PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness of a hydrogel dressing as an analgesic adjunct to first aid for the treatment of acute paediatric burn injuries: A prospective randomised controlled trial
AUTHORS	Holbert, Maleea; Kimble, Roy; Chatfield, Mark; Griffin, Bronwyn

VERSION 1 – REVIEW

REVIEWER	Baljit Dheansa Queen Victoria Hospital East Grinstead UK
REVIEW RETURNED	24-May-2020

GENERAL COMMENTS	This is a detailed study which has attempted to answer a question that many burns clinicians have asked. The data that has been collected and analysed comes to, what I think is, an appropriate conclusion. However there are significant gaps that need addressing and some clarity on the presentation of the data to aid the readers. I will address the limitations first. You have described some of these in your discussion but I think there are more. Very little data is presented on pre-hospital care and this may have relevance. I note that a significant number of patients had film or Burnaid applied prior to arrival to the ED (I assume that this is what is described in the bottom of Table1) and subsequently they had a different intervention after randomisation. How many received first aid prior to the ED and how many had it in ED? Was there a difference in time to first aid as this is not documented? Did any get two sets of first aid? When was analgesia administered and was a standard protocol applied? What dressings did patients originally arrive in and was any analgesia given prior to application of the intervention dressing (not clear from the manuscript)? A time point of 20 minutes for application was applied but was there any previous justification for this? There appear to significant data missing in table 2 or certainly fewer numbers in group especially in the control group (for example in the pre-dressing FLACC line). Why is this? This is also the case in Table 3 especially for control patients in the pulse and alpha amylase groups. Over 140 patients who were potentially eligible were not recruited. The intervention is primarily aimed at the pre-hospital setting as you detail in your introduction and so assessing this in ED may not be standard practice: this therefore could be considered an artificial situation as often temporary dressings in ED may be short term only. What is the usual practice in ED? These may all have some confounding and should be clarified or documented. The labelling/description of what is being described is not totally clear. I would suggest that you are more specific and clear about

	your intervention/control in the data tables. In Table 2 you say "pre dressing" and "post dressing" when you mean pre and post application of the intervention/control while "pre and post silver" describes application of the definitive dressing. This is more relevant when you look at appendix B which I presume is describing out patient dressing changes later on down the line. In your pre trial protocol you mentioned scar scoring at 3 and 6 months. Was this done? One of the biggest limitations appears to be the discrepancy in scar scores between your data and the data used for the power calculation. It would be useful to see how you would address this and other limitations as well as giving a bit more detail on what you suggested in regards to a follow up pre-hospital trial. Taking into account the above would you recommend a repeat or modified trial protocol?

REVIEWER	E.M.M. van Lieshout Erasmus MC, University Medical Center Rotterdam, The Netherlands
REVIEW RETURNED	28-May-2020

GENERAL COMMENTS	The authors performed an RCT aimed to compare the effectiveness of two acute burn dressings, Burnaid® hydrogel dressing and plasticized polyvinylchloride film, on reducing acute pain scores in paediatric burn patients following appropriate first aid. Based on the results, they were not able to show a clear benefit of Burnaid® hydrogel dressing as an analgesic adjunct to first aid for the treatment of acute paediatric burns. Overall, the topic has great clinical relevance and the study is generally well conducted. The manuscript is well written. However, there are some issues that need to be addressed. Major issues: 1. Study design: if there is no indication of one type of dressing being superior to the other, I could also imagine a non-inferiority design could be chosen. A clear rationale for the superiority design should be added, or the introduction should mention potential benefits of the intervention. If saran wrap has been used with good results, what benefit was expected from the burnaid intervention? It should fill a gap in order to be beneficial over Saran wrap. Somehow this in not fully clear from the information provided in the study. 2. Section 2.7.1: details on the validity of FLACC scale and a reference are missing. 3. Discussion: As correctly mentioned, the pain scores were generally low, and may explain why an effect of the intervention could not be shown. This raises the question if the proper population has been studied. Only few patients in high pain risk stratum were included, and this might explain the non-significant outcome of the study for the pain outcomes. Was the low number of patients in the high pain risk stratum expected? If not, why was the population different than expected? Perhaps a bit out of focus of the RCT, but would there be a rationale for using Burnaid other than only pain control? Minor issues: 1. Page 3 lines 20-24: The sentence is quite long and difficult to follow.

	2. Design: why are only 393 patients screened while the methods mentions that 1200 paediatric patients are treated per year? 3. Methods: details on the size of the VAS scales and meaning of the minimum and maximum value is better mentioned in the Methods section than in the Results section. This also applies to details about the review panel that scored the re-epithelialisation (3.3.2). 4. Sample size: the manuscript mentions the SD for the groups to be 2.7, whereas the published protocol mentions 2.4. Which one is true? 5. Data analysis: the statistical methods used are fully different from what is mentioned in the protocol. A rationale for this modification should be provided. 6. Data analysis, “Each model included data …….. in the intervention group”: This sentence mentions “assumed no population differences at baseline”. From Table 1 it looks like age is skewed. If so, why was it not included in the models? 7. Adverse events: I may have overlooked this, but did the methods mention adverse events as outcome measure or clinical data collected?

REVIEWER	Folke Sjöberg Professor, M.D., Director The Burn Center, Linköping University Hospital, and Department of Clinical and Experimental Medicine, Linköping University S-581 85 Linköping
REVIEW RETURNED	09-Jun-2020

GENERAL COMMENTS	BMJ Open Manuscript ID bmjopen-2020-039981: Effectiveness of a hydrogel dressing as an analgesic adjunct to first aid for the treatment of acute paediatric burn injuries: A prospective randomised controlled trial by Dr. Maleea and co-workers. In this prospective randomized trial, the early analgesic effectiveness was investigated in two types of dressings for paediatric burns. One based on a hydrogel, the other on PVC plasticised polyvinylchloride film (control). The conclusion being contrary to that as hypothesised prior to the study, a clear benefit of the more advanced Burnaid hydrogel was not identified. Major comment This is a well thought of and properly conducted study in an important area of burn care, i.e., that of early analgesia and proper first dressing applications in children burns. The study is adequately addressing these issues, but a significant shortcoming of the study, is that the pain level presented by the children and which has been properly investigated by scientifically validated tools is low. Significantly lower than anticipated pre-study. This complicates the finding of no difference between dressings. This needs to be even further emphasised in the manuscript. In line with this is also that the “successful” pain strategy is based on an individualized, multimodal pain treating strategy, that is involving many different approaches. This makes the homogeneity of each cohorts further limited and the chance of finding a difference even less. In order to address the presented shortcomings listed above a major message in the discussion needs to be that pain treatment for this patient cohort today, by using a multimodal pain treatment

	strategy , is rather successful and the chance of finding a dressing that makes a difference difficult. The finding of low pain levels in this situation is rather new especially in relation to the references presented in the introduction. This should be elaborated upon in the discussion. This message, i.e., low pain levels may even be important to include in e.g., the title, as: Does separate dressings contribute in the final pain level experienced in paediatric scalds, beyond a multimodal pain treatment strategy in an RCT?

