PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Multicenter observational study on practice of pre-hospital management of hypotensive trauma patients: the SPITFIRE study protocol
AUTHORS	Tartaglione, Marco; Carenzo, Luca; Gamberini, Lorenzo; Lupi, Cristian; Giugni, Aimone; Mazzoli, Carlo Alberto; Chiarini, Valentina; Cavagna, Silvia; Allegri, Davide; Holcomb, John; Lockey, David; Sbrana, Giovanni; Gordini, Giovanni; Coniglio, Carlo; SPITFIRE, Study Collaborators

VERSION 1 – REVIEW

REVIEWER	ter Avest, Ewoud Medical Centre Leeuwarden, ED
REVIEW RETURNED	09-Mar-2022

GENERAL COMMENTS	Thank you for the opportunity to review this interesting paper, in which the authors propose to investigate the effect of variation in clinical practice amongst Italian HEMS crews on mortality (and a whole range of secondary endpoints) in hypotensive trauma patients. The authors should be credited for this initiative, that has the potential to answer some important questions in prehospital care in the future. The study protocol is overall well written, and very relevant for the pre-hospital community. However, I do have a few questions/remarks: GENERAL This study protocol holds the middle between a description of a proposed registry, and a description of several studies that can potentially be carried out with such a registry. This is reflected by the study aim as formulated by the authors throughout the manuscript: In the abstract (page 2) and the introduction section (page 4) the study aim is described as “to investigate the effect of variation in clinical practice amongst Italian HEMS crews on mortality (and a whole range of secondary endpoints) in hypotensive trauma patients, whereas in the strengths and limitations section (page 2) the aim is described as “…describing the current clinical practice of prehospital damage control resuscitation of hypotensive trauma patients”. At the end of the introduction section (page 4, lines 18-20) the authors mention that “This observational study was designed to be a registry of the sickest injured patients attended by HEMS throughout Italy”.

	These are three different aims. I suggest the authors rephrase the aims and describe a proposal for the creation of a national registry of patients with hemorrhagic shock, with the aim of investigating the relative influence of practice variation on outcome. ABSTRACT/ STRENGTH AND LIMITATIONs SECTION Primary endpoint: “the effect size of variation in clinical practice”: • Which specific treatment factors/ practice factors are considered to estimate the effect size of clinical practice? Will effect sizes of separate interventions provided be considered separately, or will an overall effect size be determined? • How will effect sizes be corrected for non-treatment factors (patient- and injury factors)? Secondary Endpoints: • I struggle with the number and variation in secondary endpoints: some of these are patient related outcome measures (hospital/ITU LOS) some are practice variation related descriptive measures (use of ultrasound, prevalence- and appropriateness of blood product administration, and some are associations of practice variation with with outcome measures (associations of prehospital factors such as blood product use with mortality and haemodynamics/ metabolic measures. I would suggest to limit the secondary endpoints to outcome measures only (as for the primary endpoint). INTRODUCTION The introduction is mainly focused on the use of blood products for PH DCR. Then suddenly (page 4, line 12) prehospital ultrasound is mentioned. I think the study should focus EITHER fully on the effects of early administration of blood products and coagulopathy prevention during DCR, OR investigate practice variation for other prehospital diagnostic and therapeutic interventions too (use of chest drains, REBOA, RSI threshold, etc). In line with this: I think the evaluation of sensitivity and specificity of prehospital ultrasound (EFAST) does not fit the study aims. METHODS ANS ANALYSIS Setting: Page 7: Recruitment started on Jan 2021st , with a proposed minimum recruitment window of three years. 22 bases so far have agreed to participate. However, only 4 of these (as per current date) carry blood products. Do the authors think this allows for enough practice variation to draw conclusions regarding the effect of early DCR on mortality? Participants: • One of the Inclusion criteria is “the confirmed or clinically likely diagnosis of shock”. How is this” confirmation” obtained in the prehospital setting? • Is the blood pressure threshold (<90mmHg) for inclusion derived by multiple measurements/ averages of NIBP, or blood pressures measured invasively? • Are patients with concomitant (vasoactive) head in juries or other causes of shock besides hemorrhage excluded? • “Unsalvageable patients are excluded” Is this at the discretion of the treating physician and before any HEMS treatments? Variables and source of data

