

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Epidemiology of injuries, treatment (costs), and outcome in burn patients admitted to a hospital with or without dedicated Burn Center (Burn-Pro); Protocol for a multicenter prospective observational study
AUTHORS	Van Lieshout, Esther M.M.; Van Yperen, Daan; Van Baar, Margriet; Polinder, Suzanne; Boersma, Doeke; Cardon, Anne; De Rijcke, Piet; Guijt, Marc; Klem, Taco; Lansink, Koen; Ringburg, Akkie; Staarink, Maarten; Schoot, Leon; van der VEEN, Alexander; Van Eijck, Floortje; Van Eerten, Percy; Vegt, Paul; Vos, DI; Waleboerg, Marco; Verhofstad, Michael; Van der Vlies, Cornelis

VERSION 1 – REVIEW

REVIEWER	Folke Sjöberg Linköping University Hospital, 581 85 Linköping
REVIEW RETURNED	17-May-2018

GENERAL COMMENTS	<p>There are a few topics that may improve the study protocol:</p> <ol style="list-style-type: none"> 1. Who is assessing the TBSA% for the study group at the non burn center- Qualifications for this person? Training? Documentation photos? 2. Do not exclude patients that die in the first 24 h as inappropriate or faulty TBSA% assessment may have been done at the non-burn center or a decision not to resuscitate may inappropriately. 3. Define criteria for healed wound in detail. 95% closure? Also this may be documented by photography and later evaluated by blinded observers? 4. The choice of research staffing at each hospital – ponder the risk of bias in any direction (being a burn center related person – favouring the burn center outcome; or a independent person not being enough trained in burn related details?
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REVIEWER	Zhaofan Xia Department of Burn Surgery, Changhai Hospital Affiliated to the Naval Medical University, Shanghai, China
REVIEW RETURNED	07-Jun-2018

GENERAL COMMENTS	<p>There are several limitation in the study design.</p> <ol style="list-style-type: none"> 1. The study aims to compare the epidemiology of injuries, treatments (costs) and outcome in burn patients admitted to a hospital with or without dedicated burn center. However, the patients recruited in hospitals with burn centers are limited only those burn surface area <10% TBSA. Those patients cannot fully presents the characters of burn patients admitted to burns centers.
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	2. The researchers chose 10%TBSA. The choice lack of scientific supports in the literature.
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REVIEWER	Tom Abbott Queen Mary University of London, UK
REVIEW RETURNED	22-Jul-2018

GENERAL COMMENTS	<p>Thanks for the opportunity to review this protocol paper. This is an interesting topic. However, I think the authors might consider reviewing their approach and/or their report of the protocol. Unfortunately, I did not find the research question clear, and I am not sure that the protocol is internally consistent in terms of methods and planned statistics. The paper reads like a study protocol that might be submitted to an ethics committee and misses out some important sections from the SPIRIT checklist - authors might consider editing their report and removing unnecessary information. I have included specific detail below.</p> <p>Introduction</p> <ul style="list-style-type: none"> - This section is quite long. The authors may be able to shorten this and still retain the main points. - I am afraid I am not quite clear about the hypothesis for this study. This could be made clearer. - The rationale for comparing one population of patients (all attending a general hospital) versus a different population of patients (TBSA <10%) attending burn centres is not clear either. Please accept my apologies if I have misunderstood, but it is not clear to me. <p>Methods</p> <ul style="list-style-type: none"> - The authors have appended the SPIRIT checklist. However they do not appear to have followed the standardised reporting format, since there are a lot of missing sections and the missing sub-headings. I would encourage the authors to re-format their manuscript accordingly to include the missing areas. - Page 11 line 8. I am not sure that the 'i.e.' is needed. Just state that this is cohort study. However, I do not agree that this is a simple cohort study since the inclusion criteria at some centres differs to other centres. - I am not sure what the exposure is? Presumably it is 'location of care' i.e. burn centre versus non-burn centre. However, since the populations at each centre is different, as reliable comparison will be difficult to make. - Outcome measure. How is burn-related injury pattern defined? Further information on the primary outcome would be helpful. - Sample size calculation. It is not clear why a sample size calculation is "not constructive". Further explanation and justification would be helpful, since the sample size calculation is informed by the desired statistical power etc and has implications for the reliability of the statistical analysis. - Statistical analysis. It is not clear whether the main exposure is a continuous of categorical variable and it is not clear to me what question the authors intend to answer with the statistical tests that have been described (page 18 line 11 onwards).
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VERSION 1 – AUTHOR RESPONSE

Response to Reviewer # 1:

1. Who is assessing the TBSA% for the study group at the non burn center- Qualifications for this person? Training? Documentation photos?

