Author’s response to reviews

Title: Spray on skin for diabetic foot ulcers: an open label randomised controlled trial

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Author’s response to reviews:

Thank you for taking the time to review our protocol and for the thoughtful comments. Please find our point by point responses below:

Reviewer: Matthew Malone

Reviewer #1: The protocol for the open label study for an intervention in DFUs is generally of a good standard. It is well written but i do have a few minor suggestions which may help improve the protocol for readership and also for your own thoughts on the study design. the majority of these have been
I do have one major question which was not defined in the protocol. Will this intervention be used in infected DFUs or DFUs with no clinical infection. This is not clear.

We will not exclude patients based on infection status – it is expected that all patients coming in to the tertiary hospitals (Fiona Stanley Hospital and Royal Perth Hospital) included in this trial will have adequate management of their infections and any known infections will be under control before inclusion into the trial. Any infections that may arise during the trial period will also be managed by the multi-disciplinary foot ulcer team appropriately.

Line 54: I think the readership would prefer to look at stats from Australia wide and then also as additional more local data.

We have added 2 more references relating to Australian data on lower limb amputations, see line 60.

Line 56: I would delineate a little more on this to conform to international understanding on minor. Some define minor as below the malleolus and others just confined to a digit or forefoot.

Thank you for your comment. We have changed the wording to say major (above the ankle) and lower (below the ankle). Originally the comment of (usually toes) was to indicate that recurrent amputations are usually due to transfer lesions causing remaining toes to be lost and not a comment about the definition of minor amputations. This definition is reiterated at line 164.

Line 73: I think it may sound better to slightly rephrase this to something like: The metrics of time to wound healing or % of wounds healed at 12 weeks (Sheehan et al) are commonly adopted arbitrary markers used in both research study designs and as a guide to services in benchmarking their practice. Wound healing is a key cost driver and influences the overall economic cost for any DFU intervention.

Thank-you for your comment but I think you may have misunderstood the sentence. The sentence is simply stating that the longer a wound takes to heal (“wound healing time”) the more expensive it is to treat. We feel the current paragraph is succinct.

Line 82: Its not novel and the technology has been around for a little while, it hasn't taken off so much in DFUs because of the cost and the complexity of obtaining the spray and steps required.

Agreed and wording has been changed.

Line 86: I would have thought that active infection would consume the biological components of Recell? You wouldn't graft an infected site?

This was an error and has been rectified. It was a small case series on 4 foot ulcers, not all diabetics and not all infected.

Line 93: Or does it increase the percentage of wounds healed at a given timepoint?

This will be our primary endpoint analyses.
Line 94: I actually think you need to add an entire section with your primary and secondary endpoints? I wanted to help point you to look at experts and previous publications on designing DFU trials:


Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double-blind, randomised, controlled trial. Edmonds M1, Lázaro-Martínez JL2, Alfayate-García JM3, Martini J4, Petit JM5, Rayman G6, Lobmann R7, Uccioli L8, Sauvadet A9, Bohbot S9, Kerihuel JC10, Piaggesi A11.

Primary and secondary endpoint definitions moved to be above the methods section. See line 147

Line 97: This needs to be referenced. Which data was used to calculate power and sample size?

Line 101: How many in each group?

This will be random but should be pretty close to a 50/50 split

Line 109: You need to have a section on how randomisation will occur? 1:1, 2:1, randomisation software??

Rectified. See line 117

Line 115: what type of DFU? Neuropathic, Neuroischemic, Ischemic?

This has not been specified in the protocol because we are not excluding based on type of ulcer. All diabetic foot ulcer types will be considered as long as they fit the inclusion and exclusion criteria. Non-diabetic ulcers will be excluded.

Will you take infected or non-infected DFUs? If so how will you define infection? How will ulcers or infection be graded - what grading system/s will you use please add - WiFi, University of texas, IWGDF/IDSA?

The paper has now been restructured and you can find we will be using WiFi classification system at line 274. As stated above we predict that infections will be under control by time of enrolment.

Line 117: what is RPH - above you label FSH but not RPH

Rectified – see line 114

Line 119: Why 6cm2? Thats quite big and will significantly reduce your recruitment ability.

Agreed. However this wound size was chosen to counteract the cost of ReCell and time taken for the procedure. See line 333 in discussion.

Line 126: No ABPI - TBI or toe pressure?

Although these are measurements collected throughout the trial period we did not want to rely on these
measurements due to their unreliability in diabetic patients (ie most diabetic patients have elevated ABPI due to calcification of vessels).

Line 130: Known Osteomyelitis, Chronic wounds? Acute wounds? Will you want to specify the duration of ulcer so will you only recruit wounds which have been present >3 months etc. If you do not delineate this it has the potential to skew results.

We are not excluding patients based on wound duration or infection. The study was designed to be as inclusive as possible given the other parameters.

Line 141: Why prontosan soak? Why is this needed?

This is the local protocol used for diabetic foot wound care at the recruiting sites.

Line 142: Why ultrasonic debridement? This is not standard care. Debridement with a scalpel or curette is by ultrasonic debridement is providing an additional therapy past that of standard of care and this may influence your outcomes?

Please see line 182.

Why are you swabbing wounds? What will they be stored for?