REVIEWER	Paolo Eusebi Regional Health Authority of Umbria, Italy
REVIEW RETURNED	08-Aug-2020

GENERAL COMMENTS	I have some concern with sample size calculation. What is the anticipated baseline mean of standard of care? Is the sample size calculated with the mixed effects model? I don't understand why the "Peak pain" observation is not missing only for FLACC (Table 2). Could you please clarify? Why we have many missing values in some pain scales? What is the anticipated treatment for missing values?

VERSION 1 – AUTHOR RESPONSE

1. Reviewer One

1.1 Reviewer's Comment:

This is a detailed study which has attempted to answer a question that many burns clinicians have asked. The data that has been collected and analysed comes to, what I think is, an appropriate conclusion. However, there are significant gaps that need addressing and some clarity on the presentation of the data to aid the readers. I will address the limitations first. You have described some of these in your discussion but I think there are more. Very little data is presented on pre-hospital care and this may have relevance. I note that a significant number of patients had film or Burnaid applied prior to arrival to the ED (I assume that this is what is described in the bottom of Table1) and subsequently they had a different intervention after randomisation.

Author Response:

We thank Reviewer One for their valuable feedback, and time reviewing our manuscript. The reviewer is correct in their assumption, and the data presented at the bottom of Table 1 (Page 13) describes prehospital dressings applied prior to randomisation. Due to the pragmatic nature of the trial, n = 7 participants in the intervention arm (Burnaid Arm) received PVC film from ambulance services before presenting to the ED. Moreover, n = 11 patients in the control arm (PVC Film Arm) received Burnaid dressings before enrolment in the trial. This is acknowledged as a significant limitation of the trial. To investigate if prehospital dressings (applied to patients' burns before randomisation in the ED) influenced the results – analyses were re-run excluding all patients who received Burnaid or PVC film (plastic wrap) before recruitment and no significant differences were identified.

1.2 Reviewer's Comment:

How many received first aid prior to the ED and how many had it in ED?

Author Response:

Unfortunately, this was not delineated during data collection. As optimal first aid (defined as 20 minutes cool running water within 3 hours of sustaining the burn) was a requirement for

enrolment in the trial, the exact minutes of water cooling was documented (in addition to other methods of first aid and analgesia). However, where the first aid was administered (at home on-scene, at a referral hospital, GP, school etc...) was not documented. This is now considered as a major limitation of this research, and will be collected for future studies.

1.3 Reviewer's Comment:
Was there a difference in time to first aid as this is not documented? Did any get two sets of first aid?
Author Response:
Optimal first aid (20 minutes cool running water within 3 hours) was an inclusion criterion for the trial, so all enrolled patients received first aid within three hours of the burn occurring. Some patients received water cooling durations longer than 20 minutes, however no enrolled participant in the trial received two consecutive sets of first aid (i.e. 20 minutes CRW on-scene and an additional 20 minutes following presentation to the ED). The exact duration from the time the burn was sustained until water first aid was administered was not recorded, however all patients enrolled in the trial were considered to have optimal burn first aid. Time taken (in minutes) to present to the ED following sustaining the injury was documented and reported in in Table 1 (Page 14).

1.4 Reviewer's Comment:
When was analgesia administered and was a standard protocol applied?
Author Response:
For patients arriving via ambulance or inter-hospital transfers, analgesia was often already on-board following presentation to the ED at the Queensland Children's Hospital (QCH). A standard protocol is used by Queensland Ambulance Services (QAS) for the management of burn injuries. This Clinical Practice Guideline details first aid, fluid resuscitation, analgesia, and acute burn dressings. Moreover, the ED at the QCH uses a Burns Procedural Pain Protocol for the treatment of acute burn injuries. All administered analgesia (given in the prehospital setting, referring centre, and following patient presentation to the ED) was documented and recorded following enrolment into the trial. The timing and dose of all administered analgesia was also documented (where possible). Fentanyl in combination with Paracetamol and Ibuprofen (± Oxycodone) were the most common medications given to patients in the ED, as well as in the prehospital setting. Thirty-six percent of patients (overall) received three different medication classes, and an addition 31% received four different pain medications during acute care. No difference in administered analgesia was identified between the two groups.

1.5 Reviewer's Comment:
What dressings did patients originally arrive in and was any analgesia given prior to application of the intervention dressing (not clear from the manuscript)?
Author Response:
Prehospital analgesia was identified as a limitation of this trial, and it is now acknowledged within the discussion (Page 21 – 22). Just under half (49%) of all participants enrolled in the trial had no acute-burn dressings applied prior to their presentation to the ED at the QCH. A number of participants (26%) received PVC film as an acute burn dressing before presenting to the ED. In addition, a subset of participants (25%) had Burnaid applied in the prehospital setting prior to presenting to the ED. Acute burn dressings administered outside the ED differ depending if the child arrived via their parents, ambulance, GP referral, or inter-hospital transfer. Queensland Ambulance Service (QAS) clinical practice guidelines recommend Burnaid and/or PVC film as acute wound coverings for the transportation of burn patients. This information was collected from each participant enrolled in the trial, and differences between patients who received prehospital PCV or Burnaid prior to their enrolment in the trial

was examined during data analysis. Future research investigation acute burn dressings will better control for the application prehospital dressings prior to enrolment. This is considered another major limitation of the research. Most patients presenting to the ED via QAS had analgesia on-board at the time of arrival. Fentanyl, Paracetamol, and Ibuprofen were the most common prehospital medications administered to participants enrolled in the trial. As most children presenting to the ED via QAS with a burn will have analgesia on-board, we aimed to determine if Burnaid could provide additional pain relief in this setting (on top of current standard care). As the ED was where the dressings were intended to be used if results of the trial were successful – Burnaid dressings needed to be able to further reduce acute burn pain in this setting (where most often patients will already have some form of analgesia).

