Author's response to reviews

Title: Cost-effectiveness of clostridial collagenase ointment on wound closure in patients with diabetic foot ulcers: economic analysis of results from a multicenter, randomized, open-label trial

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Author's response to reviews: see over
A Note to Our Reviewers...
The authors would like to thank the reviewers for taking the time to evaluate our manuscript. The comments received were insightful and the resulting revisions have made this a stronger research report.

Reviewer: 1
I have been asked to review this paper primarily from a wound care perspective. Given I am not commenting in detail on the modelling used in this paper I will list my comments below as a narrative as opposed to using the specific headings above.

1. **Comment:** I don’t believe this paper will hold wide appeal for the readers of JFAR. The modelling used is extremely technical and as described by the authors is not easily understood by the ‘lay person’. I feel there are issues with the methods used to evaluate the wound care product that is the subject of the economic analysis and although I have only a very basic understanding of the Markov model used for forward cost projection I am not convinced that the model took in to account the truly multifactorial nature of DFUs. There are several variables that determine whether a DFU re-occurs (biomechanics, off-loading, footwear, compliance) or stays healed and I wasn’t convinced that the modelling takes all of these in to account. Other comments/queries are listed below:

   **Response:** The authors respectfully disagree. While we agree that DFUs are multifactorial in nature, the purpose of this study was to assess if clostridial collagenase ointment with an enzymatic debriding agent was an effective adjunct therapy to serial sharp debridement using results from a prospective, randomized controlled trial conducted in the U.S. While the model is limited to the clinical trials protocol, clinicians who participated in the trial were allowed to use their own self-selected treatment regimens. Clinician’s treatment regimens were selected in order to emulate ‘real-world’ clinician practice patterns and preferences. Furthermore, additional information regarding offloading has been added to the study for clarification. Since the perspective of this study was the third-party payer (specifically the Centers for Medicare and Medicaid Services), certain costs for DFU (ie, offloading) were not included, because the patient is responsible for these direct costs and not the third-party payer.

   “**Investigator’s treatment regimens were selected in order to emulate ‘real-world’ clinician practice patterns and preferences.**”

   “**The costs of offloading were not included in this analysis. CMS does not cover reimbursement of offloading devices for the treatment of DFU, except the Total Contact Cast (TCC) [40]. Since TCC was not used in this trial, costs for offloading devices were not included in the economic model as they are a direct cost to the patient.**”
2. **Comment:** "CCO is often used......." I am not aware of this product being available in Australia so I feel this comment is not accurate. How do the authors judge how widely it is used elsewhere?

   **Response:** This sentence has been re-worded in the abstract and information regarding CCO utilization in the hospital outpatient departments in the U.S. has been added to the Introduction.

   “A pharmacoepidemiology analysis of 96 hospital-based outpatient wound centers revealed that, of 21,677 DFUs treated from 2007-2012, approximately 17% received CCO [28].”

3. **Comment:** The reference to the effectiveness of Santyl on Pressure Ulcers is not transferable to DFU as the etiology and physiology of the wounds is very different.

   **Response:** We agree with the reviewer that the etiology and pathophysiology of pressure ulcers and diabetic foot ulcers are vastly different. However, the techniques used for the removal of necrotic tissue are similar across wound types. The physical removal of necrotic tissue is independent of wound etiology. The pressure ulcer reference was provided to demonstrate that in a randomized-controlled trial CCO provided complete and effective debridement of necrotic tissue in pressure ulcers. The point of reference was to demonstrate the CCO is a safe, effective and economical debriding agent for chronic wounds.

4. **Comment:** As the authors discuss the sample size is small.

   **Response:** We agree with the reviewer that the sample size is small. This has been listed as a limitation in the Discussion.

   “The clinical data used in this analysis were derived from a clinical trial conducted in 7 outpatient sites in 5 states with a relatively small patient sample (55 patients); therefore, the results cannot necessarily be generalized to other dressings, health care settings, or to wounds of other etiologies.”

