PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Sepsis and Critical Illness Research Center Investigators: protocols and standard operating procedures for a prospective cohort study of sepsis in critically ill surgical patients
AUTHORS	Loftus, Tyler; Mira, Juan; Ozrazgat-Baslanti, Tezcan; Ghita, Gabriella; Wang, Zhongkai; Stortz, Julie; Brumback, Babette; Bihorac, Azra; Segal, Mark; Anton, Stephen; Leeuwenburgh, Christiaan; Mohr, Alicia; Efron, Philip; Moldawer, Lyle; Moore, Frederick; Brakenridge, Scott

VERSION 1 - REVIEW

REVIEWER	Ashham Mansur Department of Anesthesiology, University Medical Center Goettingen, Germany
REVIEW RETURNED	10-Dec-2016

GENERAL COMMENTS	This is a well-conducted study that provides an interesting approach for treatment of patients with sepsis. Especially, the fact that the computed tool maybe updated including further determinants of sepsis outcome is very interesting. Please consider discussing the necessity of adding other factors of outcome to the computerized tool, eg genetic variants (J Investig Med. 2014 Mar;62(3):638-43) and concomitant medication and co-morbidities that may impact on outcome of sepsis patients. very interesting study about

REVIEWER	JL Vincent University of Brussels
REVIEW RETURNED	19-Feb-2017

GENERAL COMMENTS	The authors present a SOP procedure for long term outcomes in surgical patients. This is a very knowledgeable group of investigators. The idea is interesting, but there are some major problems precluding the use of the database for good scientific publications. 1-The authors wish to study the long-term outcomes in septic patients, but the inclusion criteria are infection (fever and associated tachycardia, altered WBC…) rather than sepsis. They also use the early warning score which was developed as an alarm signal, primarily for nurses. It does not include the sepsis criteria. As an example, a patient with fever and associated tachycardia and a RR of 16/min or a systolic BP of 96 mmHg would reach a score of 6 or above. A doctor should be called for a suspicion of infection. I presume the authors are not interested in the follow-up of all infected

	patients, but if they are, they should say it. In our common language, what we call sepsis is an infection with some degree of organ dysfunction. 2-As it is, there will be no comparative group. I realize the difficulty to enroll a control group, but it would be better to have some comparison between septic and a group of non-septic patients. An alternative would be to study infected patients and separate according to the presence or absence of sepsis. 3-The concept of chronic critical illness, proposed by some, does not make much sense. The authors wish to study long term complications potentially associated with PICS. It will be important to separate these complications from those related to other factors (the underlying disease/comorbidity, the neurological consequences of severe brain damage, another trauma, etc.) Other comments -why do the authors not include IL-7 levels? -The figure 1 is outdated. These concepts of SIRS and CARS should be deleted. Minor -'consent is not able to be obtained after 96 hours': please rephrase

REVIEWER	Brent W. Winston Departments of Critical Care, Medicine and Biochemistry and Molecular Biology Cumming School of Medicine University of Calgary Calgary, Alberta, Canada
REVIEW RETURNED	04-Apr-2017

GENERAL COMMENTS	Review in general: The authors acknowledge that sepsis is a common, costly, and morbid cause of critical illness and this protocol focuses on sepsis in trauma and surgical patients. They also acknowledge that sepsis resuscitation and critical care support strategies have led to improved in-hospital mortality. The authors suggest that the improvement in mortality results in patients now surviving to enter a state of chronic critical illness (CCI), persistent low-grade organ dysfunction, and poor long-term outcomes driven by the persistent inflammation, immunosuppression, and catabolism syndrome (PICS). They have created a Sepsis and Critical Illness Research Center (SCIRC) to provide a platform to study and understand the prevalence and pathogenesis of CCI and PICS at a mechanistic level across multiple medical disciplines hoping this will lead to the development of novel management strategies and targeted therapies. The authors describe the design, study cohort, and standard operating procedures used in a prospective study of human sepsis at a level 1 trauma center and tertiary care hospital providing care for over 2,600 critically ill patients annually. This includes the implementation of an automated sepsis surveillance initiative, augmentation of clinical decisions with a computerized sepsis protocol, using strategies for direct exportation of quality-filtered data

