing Community attempt to improve clinical research in wound healing research generally with the first focus on improving VLU research? Yes 100% No 0%.
12. Should we organize a wound care clinical trials network, similar to cancer cooperative groups, that ensures quality control within and between centers? Yes 96% No 4%. Comments from the audience suggested this is a formidable challenge organizationally and requires substantial financial support. Nevertheless, such a research network should be a long-term goal.
13. Should there be a research core group that can provide guidance and/or develop model guidelines for wound healing research generally and leg ulcer research specifically using existing standards? Yes 96% No 4%. Comments were made that such a core group were to act as consultants using present international standards and not as "statistics police."
14. Should such a core research group suggest specific competencies expected for persons preforming clinical wound healing evaluation research? Yes 67% No 33%. Rejected, because the vote did not reach 75%; the concern was that such a group could become a regulatory authority.
15. If a clinical trial network is developed, should there be site requirements to gain admission to such a network? Yes 100% No 0%. The difference between this response and the previous question[14] relates to the ability to specify requirements for admission and would include not only qualifications for the PI but include other health care providers such as nurses, fellows, etc., for their specific tasks. Furthermore, it institutes a standard quality-monitoring program.
16. Should the network be funded and managed Yes 96% No 4%.

17. Is there an organization or consortium of existing organizations, free of conflicts of interest, that could house such a center Yes 20% No 80% This indicates that at the present time the participants felt there was no existing organization that could house such a network.
18. Could there be an organization or consortium of organizations, free of conflicts of interest that could house such a center? Yes 85% No 15%. The transcript of the meeting details a prolonged discussion of organizational suggestions. There appeared to be general agreement that a new core group selected from present wound care and research leadership, be identified to develop specific organizational and needs guidelines. Individuals serving in this second small Core Group should be proven leaders in wound care, in deliberations free of conflicts of interest, energetic, and committed to improving wound care research. A second broader consortium of representatives from interested wound care and research organizations should provide advice and direction to the core group. The goal for the core group should be formulating a specific organizational plan to develop a robust, durable mechanism to improve the quality of clinical wound healing research.
19. Could patients be involved in clinical wound research protocol development? Yes 77% No 23%. This provoked an extensive discussion. Our English colleagues reported that national authorities required patient participation in the design and implementation of clinical wound healing research. Furthermore, patient input facilitated recruitment of patients in studies and enlisted patients as advocates for wound healing research. The recently created US Agency Patient-Centered Outcomes Research Institute (PICORI) has a focus on facilitating patient input into research. The FDA has recently published a paper in JAMA advocating for patient involvement in clinical research.[31] Finally, there is increasing emphasis throughout the medical literature advocating the patient perspective be included in clinical research.
20. Could patients be involved in protocol development Yes 74% No 26%. There was some anxiety that patient who are not clinical researchers might not understand research goals or methodologies.
21. Could patients be involved in interpretation of study results? Yes 56% No 44%. This suggestion was rejected on the grounds that interpretation of data was a sophisticated scientific research skill.
22. Could patients be involved in the implication of study results? Yes 80% No 20%.
23. Could patients be invited to comment on plain language summaries or on reviews prior to publication? Yes 96% No 4%.
24. Should we develop a patient advocacy network, similar to cancer, which educates patients about the research process, types of protocols and new developments? Yes 96% No 4%.

CONCLUSION

The present status of clinical leg ulcer healing research was reviewed by 25 experts over 2 days on September 28 and 29, 2015. The discussions were recorded for accuracy and anonymous voting technology was used to quantify opinion. The first phase of the meeting analyzed recent multiple CER and information prepared by the Cochrane Wound Healing Group. These data established that published clinical wound healing research frequently does not meet present (2015) evidence based standards and improvement in quality is a high priority. Specific areas requiring work were highlighted and approaches to overcoming existing challenges were proposed.

The second part of the meeting was spent outlining an action plan to resolve present deficiencies. There was agreement that clinical wound healing research needed improvement especially in the older population with a high frequency of comorbid conditions. A standardized model template for collecting information about diagnosis and evaluation of the effect of interventions on healing of all types of leg ulcers was considered a high priority. Such a model template could be modified depending on the specific etiology of the leg ulcers. It was considered important to establish better, generally agreed on tools, to establish degree of morbidity. Surgical interventions including procedures and devices need special attention. There was universal agreement that sources of funding and conflicts of interest needed to be disclosed in presentations and all publications. All clinical research studies should be registered with appropriate authorities. There was substantial enthusiasm for a clinical research network with quality standards for membership and an advisory research core available to investigators. Such a network should be funded and actively managed to insure long-term viability. The governance of such an entity needs to be established by the wound care community. The present trend to integrate patients into the clinical research process was endorsed and there was enthusiasm to develop patient advocacy for wound healing research. Over the next 6 months, steps will be taken to implement these recommendations.

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ATTENDEES AT MEETING

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Cohen, MD, Scott Covington, MD FACS, CWHS, Carolyn Fife, MD, John Lantis, MD, Shaden Marzouk, MD, Jeffrey Nelson MD, Marcia Nusgart, RPh, Nathan Parsons, MD, Tania Phillips, MD, Joe Rolley, MD, Pamela Scarborough, PT, DPT, MS, CDE, CWS, Randy Schwartz, MD, Thomas Serena, MD, Terry Treadwell, MD, Hung Tseng, PhD, James Wilcox, RN, BSN, ACHRN, WCN.

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