1.6 Reviewer's Comment:
A time point of 20 minutes for application was applied but was there any previous justification for this?
Author Response:
Twenty minutes was chosen as the standardised time duration for dressings to be applied in the ED for two reasons. First, this duration was predicted to be the time taken from patient presentation to assessment by the Paediatric Surgical Team in the ED – prior to wound debridement and silver dressing application. This time duration was discussed with key stakeholders, such as ED Consultants, Surgical Consultants, Emergency Nursing Staff, and relevant knowledge users prior to recruitment and data collection for the RCT. Second, 20 minutes has previously been used as the standardised time duration for the application of hydrogel dressings and Aloe Vera in burn porcine models (1). As little-to-no research has been conducted examining acute burn dressings in a paediatric ED setting, and Burnaid dressings do not provide a minimum duration for dressing application, 20-minutes was used as a standardised duration to ensure consistency between participants.

1.7 Reviewer's Comment:
There appear to significant data missing in table 2 or certainly fewer numbers in group especially in the control group (for example in the pre-dressing FLACC line). Why is this? This is also the case in Table 3 especially for control patients in the pulse and alpha amylase groups.
Author Response:
Table 2 contains missing data for the pain assessment timepoint labelled 'Pre-dressing application' (which aimed to measure pain pre-application of the randomised dressing) for one main reason. As PVC film is a common prehospital acute burn dressing (and is also the only acute burn dressing used in EDs across Queensland) some participants had PVC film applied to their burns before recruitment into the trial. In some cases, PCV film was still applied to patient's burns upon presentation to the ED. If a patient was randomised to the control group (to receive PVC film) and already had PVC film applied to their burns, these dressings were left in place as to not subject a paediatric burn patient to an unnecessary change of dressing. However, for those participants, pain assessed prior to the application of the randomised dressing (i.e. Pre-Dressing Application) could not be assessed if paramedics were no longer present after handover.
It is also important to note that pulse rate, temperature, and salivary measures of alpha-amylase were also collected (alongside pain scores) at this timepoint. So if a patient already had an acute burn dressing applied, and was subsequently randomised to receive that same dressing – pain prior to the application of that dressing could not be assessed and pulse rate and stress could also not be measured. This is acknowledged as a limitation of the trial, which arose during data collection, and future studies will aim to correct or prevent this issue.

1.8 Reviewer's Comment:

Over 140 patients who were potentially eligible were not recruited. The intervention is primarily aimed at the pre-hospital setting as you detail in your introduction and so assessing this in ED may not be standard practice: this therefore could be considered an artificial situation as often temporary dressings in ED may be short term only. What is the usual practice in ED? These may all have some confounding and should be clarified or documented.
Author Response:
We thank Reviewer One for their valuable feedback, and time reviewing our manuscript. This trial relied on ED and Surgical Staff to contact the lead investigator for potential participants presenting to the ED. One researcher recruited all participants enrolled in the trial, and was 'on-call' for 12 months recruiting for this trial (7am to 9pm). Of the N = 140 missed potential participants, n = 108 (77%) of these missed recruits were the result of ED and/or Surgical Staff not notifying the investigator of the eligible patient presenting to the ED. Moreover, n = 11 eligible patients were missed because the investigator arrived post-wound debridement and it was too late to randomised the child. Twenty-one patients were missed as caregivers declined to be approached for research. This data is outlined in Figure 1. CONSORT Flow Diagram, and is further acknowledged as a limitation of the trial. Usual practice in the ED (Australia wide) following 20 CRW burn first aid is the application of PVC film (plastic/saran wrap). The aim of this investigation was to determine if these dressings could provide additional analgesia in the ED, as HBD are common amongst ambulance services however EDs have only one acute burn dressing available for acutely burned patients.

1.9 Reviewer's Comment:
The labelling/description of what is being described is not totally clear. I would suggest that you are more specific and clear about your intervention/control in the data tables. In Table 2 you say "pre dressing" and "post dressing" when you mean pre and post application of the intervention/control while "pre and post silver" describes application of the definitive dressing. This is more relevant when you look at appendix B which I presume is describing outpatient dressing changes later on down the line.
Author Response:
We have taken on-board this feedback and made the appropriate changes. To facilitate ease of comprehension, and to be more specific and clear about the intervention/control data tables, the labelling used for pain assessment timepoints during acute care in the ED (as well as during follow up outpatient care) have been changed. The labels used for data collection timepoints described in Figure 2. Pain assessment timepoints during acute and follow up care have now been used within Table 2 (Page 15), Table 3 (Page 17), and Appendix B (Pain at Outpatient Follow Ups). The reviewer is correct and the "Pre-dressing" timepoint presented in Table 2 describes pain assessed pre-dressing application of the randomised dressing (Burnaid or Plastic), Pre-silver describes pain assessed pre-silver dressing application (which are definitive dressings), and Appendix B describes outpatient dressing change data, and not acute care data collected in the ED.

1.10 Reviewer's Comment:
In your pre trial protocol you mentioned scar scoring at 3 and 6 months. Was this done? One of the biggest limitations appears to be the discrepancy in scar scores between your data and the data used for the power calculation. It would be useful to see how you would address this and other limitations as well as giving a bit more detail on what you suggested in regards to a follow up pre-hospital trial. Taking into account the above would you recommend a repeat or modified trial protocol?
Author Response:
We apologise if there is some confusion regarding sample size calculations for this investigation. Sample size was estimated at 29 experimental (intervention) participants and