5. **Comment:** Both the treatment and follow up periods are short in terms of provision of wound care and it is not clear to me what care if any was provided in the follow up phase.

   **Response:** The authors apologize for the confusion. Information regarding the follow-up phase has been added to the Methods.

   “Treatment was given for 6 weeks and patients were followed for up to an additional 6 weeks or to complete wound closure, whichever occurred first. During the 6-week follow-up phase all ulcers (in both treatment groups) which had not closed received daily dressing changes consisting of a foam primary dressing and a single layer cast padding held in place with a self-adherent bandage. All patients agreed to wear an offloading boot or other appropriate device.”

6. **Comment:** According to the results the cost of care provided was virtually the same during the actual study period and only swings in favour of CCO during the economic modelling,
this will be of little interest to the working clinician who will work in a health care environment that is very focused on short term outcomes only.

**Response:** The authors respectfully disagree. As the reviewer previously mentioned, DFUs are multifactorial in nature. The longer a wound remains open and unhealed, the greater the risk for infection, decreased quality of life and higher cost of care. Although the initial cost for some advanced therapies is higher, if the treatment provides additional clinical benefit and is able to close the wound earlier, clinicians can incorporate these treatments into their current practice regimens. The relevance of health economics to the clinician has been added to the Introduction.

“As healthcare costs continue to increase at an exponential rate, it is important that clinicians understand the cost-effectiveness of the care they are administering to wound care patients so that treatment that provide increased clinical benefit and are considered cost-effective are utilized [15].”

7. **Comment:** The dressings used on the control group are not necessarily appropriate comparators with CCO as according to the authors CCO is primarily a debriding agent whereas Silver dressings including Silver Sulphadiazine which made up over 50% of the control group are for use in managing infection and exudate. So in essence the authors are not comparing like with like. Given that Silver based dressings are also very expensive does this perhaps bias the comparison of costs with use of CCO? The use of the Hydrogel in one of the control group participants would have made an interesting comparison as it is used as a form of debridement and also is a lot cheaper than anything silver based so may have come out in favour of the control.

**Response:** The reviewer is correct in his statement that we are not comparing “like with like”. However, the comparison of “like with like” was not the objective of this economic analysis nor was it the objective of the clinical study on which the economic analysis was based. The purpose of this study was to demonstrate that the clinical synergy achieved by combining serial sharp debridement with CCO improves outcomes to such a degree that adjunctive CCO therapy adds no additional cost to wound care and can be cost saving.

We respectfully disagree with the reviewers comment that silver dressings are very expensive and may bias the results in favor of CCO. A quick check on the U.S. cost of silver sulfadiazine relative to CCO shows that silver sulfadiazine costs approximately $10.62 per 50 gram container ($0.21/gram) compared to $199.77 per 30 grams for CCO ($6.66/gram). This study used 2013 prices, where the cost of silver sulfadiazine was $9.94 per 50 gram container ($0.20/gram) compared to $182.76 per 30 grams for CCO ($6.10/gram).

Regarding the reviewer’s statement on hydrogels, the reviewer unknowingly supports the conclusions of this study. Hydrogels are often promoted as “autolytics” with little to not evidence to support this claim. When a hydrogel was directly compared with CCO in a prospective RCT, as described in our reference to the pressure ulcer study, the hydrogel was proven to be clinically inferior to CCO. In the pressure ulcer economic analysis the hydrogel was determined to be more expensive overall due to its ineffectiveness as an autolytic debriding agent in spite of its low cost relative to CCO. Regarding the cost of the
comparators, all of them are inexpensive relative to CCO and thus comparator costs do nothing to bias the economic results in favor of CCO. The comparator cost information is presented in Table 2 Unit Costs in the manuscript.

8. **Comment:** During the treatment phase of the study the wounds were dressed daily however economic modelling was based on weekly dressings?
   **Response:** Weekly transition rates incorporated all daily dressings and cleanings that occurred throughout the week. This information has been clarified in the Methods.
   “Weekly transition rates incorporated all daily dressings and cleanings that occurred throughout the week.”