	• Suggestion: also collect data on transport mode to hospital and interventions performed during transport? • Table 2 hospital data: “Emergency department outcome data” suggestion also to collect DBP to allow calculation MAP and to distinguish various anatomical injury types in hemorrhagic shock Plan for analysis & Sample size Based on an expected mortality of 20%, the aim is to recruit >500 patients (in the initial protocol published under NCT 04760977 this number was 400). This would allow 120 co-variates in the final regression model. However, in order to be able to quantify the effect of practice variation on outcome, one has to distinguish the practice effect from the variation in injuries, physiology, baseline characteristics etc. As a result, it is likely that more than 10 variables need to be entered as co-variates in the regression model. Can the authors provide information for which patient- and injury factors they want to correct to distinguish the practice effect in order to support their chosen sample size? Textual Page 2, line 55: change “improved outcomes” to “outcomes” Page 3, line 29 “based of” should read “based on” Page 3”line 31-38” Improved survival has been reported…” Worth mentioning the RePHILL trial here too as a reference, wherein no improved survival was found ? Page 8” HEMS interventions”. Change “high flow vascular access” to “wide bore” Page 10, line 53 “written warnings” change to “:reminders”? I am looking forward to review a revised paper of this study protocol

REVIEWER	Butt, Warwick Royal Children's Hospital M, intensive care Unit
REVIEW RETURNED	26-Mar-2022

GENERAL COMMENTS	A very important initiative which is likely to produce meaningful results which is likely to lead to a national registry and a long term, quality improvement program..good luck

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Ewoud ter Avest, Medical Centre Leeuwarden

Comments to the Author:

Thank you for the opportunity to review this interesting paper, in which the authors propose to investigate the effect of variation in clinical practice amongst Italian HEMS crews on mortality (and a whole range of secondary endpoints) in hypotensive trauma patients.

The authors should be credited for this initiative, that has the potential to answer some important questions in prehospital care in the future. The study protocol is overall well written, and very relevant for the pre-hospital community. However, I do have a few questions/remarks:

-> Thank you for your time and your in-depth revision.

GENERAL

This study protocol holds the middle between a description of a proposed registry, and a description of several studies that can potentially be carried out with such a registry. This is reflected by the study aim as formulated by the authors throughout the manuscript:

In the abstract (page 2) and the introduction section (page 4) the study aim is described as “to investigate the effect of variation in clinical practice amongst Italian HEMS crews on mortality (and a whole range of secondary endpoints) in hypotensive trauma patients, whereas in the strengths and limitations section (page 2) the aim is described as “…describing the current clinical practice of prehospital damage control resuscitation of hypotensive trauma patients”. At the end of the introduction section (page 4, lines 18-20) the authors mention that “This observational study was designed to be a registry of the sickest injured patients attended by HEMS throughout Italy”.

These are three different aims. I suggest the authors rephrase the aims and describe a proposal for the creation of a national registry of patients with hemorrhagic shock, with the aim of investigating the relative influence of practice variation on outcome.

-> Thank you for your comment that helped us clarify the aims section of the paper. This section has been revised as for your suggestions, please see the highlighted copy.

ABSTRACT/ STRENGTH AND LIMITATIONs SECTION

Primary endpoint: “the effect size of variation in clinical practice”:

- Which specific treatment factors/ practice factors are considered to estimate the effect size of clinical practice? Will effect sizes of separate interventions provided be considered separately, or will an overall effect size be determined?

Thank you for your comment, this part of the paragraph was not clear effectively.

Primary endpoint is composed of an exploration of factors associated with mortality in this cohort and evaluations of the effect size of single interventions.

In particular, red blood cells and blood product transfusions as well as REBOA will be evaluated for effects size estimation.

Separated evaluations for the effect sizes of different interventions will be performed by the building of propensity-score adjusted models for the specific intervention.

- How will effect sizes be corrected for non-treatment factors (patient- and injury factors)?

Patients and injury factors will be considered as covariates for the final model adjustment in the multivariable logistic regression analysis.