	from the electronic medical record to a research database, and for long-term follow-up. This is a very important area of study in which there is very limited data to date and this group is commended for undertaking this initiative. Also, the tools both developed and planned may be useful to study these patients currently and in the future. The following are suggestions to consider to improve this protocol. 1) There is a good description of the overall protocol but it may be useful to be more specific in the goals of this protocol and study. 2) In the study design area, the term 'surgical sepsis' needs to be more clearly defined. For example, pneumonia and sepsis in the post op period is common; is it to be included in this protocol? 3) Importantly, it is clear that the programs have been written to include the old definitions of sepsis and although the authors do state that the new definitions will be applied as well (page 8), there is no mention of using qSOFA as a screening measure and how this may impact the findings. Analysis using the new definition and SOFA but also using screening with qSOFA would be very useful as the definition of sepsis morphs towards a new understanding. For example in a recent paper by Eli J. Finkelsztein, et al., (in Critical Care, 2017, 21:73 DOI 10.1186/s13054-017-1658-5) they found that "in patients with suspected infection who eventually required admission to the ICU, qSOFA calculated before their ICU admission had greater accuracy than SIRS for predicting mortality and ICU-free days. 4) It would be worth highlighting the computerized sepsis protocol algorithm if it has not been published elsewhere. This could be described in a supplement to the protocol itself. 5) Regarding consent – if consent is deferred for up to 96 hours it is called a 'deferred consent' rather than a waiver of consent. This should be corrected in the protocol. 6) Page 9. Exactly how is the quality and the accuracy of the transformed data going to be validated. This is not clear. Will it be compared to primary source data? Data from the chart? This needs a bit more thoroughly explanation. 7) There is no explanation of how samples are going to be collected and stored. Vigilance in sample collection and storage is necessary. For assistance, there are a number of biobanks and studies that have on line SOP's for sample collection and storage. 8) Related to above, there is a real opportunity to bank biological material through this type of protocol especially if there is already sampling being done. Will there be a biobank of samples available for future testing? New data may suggest new techniques to examine new molecules. Current analysis of biological material must consider small molecules, proteins, DNA and RNA and biospecimen collection and storage can be achieved quite economically if one is already collecting blood samples for analysis. Proper collection and biobanking of well-annotated samples should be considered and encouraged and if undertaken should be described in the protocol. 9) Page 10. Protocolized bedside ECHOcardiography for volume status should be more precisely detailed in the protocol as should

	details about metabolic cart analysis. 10) Page 12. CT scan measures of muscle mass itself does not confer muscle function. It is muscle function that is most closely tied to outcome. Please refer to findings of Claudia dos Santos, et al. AJRCCM, 2016. 194(7):821 and Jane Batt, et al., Intensive Care Medicine 43(4):584. Some measure of muscle function along with muscle mass may be of value for prediction purposes. Other minor corrections: 1) page 2, 3rd text line should read “survive to enter a state” 2) page 3, 3rd point should read “by deficiencies in our understanding” 3) page 7, subject recruitment section first line should read, “When a patient is diagnosed”

REVIEWER	Richard Hotchkiss MD Washington University I am on the Oversight Committee for a P01 from this institution.
REVIEW RETURNED	12-Apr-2017