9. **Comment:** This maybe just my ignorance with relation to the modelling however I am not sure why death is included as part of the analysis?
   **Response:** Since results were extrapolated out to 1-year, death was included in order to emulate a ‘real-world’ scenario and account for the overall mortality rate of the U.S. population over 1-year for individuals 35 years of age and older. This information has been added to the Methods.
   “Since results were extrapolated out to 1-year, death was included in order to capture the overall mortality rate of the U.S. population for individuals 35 years or age and older.”

10. **Comment:** Looking at the wound measurements recorded it appears the wounds treated with CCO started to increase in size again post treatment phase however those in the control group stayed the same, so again it doesn't appear the use of CCO is more beneficial until the modelling projection is undertaken.
    **Response:** The reviewer is correct in his observation that in the clinical study by Motley et al. (WOUNDS 2014) that the CCO group showed a slight quantitative wound enlargement by approximately 0.25 cm$^2$ once treatment with CCO ended. However, this enlargement was not statistically different from the end of treatment measurement and the “end of study” measurement that occurred 6 weeks after CCO was discontinued. The results presented in the Motley et al. graph that the reviewer is referring to are that the CCO group demonstrated a significant reduction in average wound size at both the “end of study” and “end of treatment” assessments while the control group showed no statistical decrease in wound size at either assessment. Additionally, and most importantly, we address the uncertainty of the CCO closure rates in the sensitivity analysis. The tornado diagram illustrates that a 50% variation, both positive and negative, in CCO closure rates does not change the overall conclusions of the economic analysis.

The reason for modeling clinical trials is to estimate the total cost per episode of care. Clinical studies, unless specifically designed to do so, rarely look at the complete episodes of care. Randomized clinical trials stop collecting data at some arbitrary time point. Health economic analyses attempt to capture the downstream costs of patient care not adequately captured during short clinical studies. Consequently, modelling of randomized clinical trials is recognized as the best method to capture the total episodic costs of care.
11. **Comment**: Given the authors are discussing "epithelialised weeks" are they suggesting that CCO promotes generation of more robust new epithelium that is less likely to re-ulcerate?

**Response**: As described in the manuscript the term “epithelialized weeks” represents the expected (average) number of weeks that the wound was closed over the 1-year time horizon. At no point in the manuscript do we make any inference that wounds treated with CCO are any more, or less, likely to re-ulcerate. Epithelialization is the formation of an epithelial barrier between the wound and the environment. Once a wound epithelializes the cost associated with wound care typically ceases. We chose to use epithelialization as the endpoint, as opposed to healing, because healing continues well after the wound epithelializes. Once the keratinocytes cover the wound they secrete proteins that form the new basement membrane, thus the process of contraction and remodeling begin and healing continues. Since this is an economic analysis we chose epithelialization because it represents the outcome at which both wound care and wound care costs cease to be a factor.

12. **Comment**: There is no detail on the types of off-loading used- was this factored in to the cost of treatment?

**Response**: This is a good point. Information regarding offloading has been added to the Methods.

> “The costs of offloading were not included in this analysis. CMS does not cover reimbursement of offloading devices for the treatment of DFU, except the Total Contact Cast (TCC) [40]. Since TCC was not used in this trial, costs for offloading devices were not included in the economic model as they are a direct cost to the patient.”

**Level of interest**: An article of limited interest

**Quality of written English**: Acceptable

**Statistical review**: Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests**: I declare that I have no competing interests.
1. **Comment:** The method compares the use of CCO with a control group with five different treatments a number, in my opinion, are a poor choice eg. wet to dry gauze, SSD cream only one patient in the control group was treated with a Hydrogel a known agent for wound debridement.

   **Response:** This is a good point. The purpose of the investigator-selected standard care group was to emulate ‘real-world’ clinician practice patterns in wound care to show the large variance that exists with regards to treatment preferences. Additional information has been added to the Methods. However, we have added this as a limitation to the study in the Discussion.

   “Investigator’s treatment regimens were selected in order to emulate ‘real-world’ clinician practice patterns and preferences.