29 control participants to detect a significant between-group difference of 1.8 in pain scores post-dressing application, assuming SD = 2.4. With power equal to 0.8, α set at 0.05, and up to a potential 20% loss to follow-up, the calculated target sample size was 72 participants. Our sample size was calculated using pain score data, not scar scores. I have tried to readjust the language within section 2.8 Statistical Analysis in the manuscript to provide some clarity for the sample size calculation.
Scar outcomes were assessed within this investigation. This data, however, is not presented within the current manuscript for two main reasons. Scar assessment data, in addition to cost-effectiveness data, were intended to be included in a standalone manuscript submitted for publication at a later date. Due to the number of secondary outcomes collected within this trial, data were separated into several publications to adhere to the Journal's word count. Furthermore, few participants enrolled in the trial (n = 1) required a skin graft, and (n = 3) a small number required scar follow up appointments. A significant proportion of participants had small to medium sized burns (1% TBSA), most of which were superficial-partial thickness in depth. In addition, both the intervention and control arm had a median of 9 days to reach 95% wound re-epithelialisation. Due to these clinical features, few participants required scar management (i.e. pressure garments, silicone, micro-needling, or steroid injections). Due to the lack of adverse scaring seen within this patient population – getting patients and caregivers to return to the hospital 3- and 6-months post-burn for scar reviews was a challenge, and loss-to-follow up was a significant issue. The QCH serves as the major referral centre for paeditric burns occurring in Queensland and Northern New South Wales. For this reason, many families enrolled in the trial were not local to Brisbane and did not wish to travel long distances for non-clinical appointments (with no reimbursement). This loss to follow up limitation will be taken into consideration for future research, and videoconferencing scar reviews as well as electronic health related quality of life surveys will be implemented for patients unable to return for in-person follow ups.
Due to the number of limitations which arose throughout the data collection, a modified trial is recommended over replication. It is recommended that future research investigating acute burn dressings (such as HBD) be conducted in the prehospital setting, where acute pain scores are anticipated to be higher, and older paediatric burn patients are in included within the sample so self-report pain scales can be utilized. In addition, measures to control for the application of different acute burn dressings and analgesia should be implemented. Furthermore, prehospital acute pain scores should be audited prior to data collection to gage median burn pain prior to conducting the trial.

2. Reviewer Two:
Overall, the topic has great clinical relevance and the study is generally well conducted. The manuscript is well written. However, there are some issues that need to be addressed.

Major issues:
2.1 Reviewer's Comment:
Study design: if there is no indication of one type of dressing being superior to the other, I could also imagine a non-inferiority design could be chosen. A clear rationale for the superiority design should be added, or the introduction should mention potential benefits of the intervention. If saran wrap has been used with good results, what benefit was expected from the burnaid intervention? It should fill a gap in order to be beneficial over Saran wrap. Somehow this in not fully clear from the information provided in the study.
Author Response:
We thank Reviewer Two for their valuable feedback, and time reviewing our manuscript. Unlike PVC film, Burnaid dressings have an evaporative cooling effect when applied onto a

burn wound (which has been documented in porcine burn models). While PVC film provides protection from the external environment, Burnaid dressings provide evaporative cooling and a reduction in sub-dermal temperatures when air currents pass over the dressing (1). This evaporative cooling effect, which is specific to hydrogel burn dressings, was the expected benefit of Burnaid in comparison to the current standard acute burn dressings. This evaporative cooling effect was also why Burnaid dressings were hypothesised to provide superior pain relief compared to PVC film. During initial development of the protocol in 2017, we aimed to determine if Burnaid was superior to plastic wrap (for the reduction of acute burn pain) rather than determine if the two dressings are equally effective.

2.2 Reviewer's Comment:
Section 2.7.1: details on the validity of FLACC scale and a reference are missing.
Author Response:
We thank the reviewer for their comment, and we apologise for this oversight in editing. We have taken on-board this feedback and have made the appropriate changes. References for the validity and reliability of the FLACC scale have been added to Section 2.7.1.

2.3 Reviewer's Comment:
Discussion: As correctly mentioned, the pain scores were generally low, and may explain why an effect of the intervention could not be shown. This raises the question if the proper population has been studied. Only few patients in high pain risk stratum were included, and this might explain the non-significant outcome of the study for the pain outcomes. Was the low number of patients in the high pain risk stratum expected? If not, why was the population different than expected? Perhaps a bit out of focus of the RCT, but would there be a rationale for using Burnaid other than only pain control?
Author Response:
The number of patients in the high pain risk stratum was lower than expected. Sometimes patients in the high pain strata were taken to theatre for immediate debridement which made them ineligible for the trial. While we assessed and estimated the number of potential participants presenting to the hospital for acute burn treatment over the recruitment period, our assessment of patients presenting with one or more of the high pain risk criteria was lower than anticipated. Furthermore, it was not expected that paediatric burn patients presenting to our ED would have such low pain scores.
Asides from its application as an acute burn dressing to protect the wound following first aid, and provide evaporate cooling, there is little evidence to support the use of these dressings for the acute management of burn injuries. Burnaid is not a substitute for running water cooling – though hydrogel burn dressings are sometimes marketed as first aid. Research from our team has shown Burnaid to not be as effective as CRW for the first aid treatment of partial thickness burns (1). In the few circumstances where there is no CRW for three hours, it can be applied as 'first aid' however Burnaid does not stop the burning process like CRW – and thus there is no ethical or clinical equipoise to run such a trial in humans.

2.4 Reviewer's Comment:
Page 3 lines 20-24: The sentence is quite long and difficult to follow.
Author Response:
We thank the reviewer for their comment, and we apologise for this oversight in editing. We have taken on-board this feedback and have made the appropriate changes to Page 3 Line 20 – 24. This sentence has been split into two sentences to facilitate ease of comprehension.

2.5 Reviewer's Comment:
Design: why are only 393 patients screened while the methods mentions that 1200 paediatric patients are treated per year?

Author Response:
More than 1200 paediatric burn patients are treated in the Burns Outpatient Department (OPD) at the Queensland children's Hospital (QCH) each year. Children treated in the Burns OPD are often referred from the QCH's own ED, surrounding local hospitals, and general practitioners. The QCH is the major referral centre for burns occurring in Queensland and Northern NSW in Australia, however not all children seen in the Burns OPD first presented to the ED at the Children's Hospital. We hope we have provided some clarity into the discrepancy between reported numbers.

2.6 Reviewer's Comment:
Methods: details on the size of the VAS scales and meaning of the minimum and maximum value is better mentioned in the Methods section than in the Results section. This also applies to details about the review panel that scored the re-epithelialisation (3.3.2).
Author Response:
We thank the reviewer for their feedback and time reviewing our manuscript. Does the reviewer recommend we add additional details within the Result Section for outcome measures? We are happy to take this feedback on-board and make the appropriate changes.

2.7 Reviewer's Comment:
Sample size: the manuscript mentions the SD for the groups to be 2.7, whereas the published protocol mentions 2.4. Which one is true?
Author Response:
We thank Reviewer Two for their time and valuable feedback. We apologise for this discrepancy and oversight in reporting. The correct expected SD for the groups was 2.4 as first reported in the published protocol - not 2.7 as reported in the results manuscript. This error has been corrected.

2.8 Reviewer's Comment:
Data analysis: the statistical methods used are fully different from what is mentioned in the protocol. A rationale for this modification should be provided.
Author Response:
The main between-group differences in primary and secondary outcomes were estimated using mixed models, as reported in the published protocol - "when analyses include multiple measures on the same participant, mixed effects methods will be used to account for probable non-independence in observations."