GENERAL COMMENTS	General Comments The purpose of this manuscript was to describe a new protocol that is useful for the recognition and management of patients with sepsis. In addition, the authors have developed a platform for the investigation of the pathophysiology of the PICS syndrome, i.e., persistent inflammation, immunosuppression, and catabolism syndrome. This group has been a leader in describing this syndrome and in studying new approaches to recognition and potential therapy of this highly lethal disorder. This manuscript provides their initial experience and recommendations. It is well written and valuable examples and protocols are provided. The discussion of patient follow up and evaluation of long term effects of sepsis are especially novel and will be of value to members of the sepsis community. The manuscript could be improved by addition of diagrams that provide an overview of the protocols, patient management, immunologic workup, summaries, etc. This would improve the manuscript considerably. Presentation of some preliminary findings, even if just an overview , would also enhance the manuscript and provide more information to the readers.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Ashham Mansur
Institution and Country: Department of Anesthesiology, University Medical Center Goettingen, Germany
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
This is a well-conducted study that provides an interesting approach for treatment of patients with sepsis. Especially, the fact that the computed tool maybe updated including further determinants of sepsis outcome is very interesting.
Please consider discussing the necessity of adding other factors of outcome to the computerized tool, eg genetic variants (J Investig Med. 2014 Mar;62(3):638-43) and concomitant medication and co-morbidities that may impact on outcome of sepsis patients.
very interesting study about
Thank you for this suggestion. To characterize immunosuppression among critically ill septic patients, we are also measuring expression of PD-1 and PDL-1 blood monocytes and CD66b+ neutrophils. This has been added to the first paragraph under the Biomarker sampling, processing, and analysis heading with a salient reference.

Reviewer: 2
Reviewer Name: JL Vincent
Institution and Country: University of Brussels
Please state any competing interests or state ‘None declared’: none

Please leave your comments for the authors below

The authors present a SOP procedure for long term outcomes in surgical patients. This is a very knowledgeable group of investigators. The idea is interesting, but there are some major problems precluding the use of the database for good scientific publications.

1-The authors wish to study the long-term outcomes in septic patients, but the inclusion criteria are infection (fever and associated tachycardia, altered WBC…) rather than sepsis. They also use the early warning score which was developed as an alarm signal, primarily for nurses. It does not include the sepsis criteria. As an example, a patient with fever and associated tachycardia and a RR of 16/min or a systolic BP of 96 mmHg would reach a score of 6 or above. A doctor should be called for a suspicion of infection. I presume the authors are not interested in the follow-up of all infected patients, but if they are, they should say it. In our common language, what we call sepsis is an infection with some degree of organ dysfunction.
Thank you for the opportunity to clarify. Following the MEWS screening process and bedside clinical adjudication, All cases that were deemed to have sepsis, severe sepsis, or septic shock by the physician or advanced practice provider at the bedside are then reviewed in detail by a faculty member of the SCIRC to ensure that the diagnosis was appropriate, and are reviewed again at weekly SCIRC sepsis adjudication meetings for the same purpose. This has been added to the first paragraph of the Study design and population section. Enrollment began prior to publication of the Sepsis-3 guidelines, and so consensus guidelines from ACCP, SCCM, ESICM, ATS, and SIS have been used. However, clinical parameters that are being collected will allow for calculation of daily SOFA scores, and so patients may also be classified according to Sepsis-3 definitions, as stated in the final paragraph of the Subject recruitment section.

2-As it is, there will be no comparative group. I realize the difficulty to enroll a control group, but it would be better to have some comparison between septic and a group of non-septic patients. An alternative would be to study infected patients and separate according to the presence or absence of sepsis.
The authors have discussed a comparison to patients with sterile inflammation due to pancreatitis, but this is not discussed in the manuscript because it has not been approved by our Institutional Review Board or implemented as part of the study. Within the existing framework, we plan to make comparisons between patients who go on to develop chronic critical illness vs. early recovery and

patients who go on to develop the persistent inflammation, immunosuppression, and catabolism syndrome vs. those who do not. Age-matched non-septic (i.e. healthy, non-hospitalized) controls are being used to provide to comparison for inflammatory, immunosuppression and catabolism biomarkers between a healthy control population, non-CCI and CCI septic populations. This has been added to the third paragraph of the Study design and population section.

3-The concept of chronic critical illness, proposed by some, does not make much sense. The authors wish to study long term complications potentially associated with PICS. It will be important to separate these complications from those related to other factors (the underlying disease/comorbidity, the neurological consequences of severe brain damage, another trauma, etc.)