This aspect was already stated in the Primary objective subparagraph of the “Plan for analysis” paragraph - *“the prehospital and trauma-related variables resulting significantly different between the two groups will be tested as covariates in a univariable logistic regression model. Finally, the multivariable model building will be performed through the least angle regression selection (LARS) ”*.

However, following your suggestion, we added further details about the final model building in the paper.

In particular, variables resulting significantly different in the univariable logistic regression model with a conservative p value (< 0.1), will be introduced in the LARS procedure for multivariable model building.

Secondary Endpoints:

• I struggle with the number and variation in secondary endpoints: some of these are patient related outcome measures (hospital/ITU LOS) some are practice variation related descriptive measures (use of ultrasound, prevalence- and appropriateness of blood product administration, and some are associations of practice variation with with outcome measures (associations of prehospital factors such as blood product use with mortality and haemodynamics/ metabolic measures. I would suggest to limit the secondary endpoints to outcome measures only (as for the primary endpoint).

The study involves the evaluation of 6 secondary endpoints. Since secondary end points are exploratory and descriptive endpoints with only hypothesis-generating purposes for further studies and not hypothesis-verification purposes, we do not feel necessary to reduce the total number of secondary endpoints “

INTRODUCTION

The introduction is mainly focused on the use of blood products for PH DCR. Then suddenly (page 4, line 12) prehospital ultrasound is mentioned. I think the study should focus EITHER fully on the effects of early administration of blood products and coagulopathy prevention during DCR, OR investigate practice variation for other prehospital diagnostic and therapeutic interventions too (use of chest drains, REBOA, RSI threshold, etc). In line with this: I think the evaluation of sensitivity and specificity of prehospital ultrasound (EFAST) does not fit the study aims.

-> We are recording a number of prehospital diagnostic procedures and interventions. Our primary aim is to describe current practice of prehospital damage control resuscitation including blood products, however we are also collecting information on all diagnostic and therapeutic procedures on the field. A recent paper by Gamberini et al (Gamberini L, Tartaglione M, Giugni A, et al. The role of prehospital ultrasound in reducing time to definitive care in abdominal trauma patients with moderate to severe liver and spleen injuries [published online ahead of print, 2021 Dec 8]. *Injury* 2021;S0020-1383(21)00990-6. doi:10.1016/j.injury.2021.12.008) suggests that prehospital ultrasound can fast-track bleeding patients (those that will also receive blood) to faster definitive care. We decided to collect ultrasound data, as a secondary objective, to allow an external validation of this concept. For clarity we have removed any reference to ultrasound in the introductio.

METHODS ANS ANALYSIS

Setting:

Page 7: Recruitment started on Jan 2021st , with a proposed minimum recruitment window of three years. 22 bases so far have agreed to participate. However, only 4 of these (as per current date) carry blood products. Do the authors think this allows for enough practice variation to draw conclusions regarding the effect of early DCR on mortality?

-> Yes, we think this allows for enough practice variation for two main reasons. First, the number of HEMS bases carrying blood products is very rapidly surging: just now, we are aware that at least 2 entire regions (Lombardia and Trentino) are on the final steps of authorisation and this will mean about 8 more bases carrying blood products in half a year. Secondly, this may allow a before and after analysis and a comparison between systems with different resources.

Participants:

- One of the Inclusion criteria is “the confirmed or clinically likely diagnosis of shock”. How is this” confirmation” obtained in the prehospital setting?

-> Thanks for the chance to clarify this aspect: inclusion criteria are hypotension and “a confirmed or clinically likely diagnosis of major hemorrhage”. We do not mention shock because, as you stated with your question, we think it may be quite tough to clinically define shock in the prehospital setting.

Whereas the clinical confirmation of bleeding is intended as “certain” or “visible” such as for external bleeding, bleeding from the chest (either bleeding from chest tube/simple thoracostomy or seen by ultrasound), bleeding from the abdomen (either seen by ultrasound or suspected for penetrating abdominal wounds), bleeding from bone fractures. Bleeding from pelvis and retroperitoneum are otherwise just suspected by clinical signs or mechanism of injury.

- Is the blood pressure threshold (<90mmHg) for inclusion derived by multiple measurements/ averages of NIBP, or blood pressures measured invasively?