2.9 Reviewer's Comment:
Data analysis, "Each model included data …….. in the intervention group": This sentence mentions "assumed no population differences at baseline". From Table 1 it looks like age is skewed. If so, why was it not included in the models?
Author Response:
Our analysis approach was the most powerful approach and was entirely appropriate for an RCT (where ANCOVA is unbiased conditional on the observed between-group difference in that outcome at baseline, but analysis of change scores is not). See the paper below and the associated correspondence: Should baseline be a covariate or dependent variable in analyses of change from baseline in clinical trials? by G. F. Liu, K. Lu, R. Mogg, M. Mallick and D. V. Mehrotra, Statistics in Medicine 2009; 28:2509–2530. Does the reviewer mean the distribution of age was not balanced between groups? Testing this with a Mann-Whitney test (because the data is skewed) gives $p = 0.10$. The reviewer may take some comfort from the fact that the main outcome analyses "adjust" (in an ANCOVA-like fashion) for a patient's outcome at baseline, i.e. between-group comparisons are kind of based on within-patient changes.

2.10 Reviewer's Comment:
7. Adverse events: I may have overlooked this, but did the methods mention adverse events as outcome measure or clinical data collected?
Author Response:
No adverse events occurred throughout data collection. No participants enrolled in the trial who received Burnaid reported an adverse reaction to dressings. As per the protocol, we allowed for the recording of adverse events. In this investigation, there were no documented adverse reactions observed in either arm of the trial. The text on Page 13 beneath Table 1 reports "no adverse events occurred in the intervention or control group".
3. Reviewer Three:
In this prospective randomized trial, the early analgesic effectiveness was investigated in two types of dressings for paediatric burns. One based on a hydrogel, the other on PVC plasticised polyvinylchloride film (control). The conclusion being contrary to that as hypothesised prior to the study, a clear benefit of the more advanced Burnaid hydrogel was not identified.

3.1 Reviewer's Comment
This is a well thought of and properly conducted study in an important area of burn care, i.e., that of early analgesia and proper first dressing applications in children burns. The study is adequately addressing these issues, but a significant shortcoming of the study, is that the pain level presented by the children and which has been properly investigated by scientifically validated tools is low. Significantly lower than anticipated pre-study. This complicates the finding of no difference between dressings. This needs to be even further emphasised in the manuscript.
Author Response:
We wish to thank Reviewer Three for their constructive comments and time reviewing our manuscript. Your comments provided valuable insights to refine out manuscript. In this document, we aim to address the issues raised as best as possible. We have taken this feedback on-board and further emphasized the major limitation of this trial (Page 21), which were the low pain scores reported following initial presentation to the ED with an acute burn.

3.1 Reviewer's Comment
In line with this is also that the "successful" pain strategy is based on an individualized, multimodal pain treating strategy, that is involving many different approaches. This makes the homogeneity of each cohorts further limited and the chance of finding a difference even less. In order to address the presented shortcomings listed above a major message in the discussion needs to be that pain treatment for this patient cohort today, by using a multimodal pain treatment strategy, is rather successful and the chance of finding a dressing that makes a difference difficult. The finding of low pain levels in this situation is rather new especially in relation to the references presented in the introduction. This should be elaborated upon in the discussion. This message, i.e., low pain levels may even be important to include in e.g., the title, as: Does separate dressings contribute in the final pain level experienced in paediatric scalds, beyond a multimodal pain treatment strategy in an RCT?
Author Response:
We have taken on-board these comments, and a major message in the discussion section has now been included emphasizing the limitations of this research, and the unexpected low pain scores from patients presenting to our ED with an acute thermal burn. We agree with the reviewer that this research limitation can also be viewed as a great success for prehospital services and ED staff at the Children's Hospital. Pain was so well controlled following initial presentation, with an overall mean pain of 1 pre-dressing application, we were unable to identify treatment related effects for the intervention.

4. Reviewer Four

4.1 Reviewer's Comment:

I have some concern with sample size calculation. What is the anticipated baseline mean of standard of care? Is the sample size calculated with the mixed effects model?

Author Response:

We thank Reviewer Four for their time and valuable feedback. The analysis associated with the sample size calculation was a t-test. (Sample size calculations are often based on simple analyses.) The anticipated baseline mean for the standard of care arm is not required (but the difference between arms at follow-up is required - in this case 1.8) to reproduce the sample size calculation:

. power twomeans 500 501.8, sd(2.4) p(0.8)
Performing iteration ...
Estimated sample sizes for a two-sample means test
t test assuming sd1 = sd2 = sd
Ho: m2 = m1 versus Ha: m2 != m1

Study parameters:
alpha = 0.0500
power = 0.8000
delta = 1.8000
m1 = 500.0000
m2 = 501.8000
sd = 2.4000

Estimated sample sizes:
N = 58
N per group = 29

4.2 Reviewer's Comment:

I don't understand why the "Peak pain" observation is not missing only for FLACC (Table 2). Could you please clarify?

Author Response:

Pragmatically, peak FLACC is a routinely collected pain score from ED staff, however it can be removed from the manuscript if reviewers find it irrelevant. Peak pain, which was assessed during wound cleaning and debridement in the ED, aimed to measure maximal pain experienced by the patient during acute care. Emergency Department (ED) staff who performed the wound debridement also assessed peak pain using the FLACC. Throughout data collection in the ED, parents/caregivers and patients were not asked to assess peak pain during initial wound debridement – only nursing staff. This is why peak pain is only presented for the FLACC scale during acute care– in addition to the other four pain assessment timepoints (pre and post-acute dressing application, and pre and post-silver application). Peak FLACC is not missing for the other pain assessment tools, it was never assessed. I hope I have provided some clarification on this raised issue.

4.3 Reviewer's Comment:

Why we have many missing values in some pain scales?

Author Response:

For the primary outcome measure, which was pain assessed post-application of the randomised dressing using the FLACC scale, no pain values were missed. However, the VAS-P is a self-report pain scale designed for children aged 8 years or older. Almost 85% of

all patients recruited into the trial were aged under seven years, and thus very few participants were able to use this scale and self-report their pain. VAS-Observer pain scores were missed in cases where parents/caregivers requested to leave the treatment room during their child's burn care, and observational pain scores could not be collected in these circumstances. Table 2 contains missing data for the pain assessment timepoint labelled 'Pre-dressing application' (which aimed to measure pain pre-application of the randomised dressing) for one main reason. As PVC film (plastic wrap) is a common prehospital acute burn dressing and is also the only acute burn dressing used in the ED across Queensland – some participants had PCV film applied to their burns before recruitment into the trial. In some cases, PCV film was still applied to patients burns upon presentation to the ED. If a patient was randomised to the control group (to receive PVC film) and already had PVC film applied to their burns, these dressings were left in place as to not subject a paediatric burn patient to an unnecessary change of dressing. However, for those participants, pain assessed prior to the application of the randomised dressing (i.e. Pre-Dressing Application) could not be assessed if paramedics were no longer presented after handover.