We agree with the reviewer that the ability to assess the contributions of pre-existing disabilities and comorbidities, which are common in septic ICU patients, is paramount to understanding the acute physiologic changes of PICS as contributors to poor long-term clinical outcomes. We hope to sharpen our understanding of the concept of chronic critical illness by assessing the influence of clinical parameters, gene analyses, and biomarker trends on long term outcomes, including PICS. The authors plan to assess complications associated with PICS by using multivariate analyses to adjust for other factors like the underlying disease, pre-existing comorbidities, the neurological consequences of severe brain damage, traumatic injury severity, and transfer from an outside facility following a period of illness during which the patient was not managed according to our protocols.

Other comments
-why do the authors not include IL-7 levels?
Although IL-7 may play an important role in the pathophysiology of sepsis and recovery from sepsis, other inflammatory cytokines were given stronger priority when resource allocation was discussed.

-The figure 1 is outdated. These concepts of SIRS and CARS should be deleted.

We while we believe current data supports the simultaneous pro and anti-inflammatory trajectories early after sepsis outlined in Figure 1, we acknowledge that the term “CARS” is outdated. We have modified the figure to remove SIRS and CARS.

Minor
-‘consent is not able to be obtained after 96 hours’: please rephrase
This has been rephrased to state, “If consent is not obtained within 96 hours…”

Reviewer: 3
Reviewer Name: Brent W. Winston
Institution and Country: Departments of Critical Care, Medicine and Biochemistry and Molecular Biology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
Please state any competing interests or state ‘None declared’: None Declared

Please leave your comments for the authors below
Review of BMJ Open Manuscript #bmjopen – 2016-015136

Article Type: Protocol

Authors: Loftus, T. et al.

Title: Sepsis and Critical Illness Research Center Investigators: standard operating procedures for a prospective cohort study of sepsis in critically ill surgical patients

Review in general:

The authors acknowledge that sepsis is a common, costly, and morbid cause of critical illness and this protocol focuses on sepsis in trauma and surgical patients. They also acknowledge that sepsis resuscitation and critical care support strategies have led to improved in-hospital mortality. The authors suggest that the improvement in mortality results in patients now surviving to enter a state of chronic critical illness (CCI), persistent low-grade organ dysfunction, and poor long-term outcomes driven by the persistent inflammation, immunosuppression, and catabolism syndrome (PICS). They have created a Sepsis and Critical Illness Research Center (SCIRC) to provide a platform to study and understand the prevalence and pathogenesis of CCI and PICS at a mechanistic level across multiple medical disciplines hoping this will lead to the development of novel management strategies and targeted therapies.

The authors describe the design, study cohort, and standard operating procedures used in a prospective study of human sepsis at a level 1 trauma center and tertiary care hospital providing care for over 2,600 critically ill patients annually. This includes the implementation of an automated sepsis surveillance initiative, augmentation of clinical decisions with a computerized sepsis protocol, using strategies for direct exportation of quality-filtered data from the electronic medical record to a research database, and for long-term follow-up.

This is a very important area of study in which there is very limited data to date and this group is commended for undertaking this initiative. Also, the tools both developed and planned may be useful to study these patients currently and in the future.

The following are suggestions to consider to improve this protocol.

1) There is a good description of the overall protocol but it may be useful to be more specific in the goals of this protocol and study.
Thank you for this suggestion. The Introduction section has been modified to state that the objective of the study is to understand the prevalence and pathogenesis of PICS at a mechanistic level across multiple medical disciplines, leading to the development of novel management strategies and targeted therapies, and the third paragraph of the Study design and population now states that within the study population, cohort analyses will include comparisons between patients who develop CCI versus patients who experience early recovery from sepsis. Among CCI patients, patients who develop PICS will be compared to patients who do not.

2) In the study design area, the term ‘surgical sepsis’ needs to be more clearly defined. For example, pneumonia and sepsis in the post op period is common; is it to be included in this protocol?
We agree that this was a problematic term and it has been removed from the first paragraph of the Study design and population section. While “surgical sepsis” implies a source of infection related to surgery, we are studying all sources of infection that may develop in surgical patients. Rather than using the broad, vague term ‘surgical sepsis’, we have been prospectively adjudicating and recording infectious source classifications by more precise terms (i.e. intra-abdominal sepsis, surgical site infection, pneumonia, catheter-related bloodstream infection, etc.).