Response: The TBSA% is assessed during physical examination by a research physician who has had elaborate training for this at the participating dedicated Burn Center. This has been added to the text (Lines 293-295 and 309-310). If digital photographs of the wounds are made these are not used for determining the % TBSA.

2. Do not exclude patients that die in the first 24 h as inappropriate or faulty TBSA% assessment may have been done at the non-burn center or a decision not to resuscitate may inappropriately.

Response: Patients are only excluded if they died in the first 24hours due to non-burn causes, for example severe head injury. That is justified in our opinion, as they are not treated for their burn injuries and would bias the mortality figures. In addition, we consider asking their next of kin for consent to use their data as being unethical. Patients who die in the first 24 hours due to the burn injuries are included. The example has been added to the text (Line 299).

3. Define criteria for healed wound in detail. 95% closure? Also this may be documented by photography and later evaluated by blinded observers?

Response: Wound closure is indeed defined as 95% closure. This is determined upon wound inspection by the research physician as well as by the treating physician or specialized wound care nurse. In case of disagreement, consensus will be reached by discussion. This has been added to the text (Lines 391-393 and 413-414). Wound closure is not determined on photographs.

4. The choice of research staffing at each hospital – ponder the risk of bias in any direction (being a burn center related person – favouring the burn center outcome; or a independent person not being enough trained in burn related details?)

Response: We acknowledge the opinion of this reviewer, but not to the extent of being pessimistic. In both settings (burn center and non-burn center), local physicians will provide the best possible care for their patients. The study does not interfere with the local treatment protocols, it only registers what is done and what the outcomes are. In order to get the most reliable and trustworthy outcome evaluation, both subjective and objective outcome are collected in this study. Outcome measures include data that are routinely registered in the patients' medical files, questionnaires completed by patients and scar assessment by a trained investigator. The same investigator will evaluate patients both at the burn center and at the non-burn center. We concur with the reviewer that the participation of multiple hospitals may introduces treatment bias, it also makes the results more generalizable. The latter has been added to the Discussion (Lines 521-522).

Response to Reviewer # 2:

1. The study aims to compare the epidemiology of injuries, treatments (costs) and outcome in burn patients admitted to a hospital with or without dedicated burn center. However, the patients

recruited in hospitals with burn centers are limited only those burn surface area <10% TBSA. Those patients cannot fully presents the characters of burn patients admitted to burns centers.

Response: As the reviewer correctly states, patients enrolled at the Burn Center are only the patients with the lowest range of burn injuries. The study does not aim to evaluate outcome for the burn patient population at the Burn Center as a whole. The population enrolled at the Burn Center is merely used as a comparator for patients admitted to a non-burn center. For the comparison to be as reliable as possible, we had to restrict enrolment at the Burn Center to a population with similar burn injuries as patients enrolled at the non-burn centers. With 10% TBSA being used as triage criterion for Burn Center admission in the Netherlands, it was decided to use this percentage as threshold. This has been mentioned more explicitly in the Abstract (Lines 106-108 and 112) and Introduction (Lines 227-229).

2. The researchers chose 10%TBSA. The choice lack of scientific supports in the literature.

Response: See also the response to comment #1 of this reviewer. The 10% TBSA has been chosen as that is the threshold used by Emergency Medical Services for triaging. This has been added to the Study Population (Line 293). The EMSB triage criteria state that patients with >10% TBSA should be triaged to dedicated Burn Center. A larger threshold would increase the eligible population at the Burn Center, but not at the non-burn center. As a consequence, comparing the Burn Center population with the non-burn center population would become biased, with the higher %TBSA at the Burn Center increasing the risk for adverse outcome and scar issues. We concur with the reviewer that the scientific evidence for this threshold is not sound, but it is the best cut-off possible given the triage scheme.