4.4 Reviewer's Comment:
What is the anticipated treatment for missing values?
Author Response:
We thank the reviewer for their questions and comments. In the mixed models, missing data were assumed to be missing at random.

Editorial Comments
1. Please revise the 'Strengths and limitations' section of your manuscript (after the abstract). This section should contain five short bullet points, no longer than one sentence each, that relate specifically to the methods. The results of the study should not be summarised here.
Author Response:
The Strength and Limitations section has been revised to adhere to the Journal's formatting guidelines, we apologise for this oversight. The results of the trial have been removed from this section (following the abstract).

2. Please ensure that your protocol reports all outcome measures for your trial and ensure that the primary and secondary outcome measures are consistent between your manuscript and the trial registry. The trial registry´ lists the pain score using the three scales (FLACC, FPS-R and VAS-P) as the primary outcome but why does the paper mention the primary outcome as being the pain score using FLACC, with FPS-R and VAS-P being "additional measures of pain? Moreover, the paper lists just a few secondary outcomes but the trial registry lists 11
Author Response:
Later advice from our biostatistician was to select one pain assessment measure and time-point as the primary outcome for the trial – however this did deviate from what was reported in the ANZCTR registered trial. Observational FLACC scores from nursing staff was reported as the primary outcome for the RCT in the published protocol in Trials. If the Editor-in-Chief recommends the primary outcome of the manuscript to be updated to the three pain scales (FLACC, FPS-R, and the VAS-P) as first reported in the trial registry for consistency, we will take on-board this recommendation and make the appropriate changes.
Of the 11 secondary outcomes reported in the registered trial, seven are presented within the manuscript (re-epithelialisation, pulse rate, temperature, analgesia, distraction techniques, alpha-amylase, and staff perspectives on the treatment). Staff perspectives on the two acute burn dressings, in addition to parent/caregiver satisfaction ratings, have now been included within the manuscript (Section 3.3.5 Page 20 – 21). These secondary outcome measures were originally omitted due to missing data points.

Respiratory rate (omitted)
Respiratory rate was difficult to record for participants in this study due to excessive movement and crying, and previous research from our team suggests it is not a useful indicator of pain or distress during burn wound treatment (2). Primary and secondary outcome measures for this trial were modelled off previous successful randomised controlled trials conducted by our team – however these were conducted within the Burns Outpatient Department rather than the ED, like the current trial. Due to the pragmatic nature of the trial, it became unfeasible for respiratory rate to be collected during acute data collection in the ED. Recruitment and data collection within a busy Emergency Department posed unforeseeable challenges, and unexpected difficulties in comparison to previous burns research conducted within our team. Future studies will be modified based on learned experiences.

Scar & Health related Quality of Life (omitted)
Collected from patients who returned for follow up care, however very high loss to follow up was experienced for 3 and 6-month scar reviews – as very few patients were referred to scar management within the research sample. This is most likely due to the low median TBSA (<1%) and median days to healing seen in the sample. In addition, as the QCH is the major referral centre for Queensland and northern New South Wales, many participants were not local to Brisbane and did not wish to travel for non-clinical appointments. This is acknowledged as a major limitation of the trial, and future studies will employ electronic surveys to reduce this missed data.

Salivary cortisol (omitted)
Emerging evidence has dismissed the relevance of cortisol when looking at its correlation to stress and re-epithelialisation in paediatric burn patients, and past research from our team suggests alpha-amylase is far more sensitive in comparison to cortisol when used as a proxy for stress in children undergoing burn wound treatment (3). Alpha-amylase was selected over cortisol due to the timing of follow up dressing changes, which occurred between 7.30 am – 11am in the Burns Outpatient Department.

Cost effectiveness (omitted)
Data collected but not reported.

References
1. Cuttle L, Kempf M, Kravchuk O, George N, Liu P-Y, Chang H-E, et al. The efficacy of Aloe vera, tea tree oil and saliva as first aid treatment for partial thickness burn injuries. Burns : journal of the International Society for Burn Injuries. 2008;34(8):1176-82.
2. Gee Kee EL, Kimble RM, Cuttle L, Khan A, Stockton KA. Randomized controlled trial of three burns dressings for partial thickness burns in children. Burns : journal of the International Society for Burn Injuries. 2015;41(5):946-55.
3. Brown NJ, Kimble RM, Rodger S, Ware RS, McWhinney BC, Ungerer JPJ, et al. Biological markers of stress in pediatric acute burn injury. Burns : journal of the International Society for Burn Injuries. 2014;40(5):887-95.

2.

VERSION 2 – REVIEW

REVIEWER	Baljit Dheansa Queen Victoria Hospital, UK
REVIEW RETURNED	06-Oct-2020

GENERAL COMMENTS	The authors have made several corrections in response to the comments made by the reviewers and have responded to these comments but the changes too the manuscript have not been as comprehensive as their answers. In regard to first aid in section 1.2(in their response document) the lack of knowing when first aid was applied is a limitation. In 1.5 they need to be specific about when analgesia was given (pre ED or in ED) and need to be more specific about this in the discussion. In 1.6 the justification for 20 minutes use of the temporary dressing is still not stated in the manuscript and highlighting this is important as there is no clear consensus on how long this should be. In 1.10 it appears to me that the basis for the power calculation was flawed because you were expecting higher pain scores - why was this? The comprehensive pain protocol you describe for the ambulance teams suggests that this was in place for some time - it appears that your numbers were too low to detect the difference. Again I think this needs to be clarified. I also note that a higher proportion of controls did not complete the full twenty minutes of treatment. This is not clearly mentioned in the manuscript - only on the Consort Flow diagram. I would also urge you to change "silver dressing" to "definitive dressing" as this will be better understood by readers. In Table 2 you need to define T1-4 - not simply stating them as Timepoint. Your responses in the response document generally have NOT made it into your revised manuscript and I think you need to do so. This wil mean you will need to rewrite rather than simply add/remove one or two sections.