3) Importantly, it is clear that the programs have been written to include the old definitions of sepsis and although the authors do state that the new definitions will be applied as well (page 8), there is no mention of using qSOFA as a screening measure and how this may impact the findings. Analysis using the new definition and SOFA but also using screening with qSOFA would be very useful as the definition of sepsis morphs towards a new understanding. For example in a recent paper by Eli J. Finkelsztein, et al., (in Critical Care, 2017, 21:73 DOI 10.1186/s13054-017-1658-5) they found that “in patients with suspected infection who eventually required admission to the ICU, qSOFA calculated

before their ICU admission had greater accuracy than SIRS for predicting mortality and ICU-free days.
The authors recognize the importance of incorporating qSOFA in this study. Based on data collected according to the original study protocol, qSOFA will be easily derived for analyses. The description of incorporating Sepsis-3 has been modified to state that qSOFA will be incorporated as well, with a salient reference.

4) It would be worth highlighting the computerized sepsis protocol algorithm if it has not been published elsewhere. This could be described in a supplement to the protocol itself.

The computerized sepsis protocol algorithm has been previously published, as highlighted in the first paragraph of the Computerized clinical decision support (CCDS) sepsis protocol section. We have added additional citations to the manuscript for reference to the interested reader.

5) Regarding consent – if consent is deferred for up to 96 hours it is called a 'deferred consent' rather than a waiver of consent. This should be corrected in the protocol.
The reviewer is correct. "Waiver of informed consent" has been changed to "deferral of informed consent" in the first paragraph of the Subject recruitment section.

6) Page 9. Exactly how is the quality and the accuracy of the transformed data going to be validated. This is not clear. Will it be compared to primary source data? Data from the chart? This needs a bit more thoroughly explanation.
Thank you, this was a typographical error. The statement was in regards to quality control analysis of data collected throughout the various cores and projects of the program, and its auditing and validation by the Database Management and Biostastistics Core. The Database Management and Biostatistics Core identifies potential outlier values and reviews the source data with SCIRC faculty when potential outliers are identified. This has been added to the first paragraph of the Data procurement and management section.

7) There is no explanation of how samples are going to be collected and stored. Vigilance in sample collection and storage is necessary. For assistance, there are a number of biobanks and studies that have on line SOP's for sample collection and storage.

The second paragraph of the Biomarker sampling, processing, and analysis section has been expanded to describe laboratory facilities, refer to best practice guidelines for biological sample collection and storage with a salient reference, training for laboratory personnel, and consistency in sample analysis, reagent use, and personnel.

8) Related to above, there is a real opportunity to bank biological material through this type of protocol especially if there is already sampling being done. Will there be a biobank of samples available for future testing? New data may suggest new techniques to examine new molecules. Current analysis of biological material must consider small molecules, proteins, DNA and RNA and biospecimen collection and storage can be achieved quite economically if one is already collecting blood samples for analysis. Proper collection and biobanking of well-annotated samples should be considered and encouraged and if undertaken should be described in the protocol.
The authors agree that there will be a great opportunity to perform future testing of new molecules and utilization of new techniques. The second paragraph of the Biomarker sampling, processing, and analysis section has been modified to state that stored samples are maintained in a biobank that will remain available for future testing.

9) Page 10. Protocolized bedside ECHOcardiography for volume status should be more precisely detailed in the protocol as should details about metabolic cart analysis.

The description of nutritional parameters has been expanded in the first paragraph of the Subject retention, clinical assessment, and long-term follow-up section to state that we are measuring nutrition provided by gastric, post-pyloric, and parenteral routes, weekly caloric and protein goals versus actual calories and protein administered, 24-hour urine collection to assess nitrogen balance, indirect calorimetry, and changes in body mass index and ideal body weight. Detailed clinical protocols for these measures have been provided in Supplemental Table 2. Additionally, a new second paragraph has been added to the Subject retention, clinical assessment, and long-term follow-up to describe criteria for performing transesophageal versus transthoracic echocardiography as well as measurements, clinical interpretation of echocardiography findings, and the implementation of treatment strategies based on echocardiography findings.