   ...At the investigator’s discretion, a hydrogel could be used if deemed necessary to maintain a moist wound environment. Wound area was measured at each study visit by using the ARANZ Silhouette™ digital image capture and wound measurement device (ARANZ Medical, Christchurch, NZ).”

   “Furthermore, this investigation was unblinded. This was chosen intentionally to allow clinically relevant standard care in the control group, with bias controlled through randomization and the use of a wound measurement device (ARANZ).”

2. **Comment:** In relation to the patient selection an ABI is a good measure to arterial supply however an alternative given is the waveform with specific details eg. Triphasic..

   **Response:** We agree with the reviewer that ABI is a good measure to arterial supply. In cases where ABI was unable to be measured, per the clinical trial protocol, a Doppler waveform consistent with adequate blood flow to the region of the foot with the target ulcer was considered an acceptable form of measurement. This information has been clarified in the Methods.

   “Key eligibility criteria included that patients have adequate arterial blood flow as evidenced by the ankle brachial index (ABI) of >0.7 and ≤1.1, be able to follow instructions and perform dressing changes at home or have a caregiver willing to perform dressing changes according to the protocol, and be willing to use an appropriate offloading device when necessary to keep weight off of the foot ulcer. Alternatively, if ABI was unable to be measured, a Doppler waveform consistent with adequate blood flow to the region of the foot with the target ulcer (biphasic or triphasic) was considered acceptable.”

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**
'I declare that I have no competing interests' below
Reviewer: 3
I have considered all the guidelines and find this study to be of acceptable standard, deserving publication.

Major revisions:
1. **Comment**: Further text is needed, even one or two sentences, about the study perspective i.e. of third-party payers. This text should specifically identify third party payers (e.g. health insurance companies and government agencies) and the types of costs that are appropriately included and excluded. Suggest that this should be undertaken on page 13 at the beginning of the section, 'Economic Outcome Definition'.
   **Response**: This is a good point. The third-party payers section under ‘Economic Outcome Definition’ has been expanded.
   "Given that the cost of care for Medicare beneficiaries with a DFU exceeds $33,000 annually for total reimbursement of all Medicare services [39], the third-party payer of interest was the Centers for Medicare and Medicaid Services (CMS).”

2. **Comment**: Page 12: probabilities were extrapolated to 52 weeks using equations appearing in Briggs (2000, 2002, 2003). Currently the approach to extrapolation is left up to the reader to pursue. Also the approach is not justified. The authors should be explicitly show the equations they used, even if in an appendix. They should also justify the use of these equations. They should also do the same regarding the probability of ulcer recurrence as derived from Persson et al (2000).
   **Response**: Supplementary Figure 1 provides the equations for event rate and transition probability calculations. Additional information regarding the probabilities has been added to the Methods.
   "These probabilities were extrapolated to 52 weeks assuming cumulative probability rates over time using equations described by Briggs et al. [34-36] [Supplementary Figure 1, Additional File 1]. Using this time-dependent Markov model provides a robust method to modeling a chronic illness, since the assumption of constant transition probabilities is considered too restrictive for applications in healthcare [36].”

3. **Comment**: Page 14, Sensitivity Analysis: the authors should give reasons for why they varied the parameters as they did.
   **Response**: Thank you for pointing this out. Justification for why parameters were varied has been added to the Methods.
   "Clinical trials invariably include wounds with a large variety of sizes and shapes. Given the uncertainty that exists in rates of healing with wounds of various sizes and shapes [41], a ±50% compared with the base case was utilized to increase the robustness of the model’s results.”
4. **Comment**: Pages 14-15 Sensitivity Analysis: A basic description of the Monte Carlo modelling is required (even just one or two sentences) - number of simulations, software etc.

   **Response**: A basic description of the Monte Carlo modelling has been added to the Methods for clarification.

   "A probabilistic sensitivity analysis was performed to evaluate parameter uncertainty by using second-order Monte-Carlo simulations of 10,000 trials in which all model inputs were varied simultaneously. This method is comprised of generating a “dummy” data set by resampling with replacement (ie, randomly selecting 1 patient at a time) from the original data set and repeating this random patient selection until the dummy data set reaches the same size as the original [32]."