REVIEWER	E.M.M. Van Lieshout Trauma Research Unit Department of Surgery, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
REVIEW RETURNED	23-Sep-2020

GENERAL COMMENTS	I would like to thank the authors for their revised manuscript. In the response letter, they have adequately addressed to comments raised by all reviewers. The manuscript has clearly improved. Unfortunately, for many comments, the author failed to make changes to the text. In many cases, only replying to the reviewers is not sufficient.

REVIEWER	Folke Sjöberg Folke Sjöberg, Professor, M.D.,Ph.D., Director The Burn Center, Linköping University Hospital, Division of Surgery, Orthopedics and Oncology, Department of Biomedical and Clinical Sciences Linköping University
REVIEW RETURNED	25-Sep-2020

GENERAL COMMENTS	The authors have adequately answered all issues raised by the reviewers

REVIEWER	Paolo Eusebi Regional Health Authority of Umbria
REVIEW RETURNED	09-Oct-2020

GENERAL COMMENTS	I thank the authors for clarifying and addressing statistical issues.

VERSION 2 – AUTHOR RESPONSE

• Reviewer Two's first comment (2.1): We have accepted this feedback and made the appropriate changes to the manuscript. A response to this comment has now been incorporated into the Introduction on Page 4 Paragraph 1.
• Reviewer Two's second comment (2.2): We have accepted this feedback, and made the appropriate changes. References for the validity and reliability of the FLACC pain scale have been incorporated into Section 2.7.1 Primary Outcome Measure (Page 8 Paragraph 2).
• Reviewer Two's third comment (2.3): This comment was a question for the authors regarding the use of Burnaid for reasons other than pain control, and the authors provided a response to this enquiry.
• Reviewer Two's fourth comment (2.4): This editing error has been corrected within the manuscript.
• Reviewer Two's fifth comment (2.5): This comment was a question for the authors regarding the number of burn patients seen in the Outpatient Department versus the Emergency Department at the Queensland Children's Hospital. The authors provided a response to this enquiry
• Reviewer Two's sixth comment (2.6): No corrections or edits to the manuscript were requested in this reviewer comment.
• Reviewer Two's seventh comment (2.7): This editing error has been corrected within the manuscript.
• Reviewer Two's eighth comment (2.8): This comment has been addressed in the manuscript text. The main between-group differences in primary and secondary outcomes were estimated using mixed models, as reported in the published protocol "when analyses include multiple measures on the same participant, mixed effects methods will be used to account for probable non-independence in observations."
• Reviewer Two's ninth comment (2.9): We have accepted the Reviewer's feedback. We have now included a statement in the manuscript describing that no baseline population differences were identified (Page 14 Paragraph 1 beneath Table 1).
• Reviewer Two's tenth comment (2.10): We have accepted the Reviewer's feedback and have included a statement in the manuscript describing adverse events. This statement can be found on Page 14 Paragraph 1.

2. Reviewer Two
2.1 Reviewers' Comments:
"I would like to thank the authors for their revised manuscript. In the response letter, they have adequately addressed to comments raised by all reviewers. The manuscript has clearly improved. Unfortunately, for many comments, the author failed to make changes to the text. In many cases, only replying to the reviewers is not sufficient."

Author Response:
We thank Reviewer Two for their feedback and time reviewing our manuscript. We have revisited Reviewer two's previous comments, and aimed to incorporate responses to these comments within the manuscript. A breakdown of Reviewer Two's comments and changes to the manuscript are described in the dot points above.

3. Reviewer Three
3.1 Reviewers' Comments:
"The authors have adequately answered all issues raised by the reviewers."

Author Response:
We would like to thank Reviewer Three for their feedback and efforts towards improving our manuscript.

4. Reviewer Four

4.1 Reviewer's Comments:
"I thank the authors for clarifying and addressing statistical issues."

Author Response:
We thank Reviewer Four for their feedback and time reviewing our manuscript. Our manuscript has undergone significant improvements following their feedback and suggested changes.

5. Reviewer One
5.1 Reviewer's' Comments:
"The authors have made several corrections in response to the comments made by the reviewers and have responded to these comments but the changes too the manuscript have not been as comprehensive as their answers. In regard to first aid in section 1.2(in their response document) the lack of knowing when first aid was applied is a limitation."

Author Response:
We thank Reviewer One for their additional feedback. We have accepted this feedback, and made the appropriate changes to the manuscript. This failure to record and document where a patient received first aid (be it on-scene in the prehospital setting with paramedics, GP or doctor's office, at home in the bath or shower, in the ED, or a combination of the above) has been further acknowledged in the text as a limitation (Page 21 Paragraph 2). Unfortunately, this information is not routinely collected by paramedics or recorded in hospital chart records. As reported in the manuscript on Page 5 under section 2.4 Participants – all participants enrolled in this trial were required to have optimal first aid (defined as 20 minutes cool running water delivered within 3 hours of the initial injury). Where a child received their first aid cooling has not been shown to influence patient outcomes, and was not predicted to influence the results of this trial. What does influence patient outcomes (such as time to re-epithelialisation and need for grafting) are rates of optimal first aid delivered within 3 hours. As this has been shown to affect patient outcomes, it was a requirement that all enrolled patients had received 20 minutes cool running water. It did not matter where a child received their first aid cooling – just as long as they had received it.

5.2 Reviewer's' Comments:
"In 1.5 they need to be specific about when analgesia was given (pre ED or in ED) and need to be more specific about this in the discussion."

Author Response:
This information (regarding the specific timing of administered analgesia) cannot be presented in the current manuscript as it was not collected or delineated during data collected. We have accepted the Reviewer's feedback and made the appropriate changes in text. This has been further described as a limitation in the manuscript, and a recommendation for future research. The following statement has now been included in the manuscript "Whilst all administered analgesia from the time the burn was sustained to initial presentation to the ED and wound debridement was recorded for all patients, where this analgesia was administered was also not delineated in the dataset and is also viewed as a significant research limitation." This specific limitation is now described in the Discussion on Page 21 Paragraph 2.

5.3 Reviewer's' Comments:
"In 1.6 the justification for 20 minutes use of the temporary dressing is still not stated in the manuscript and highlighting this is important as there is no clear consensus on how long this should be."

Author Response:
We have accepted the reviewer's feedback and made the appropriate changed to the manuscript.

Justification for the 20-minute time frame the dressings were applied for has now been described in great detail within the Methods on Page 7 Paragraph 2.