Response to Reviewer # 3:

1. Introduction: This section is quite long. The authors may be able to shorten this and still retain the main points.

Response: The Introduction has been shortened and is more focused now.

2. Introduction: I am afraid I am not quite clear about the hypothesis for this study. This could be made clearer.

Response: The hypothesis has been added at the end of the Introduction (Lines 229-232).

3. Introduction: The rationale for comparing one population of patients (all attending a general hospital) versus a different population of patients (TBSA <10%) attending burn centres is not clear either. Please accept my apologies if I have misunderstood, but it is not clear to me.

Response: See response to comment #2 of reviewer #2.

4. Methods: The authors have appended the SPIRIT checklist. However they do not appear to have followed the standardised reporting format, since there are a lot of missing sections and the missing sub-headings. I would encourage the authors to re-format their manuscript accordingly to include the missing areas.

Response: Following editorial requests, the SPIRIT Checklist has been replaced with the STROBE checklist. Headings were changed or added as appropriate (Lines 245, 262, 283, 386, 412, 466 and 472).

5. Methods: Page 11 line 8. I am not sure that the 'i.e.' is needed. Just state that this is cohort study. However, I do not agree that this is a simple cohort study since the inclusion criteria at some centres differs to other centres.

Response: 'i.e.' has been removed as requested (Line 246). We chose to use 'cohort study' since the study compares two cohorts of patients. The additional criterion (<10% TBSA) for the Burn Center was made with the aim to achieve similar burn wound severity in both cohorts (see also response to comment #2 of reviewer #2 and comment #3 of this reviewer).

6. Methods: I am not sure what the exposure is? Presumably it is 'location of care' i.e. burn centre versus non-burn centre. However, since the populations at each centre is different, as reliable comparison will be difficult to make.

Response: The exposure is indeed the 'location of care'. As mentioned above the eligibility criteria were designed to get similar groups for both locations of care.

7. Methods: Outcome measure. How is burn-related injury pattern defined? Further information on the primary outcome would be helpful.

Response: The burn-related injury pattern is defined by a number of items. These represent the injuries (presence/absence of inhalation injury, body regions burned, and extent of burns) and the burn mechanism (burn etiology and setting). This has been added to the text, and the order of the items has been changed to better reflect these two elements (Lines 306-313).

8. Methods: Sample size calculation. It is not clear why a sample size calculation is "not constructive". Further explanation and justification would be helpful, since the sample size calculation is informed by the desired statistical power etc and has implications for the reliability of the statistical analysis.

Response: The primary aim is to make an epidemiological description of the cohort at the non-burn centers. Given this aim and the lack of data on the population of interest, no sample size calculation was made a priori. Instead, we choose to enroll as many patients as possible within the timeframe allowed by the funder. That will give the most accurate data possible. The text has been reworded (Lines 417-419).

9. Methods: Statistical analysis. It is not clear whether the main exposure is a continuous of categorical variable and it is not clear to me what question the authors intend to answer with the statistical tests that have been described (page 18 line 11 onwards).

Response: The main exposure is the type of care (i.e., hospital with or without Burn Center). That is a categorical variable, and is mentioned more explicitly in the Statistics section (Lines 441-442). The descriptive analysis is aimed to report details for the two cohorts separately. The univariate analysis is aimed to compare the two cohorts, which is also added to the text for clarification (Line 448).

VERSION 2 – REVIEW

REVIEWER	Folke Sjöberg
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	Folke Sjöberg, Professor, M.D., Director, The Burn Center, Linköping University Hospital, and Department of Clinical and Experimental Medicine, Linköping University, 581 85 Linköping, Sweden
REVIEW RETURNED	14-Sep-2018

GENERAL COMMENTS	The authors have adequately responded to the queries of the reviewers and the protocol reads well now. Given the appropriate responses made in conjunction to adequate changes in the manuscript I suggest accept
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