5. **Comment**: Figures: None of the figures have headings, please provide.

   **Response**: The authors apologize for the confusion. Per the editorial requirements of the journal, the Figure legends are located on page 33 near the end of the manuscript.

**Minor revisions:**

6. **Comment**: Figure 1 is confusing: For the treatment phase, the box labelled 'Clostridial Collagenase Ointment (CCO) + Sharp' is not connected to a box labelled 'Healed Words'. This implies that healed wounds are not noted for the experimental group. Can the diagram be improved accordingly?

   **Response**: Figure 1 has been updated for clarification.

7. **Comment**: Re: page 19, the phrase, 'the therapeutic effect of CCO+SD was approximately 30% greater than for the Control" Should the 30% be 25% (35-28=7)/28=0.25.

   **Response**: Thank you for pointing this out. This value has been corrected to say 25% in the Results and Discussion sections.

8. **Comment**: Supplementary Table 1 should be included in the text close to the Figures 2. It is necessary to see both Figure 2 and Supplementary Table 1 to readily understand the Markov modelling.

   **Response**: We agree with the reviewer that Supplementary Table 1 should be included with the text close to Figure 2. Given the Figure and Table limit of the journal, Supplementary Table 1 will be changed to a new Table 1 and Figure 6 will be changed to Supplementary Figure 2. This will place both of the sensitivity analyses in the Supplementary files.

9. **Comment**: Page 10, section, Economic Analysis: This was the only one of two sections of the entire article where I found the writing cumbersome, due to long sentences with too many clauses. The section is not so much ‘badly written’ - but the paper would benefit from some work on the expression here. The section is very important.

   **Response**: We agree that the writing in the Economic Analysis section was ‘wordy’ and cumbersome. This section has been modified and condensed.
10. **Comment**: Last sentence in page 17, leading into text at the top page 18: This section refers to Supplementary Table 2, which is titled 'Monte Carlo Simulation Results'. For the sake of consistency, suggest making some reference to Monte Carlo Modelling in the text - rather than just 'probabilistic modelling'.

**Response**: This is a good suggestion. The Results have been modified to include Monte Carlo simulation for clarification.

“Results from the probabilistic sensitivity analysis (ie, Monte Carlo Simulation) indicated that the costs for CCO + SSD were lower compared with Control.”

11. **Comment**: Suggest some description on how the findings are pertinent to the policies of third party payers.

**Response**: This helpful comment allowed us to expand upon the relevance of these findings and their applicability to third party payers. Information has been added to the Discussion.

“Findings from the current investigation indicate how the addition of CCO to DFU treatment can reduce the total direct cost of DFU care to the payer.”

“Annual healthcare costs associated with chronic wound treatment in the U.S. approaches $33 billion [44-45]. Overall, the U.S. spends twice as much per capita as the United Kingdom, Sweden, and the Netherlands, yet these countries achieve better overall health outcomes [46]. In 2006 the Tax Relief and Health Care Act was passed, which authorized the establishment of a pay-for-performance program known as Physician Quality Reporting Initiative (PQRI) wherein payment is linked to whether the clinician performs certain tasks in a given time frame for specific patients [47]. Currently there is a PQRI measure relating to diabetic “foot care”, specifically, performing peripheral neuropathy evaluation and prescribing appropriate footwear [47]; however, offloading of existing DFU is not a PQRI measure. As the population ages and the prevalence of diabetes and obesity increase it will be important for third-party payers, such as Medicare and Medicaid, to evaluate the efficacy and effectiveness of treatment practice patterns and PQRI measures in wound care.”

Thank you for allowing me to review this report,

Rod Ling
Hunter Medical Research Institute
Australia

**Level of interest**: An article whose findings are important to those with closely related research interests

**Quality of written English**: Acceptable

**Statistical review**: Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests**: I have no competing interests.