Wounds will be swabbed for potential further research into wound microbiome.

This wound bed preparation is not very standard. Most standard WBP is sharp conservative debridement and cleansing of the wound with saline. Its pretty standard and will standardise an approach which does not include a list of different treatments all of which could in themselves influence the results:

antiseptic cleanse, hydrogel, ultrasonic detriment.....

This is the standard protocol for diabetic wound care used for inpatients at the recruiting hospitals.

Why on wounds >1cm use NPWT again this in itself can influence your results. There are too many variables before you start the actual REcell treatment that could influence outcome.

We appreciate your comments that this is not the ‘standard’ treatment for diabetic foot ulcers, however this is the standard treatment protocol for diabetic foot wounds at the recruiting hospitals. We understand that it is not common practice however this protocol will be used on all patients before randomisation takes place. If the patient is randomised to the control group – this protocol will likely continue until no longer necessary (e.g. NPWT will be removed when appropriate granulation is achieved, IntraSite conformable will be used until another wound dressing is deemed more appropriate etc).

My take on this is maybe you just need to set the scene a little better and explain in the protocol that prior to any administration of ReCell the wound bed must be to an adequate requirement. That requirement being the need to remove non-viable tissue etc.

We have revised the wound bed preparation section and hope that it is more clear. See line 175
Again, will these wounds be infected? Do you need to gain adequate source control prior to application.

Yes we expect that infections will be under control prior to enrolment in the study.

Line 166: outcomes or endpoints should be separated from study visit schedule to make it clearer.

This has been revised. See line 150

Line 168: You really don’t see patients until 4 weeks after starting a clinical trial? I think this timepoint is far too long

Actually we have found this timepoint to be more than adequate. However it should be noted that one of the inclusion criteria is that patients are able to be followed up by a home nursing service run by Silver Chain. Silver chain will undertake weekly assessment photographs of the wounds and can alert the investigators should the patient require an earlier appointment.

Line 169: So earlier on I suggested you create an actual endpoint paragraph. Here is the endpoint - the % of wounds healed between groups at 26 weeks?

The flow of the manuscript has now been restructured to make this more clear.

Line 182: As above

Reviewer: Anabelle Mizzi

Reviewer's report:

This paper explains the design and process of a randomised controlled trial aimed to assess the efficacy of a novel method of treatment for DFUs. The topic is highly relevant and important in the field and I look forward to see their results. The paper is very well written and may need some minor clarifications regarding the randomisation and recruitment (inclusion criteria) process.

Abstract

Line 34: change 150 to One hundred and fifty - changed

Study population

This section needs to be more clear. Will the participants be recruited immediately after diagnosis of DFU? Will you be recruiting participants who have had the DFU for several weeks?

The study population will be screened from patients attending the Fiona Stanley (FSH) or Royal Perth Hospital (RPH) inpatient or outpatient multidisciplinary foot units during the recruitment period. There is no exclusion criteria based on duration of wound.

How will randomization take place? Will the researchers be blind for randomization? Will the 150 participants be split into 2 groups following randomization? That is, each group will have 75 participants?
Randomization will be performed via a randomisation program built into the REDCap data management system. Researchers will be blinded to the randomisation algorithm. The randomisation program will randomly assign patients to treatment or control with variable block sizes that are randomly 2, 4 or 8.

Line 120: Define 'suitable' for spray on skin. May be a source of bias here or else perhaps state earlier on that spray on skin is suitable only on ulcers with specific criteria. Will the other group have the same criteria as it is not clear since the inclusion criteria state 'suitability for spray on skin' only.

Because ReCell has not been used in this manner before, this inclusion criteria was added to give clinicians an ability to exclude patients if there was a concern about ReCell causing a deterioration in the wound and potentially causing harm to the patient. When the protocol was written we really did not know what to expect in terms of which wounds would make us uncomfortable about inclusion. Because the study is now underway we have a better idea about what that would mean. Primarily there is a concern about sinuses, heavily exuding wounds and/or wounds with a large percentage of bone on view. The other concern are for wounds that are malignant in nature.

Line 125: do you mean Duplex instead of Doppler?

No we did not, perhaps the term visualised was misleading. There may be some patients that may only have peripheral arterial testing done via a handheld Doppler.

Line 136: how will this be determined? May also be a source of bias since sometimes weaker/ frail patients find it more difficult to attend.

During the screening process we ask patients if they intend on travelling/being away from their home for any period of time within the next 12 months and if their travel plans will interfere with the follow-up time points they will be excluded for this reason. We do not envision this affecting the frail patients that would normally have to attend Podiatry Outpatient clinics for review regardless of inclusion in the trial.

Line 177: Perhaps this section needs some more info similar to what is presented for the participants who will be receiving the spray on skin treatment. EG: will they have the same wound bed preparation? What is 'standard podiatry treatment'? Will these patients also be treated by VAC?

All patients will receive the same pre-intervention protocol prior to randomisation into the trial including ultrasonic debridement on the day of randomisation. This ‘pre intervention protocol’ is the standard post-operative diabetic foot ulcer wound care procedure for patients having a minor foot amputation or surgical debridement at Fiona Stanley Hospital.

Discussion

Line 322: Write WA in full - changed

We hope these changes address any residual concerns regarding our manuscript.