-> The <90mmHg pressure threshold is taken as an instant value from any reliable measurement, as for inclusion is needed just a single episode of hypotension at any time of the prehospital phase.

- Are patients with concomitant (vasoactive) head injuries or other causes of shock besides hemorrhage excluded?

-> No, if a patient meets inclusion criteria is included, even if having concomitant head injury.

- “Unsalvageable patients are excluded” Is this at the discretion of the treating physician and before any HEMS treatments?

-> Yes, this is at the discretion of the HEMS physician and happens before any medical treatment. We considered that if any medical treatment is made, the patient has not been considered unsalvageable.

Variables and source of data

- Suggestion: also collect data on transport mode to hospital and interventions performed during transport?

-> Yes, we are collecting that data too. We believed that these data were not of interest to this paper but we're collecting all that sort of technical and logistical details and we're more than happy to share the complete eCRF upon request.

- Table 2 hospital data: "Emergency department outcome data" suggestion also to collect DBP to allow calculation MAP and to distinguish various anatomical injury types in hemorrhagic shock

-> Thanks for this suggestion. We have added DBP in the eCRF (and paper).

Plan for analysis & Sample size

Based on an expected mortality of 20%, the aim is to recruit >500 patients (in the initial protocol published under NCT 04760977 this number was 400). This would allow 120 co-variates in the final regression model. However, in order to be able to quantify the effect of practice variation on outcome, one has to distinguish the practice effect from the variation in injuries, physiology, baseline characteristics etc. As a result, it is likely that more than 10 variables need to be entered as co-variates in the regression model. Can the authors provide information for which patient- and injury factors they want to correct to distinguish the practice effect in order to support their chosen sample size?

*-> Dear reviewer, it is not clear to us which is the calculus you performed to achieve the number of 120 covariates. The rule of thumb usually adopted for sample size estimation in logistic regression is 10 events (deaths) for each covariate. Since estimated mortality is 0.2 (20%), 0.2 * 500 = 100 death events. Finally 100 deaths / 10 death per covariate = 10 covariates.*

We reperformed the calculus with GPower 3.1.9.4 and obtained almost the same results:

z tests - Logistic regression

Options: Large sample z-Test, Demidenko (2007) with var corr

Analysis: A priori: Compute required sample size

Input: Tail(s) = Two

Odds ratio = 1.5

Pr(Y=1|X=1) H0 = 0.2

α err prob = 0.05

Power (1-β err prob) = 0.95

R^2 other X = 0

X distribution = Normal

X parm μ = 0

X parm σ = 1

Output: Critical z = 1.9599640

Total sample size = 503

Actual power = 0.9503087

Concerning the number of variables needed, we believe that a final model (obtained at the end of a least angle selection procedure dropping less informative variables) of 10 covariates in the final model should be a good compromise.

Textual

Page 2, line 55: change “improved outcomes” to “outcomes” -> *corrected*

Page 3, line 29 “based of” should read “based on” -> *corrected*

Page 3”line 31-38” Improved survival has been reported…” Worth mentioning the RePHILL trial here too as a reference, wherein no improved survival was found ? -> *We added a brief citation of the RePHILL trial based on the fact that, even though results are clear, the contest and interpretation of its results is far from being conclusive about the effects of prehospital blood products administration.*

Page 8” HEMS interventions”. Change “high flow vascular access” to “wide bore” -> *corrected*

Page 10, line 53 “written warnings” change to “:reminders”? -> *corrected*

I am looking forward to review a revised paper of this study protocol

Reviewer: 2

Prof. Warwick Butt, Royal Children's Hospital M

Comments to the Author:

A very important initiative which is likely to produce meaningful results which is likely to lead to a national registry and a long term, quality improvement program..good luck

-> *Thank you.*

VERSION 2 – REVIEW

REVIEWER	ter Avest, Ewoud Medical Centre Leeuwarden, ED
REVIEW RETURNED	13-May-2022

GENERAL COMMENTS	Thank you for the opportunity to review the revised version of your manuscript. I think the manuscript has in proved in clarity, and I am happy with the answers provided to my previous questions. Please note that my affiliation as represented for the review is not correct. It should be University Medical Center Groningen, University of Groningen, department ion Emergency medicine, the Netherlands