5.4 Reviewer's' Comments:
"In 1.10 it appears to me that the basis for the power calculation was flawed because you were expecting higher pain scores - why was this? The comprehensive pain protocol you describe for the ambulance teams suggests that this was in place for some time - it appears that your numbers were too low to detect the difference. Again I think this needs to be clarified."

Author Response:
We have accepted the Reviewer's feedback and made the appropriate changes to the manuscript. We have provided additional clarification on Page 20 Paragraph 2 stating "A significant effect of the intervention on reducing acute burn pain might not have been identified in this trial because pain scores were so low following patient's first presentation to hospital for their burn". To address the first point, a senior biostatistician within our research team performed the power calculation for the trial prior to commencement. Power calculations were performed using the best available data at the time (in 2016) and were calculated using results from a previous successful RCT from our team, which examined different (definitive) burn dressings in children in an outpatient setting. In 2016 – no acute burn trials had been conducted in children in the Emergency Department to inform our expected pain scores. For this reason, power calculations were made using RCT data conducted in the Burns Outpatient Department during a child's burn dressing change – as this was the best data available to us at the time.

5.5 Reviewer's' Comments:
"I also note that a higher proportion of controls did not complete the full twenty minutes of treatment. This is not clearly mentioned in the manuscript - only on the Consort Flow diagram. I would also urge you to change "silver dressing" to "definitive dressing" as this will be better understood by readers."

Author Response:
A justification and explanation for the proportion of control participants who did not keep their acute dressings on for the full 20-minute duration can be found on Page 14 – Paragraph 1, beneath Table 1. This section states "Sixteen participants (n = 4 intervention and n = 12 control) did not keep their randomised dressings on for the required 20-minute duration. Two main factors challenged dressing adherence during acute data collection in the ED. First, excessive wound exudate beneath the PVC film caused the dressings to slip off participant's burns. Second, a number of paediatric patients pulled at and removed their own dressings. Fidelity in these instances was compromised.". We have also accepted Reviewer One's feedback, and made the appropriate changes to the manuscript. The term "silver dressing" has been changed to "definitive dressing" to facilitate understanding to a broader audience.

5.6 Reviewer's' Comments:
"In Table 2 you need to define T1-4 - not simply stating them as Timepoint. Your responses in the response document generally have NOT made it into your revised manuscript and I think you need to do so. This wil mean you will need to rewrite rather than simply add/remove one or two sections."

Author Response:
We have accepted Reviewer One's feedback, and made the appropriate changes to the manuscript regarding timepoint labelling. Timepoints 1 – 4 have now been defined beneath Table 2 in the table legend. This edit can be found on Page 16 beneath Table 2 in the manuscript. Furthermore, the timepoint labels have been updated and defined beneath Table 3 on page 18. Moreover, authors have aimed to better incorporate responses to previous Reviewer comments within the manuscript.

VERSION 3 – REVIEW

REVIEWER	Baljit Dheansa Queen Victoria Hospital East Grinstead UK
REVIEW RETURNED	01-Dec-2020

GENERAL COMMENTS	Thank you for addressing the comments made by me and the other reviewers. I would like you to address the issue of failure to maintain the twenty minute application of the first aid dressing in 20 minutes (mostly control) as a limitation. The new paragraph you inserted: "Fourth, where a patient enrolled in the trial received their first aid cooling was not delineated in the dataset and this is considered to be a limitation of the trial. In addition, whilst all administered analgesia from the time the burn was sustained to initial presentation to the ED and wound debridement was recorded for all patients, where this analgesia was administered was also not delineated in the dataset and is also viewed as a significant research limitation." could be written more clearly as it I found it difficult to understand what you were trying to say. I would also be more specific: is it a limitation or not? Saying it is viewed as a limitation is not appropriate. I would also want you to acknowledge the significant limitations to the study in the conclusion as these have clearly had an impact on the data and therefore any conclusions one can make.

REVIEWER	E.M.M. Van Lieshout Trauma Research Unit Department of Surgery, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
REVIEW RETURNED	14-Nov-2020

GENERAL COMMENTS	I would like to thank the authors for their revised manuscript. I have no further questions.

VERSION 3 – AUTHOR RESPONSE

Response to Reviewer One Comments
Effectiveness of a hydrogel dressing as an analgesic adjunct to first aid for the treatment of acute paediatric burn injuries: A prospective randomised controlled trial
Manuscript ID: bmjopen-2020-039981.R3

Reviewer One Comment:
Thank you for addressing the comments made by me and the other reviewers. I would like you to address the issue of failure to maintain the twenty-minute application of the first aid dressing in 20 minutes (mostly control) as a limitation.

Author response:
We thank Mr Dheansa for their time and assistance reviewing our manuscript, and for the provided feedback. We have accepted this suggestion, and made the appropriate changes to the manuscript. This failure to maintain the full 20-minute dressing application for a number of patients (predominantly control patients) has been acknowledged as a limitation within the Discussion section. This limitation

description can now be found on Page 21 Paragraph 2.

Reviewer One Comments:
The new paragraph you inserted "Fourth, where a patient enrolled in the trial received their first aid cooling was not delineated in the dataset and this is considered to be a limitation of the trial. In addition, whilst all administered analgesia from the time the burn was sustained to initial presentation to the ED and wound debridement was recorded for all patients, where this analgesia was administered was also not delineated in the dataset and is also viewed as a significant research limitation." could be written more clearly as it I found it difficult to understand what you were trying to say. I would also be more specific: is it a limitation or not? Saying it is viewed as a limitation is not appropriate.

Author response:
We have accepted the reviewer's feedback and made the appropriate changes. The paragraph described above has been edited to improve clarity and comprehension. This updated paragraph can be found on Page 21 Paragraph 2, and now reads "Fourth, where paediatric burn patients received their first aid cooling (i.e. on-scene with paramedics, at home in the shower, or within the ED) was not delineated in the dataset, and this is acknowledged as a significant limitation. In addition, whilst all administered analgesia was documented for participants, where this analgesia was administered was also not delineated in the dataset. This is further acknowledged as a significant research limitation."
In addition to this, the phrase "viewed as a limitation" has also been removed from this section of the manuscript, as per the reviewers' request.

Reviewer One Comment:
I would also want you to acknowledge the significant limitations to the study in the conclusion as these have clearly had an impact on the data and therefore any conclusions one can make.

Author response:
We have accepted the reviewer's feedback and made the appropriate changes to the document. The limitations described within the Discussion section have now been acknowledged in the Conclusion of the manuscript, to ensure all readers are aware of the research limitations. This manuscript update can be found on Page 22 Paragraph 3.