10) Page 12. CT scan measures of muscle mass itself does not confer muscle function. It is muscle function that is most closely tied to outcome. Please refer to findings of Claudia dos Santos, et al. AJRCCM, 2016. 194(7):821 and Jane Batt, et al., Intensive Care Medicine 43(4):584. Some measure of muscle function along with muscle mass may be of value for prediction purposes.

Thank you for making this point. The description of skeletal muscle high-resolution respirometry in the first paragraph of the Biomarker sampling, processing, and analysis section has been expanded to state that we will also perform assessments of muscle morphology and myosin/actin ratio by histochemistry, and measurement of FoxO3A, MuRF1, MAFBx, BNIP, calpains, and 20S proteasome activity. A description of the technique has also been added. Additionally, there are functional measures of strength and physical function being performed during the outpatient long-term follow-up phase of the study, described in the fourth paragraph of the Subject retention, clinical assessments, and long-term follow-up section.

Other minor corrections:

1) page 2, 3rd text line should read “survive to enter a state”
The third sentence in the Introduction section of the Abstract has been revised and now reads, “survive to enter a state.”

2) page 3, 3rd point should read “by deficiencies in our understanding”
The third bullet point in the Strengths and limitations of this study section has been revised and now reads “by deficiencies in our understanding.”

3) page 7, subject recruitment section first line should read, “When a patient is diagnosed”
The first sentence in the first paragraph of the Subject recruitment section has been revised and now reads “When a patient is diagnosed.”

Reviewer: 4
Reviewer Name: Richard Hotchkiss MD
Institution and Country: Washington University
Please state any competing interests or state ‘None declared’: I am on the Oversight Committee for a P01 from this institution.

Please leave your comments for the authors below
General Comments
The purpose of this manuscript was to describe a new protocol that is useful for the recognition and management of patients with sepsis. In addition, the authors have developed a platform for the investigation of the pathophysiology of the PICS syndrome, i.e., persistent inflammation, immunosuppression, and catabolism syndrome. This group has been a leader in describing this

syndrome and in studying new approaches to recognition and potential therapy of this highly lethal disorder.

This manuscript provides their initial experience and recommendations. It is well written and valuable examples and protocols are provided. The discussion of patient follow up and evaluation of long term effects of sepsis are especially novel and will be of value to members of the sepsis community.

The manuscript could be improved by addition of diagrams that provide an overview of the protocols, patient management, immunologic workup, summaries, etc. This would improve the manuscript considerably.
Thank you for this suggestion. Tables and figures have been added to illustrate indications for blood transfusion (Table 2), our delirium protocol (Supplementary table 1), our nutrition protocol (Supplementary table 2), and our daily wake up and breathe protocol (Supplementary figure 1).

Presentation of some preliminary findings, even if just an overview, would also enhance the manuscript and provide more information to the readers.
To present preliminary findings and describe the study population, Table 3 has been added to describe patient demographics, comorbidities, illness severity, length of stay, and discharge disposition. The second paragraph of the Study design and population section now refers to Table 3.

VERSION 2 – REVIEW

REVIEWER	Ashham Mansur Department of Anesthesiology, University Medical Center Goettingen, lower saxony, Germany
REVIEW RETURNED	25-May-2017

GENERAL COMMENTS	My suggestions have been addressed adequately.

REVIEWER	Brent Winston University of Calgary Bumming School of Medicine Departments of Critical care, Medicine and Biochemistry and Molecular Bilogy HRIC 4C64 3280 Hospital Dr. N.W. Calgary, AB Canada T2N 4Z6
REVIEW RETURNED	30-May-2017

GENERAL COMMENTS	Review: I thank the authors for addressing the majority of this reviewer concerns in the revised protocol. The only suggestion would be a more clear description of strength assessment other than just grip strength assessment as muscle sarcopenia is an important outcome assessment.

REVIEWER	Richard Hotchkiss Washington University School of Medicine
REVIEW RETURNED	15-May-2017

GENERAL COMMENTS	Now acceptable