Author’s response to reviews

Title: Development of a clinical prediction rule for sepsis in primary care: protocol for the TeSD-IT study

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Version: 1 Date: 15 Apr 2020

Author’s response to reviews:

Dear editor,

Thank you for reviewing our manuscript “Development of a clinical prediction rule for sepsis in primary care: protocol of the TeSD-IT study” (DAPR-D-20-00006). The comments of the reviewers were helpful to improve our manuscript. A point-by-point response is listed below.

Although everybody’s lives and routines are affected by the COVID-19 pandemic, luckily the consequences for the TeSD-IT study are limited. We already had enough patients included in the TeSD-IT study (357 in total) before the pandemic made it impossible to continue to enrol patients in the study in the second week of March.

Therefore we can precede with the analyses, and no major problems are foreseen at this moment concerning our research.

All co-authors approved the revised manuscript, and we hope it is considered for publication in Prognostic and Diagnostic Research.
With kind regards, on behalf of the co-authors,

Feike Loots

Reviewer #1: 2 protocol of the TeSD-IT study Prepositions are almost arbitrary, but "protocol for" is easier on my ear. Google finds 3 times as many "protocol for"-s.
Authors response: Changed as suggested

Reviewer #1: 34 We will … Tenses go backwards and forwards rather randomly.
Authors response: We now use the future tense consistently

Reviewer #1: 34 The following candidate predictors are prospectively recorded It is a pity that GP's did not record the most likely site of infection and their confidence in their guess.
Perhaps the discussion section could explain why this was not done?
Authors response: The main goal of the study is to identify patients at risk of progression of sepsis regardless the source of infection. Although it is interesting to assess the accuracy of the diagnosis of the GP this information will likely not add to the model. Furthermore, the final diagnosis can be equivocal, especially in patients treated at home.

Reviewer #1: 35-36 1) age; 2) body temperature; 3) systolic blood pressure; 4) heart rate; 5) respiratory rate; 6) peripheral oxygen saturation; 7) altered mental status; 8) rigors and 9) rapid illness progression.
Items 1 - 6 are parameters
Items 7 - 9 are values of parameters
For precision and consistency, for 7 - 9 consider mental status, history of rigors, rate of progression
Authors response: Changed as suggested

Reviewer #1: 50 samples will be retrieved samples will be obtained?
Authors response: Changed as suggested

Reviewer #1: 52 validation is needed validation will be needed
Authors response: Changed as suggested

Reviewer #1: 69-70 but patients' early stages of sepsis are often presented in primary care.
But patients often present in primary care in the early stages of sepsis
Authors response: Changed as suggested

Reviewer #1: 72 patients can be treated at home or have to be referred to a hospital A patient can safely be treated at home or should be referred to a hospital
Authors response: Changed as suggested

Reviewer #1: 84-85 Besides the white blood count, the SIRS parameters are heart rate &lt;90/min, respiratory rate &gt;20/min, and a body temperature &lt;36°C or &gt;38°C. In this sentence A parameter is a variable that can take a range of values.
A criterion is a specified value of a parameter, and it is used as a threshold for some decision about classification or action.
In this example, "heart rate" is a parameter, while "heart rate <90/min" is a criterion used in the definition of SIRS.
So, this sentence should be: "...the SIRS criteria are ..."
Authors response: This is corrected

Reviewer #1: 90  The parameters used in the qSOFA  As above: The criteria used in the qSOFA
Authors response: This is corrected

Reviewer #1: 94  have all shown to increase  have all been shown to increase
Authors response: Changed as suggested

Reviewer #1: 95  Both signs and symptoms as well as additional biomarkers like CRP, lactate and PCT are however not evaluated for early detection of sepsis in primary care. Do you mean such as CRP, lactate, and PCT? Do you mean such as "potential point of care tests"?
The name of the study implies that CRP, lactate, and PCT are available as point of care tests, but this is not stated explicitly anywhere. This is a good place to do so.
Authors response: Changed as suggested.

We added to the Methods section (Candidate predictors): “CRP, lactate and PCT are currently available as POCT”.

Reviewer #1: 119 - 120  Condition that requires secondary care assessment in case of ... A condition that requires secondary care assessment if there are ...
Authors response: Changed as suggested

Reviewer #1: 129  Candidate predictors were considered when they were expected to ... Candidate predictors were selected if there was evidence to suggest that they might usefully contribute to the diagnosis of sepsis, and if they can be easily and objectively measured by GPs
Authors response: Changed as suggested

Reviewer #1: 137 -138  the NICE sepsis guideline specifically recommends to further evaluate PCT in sepsis research  The NICE sepsis guideline recommends research to further evaluate the use of PCT point of care tests for diagnosing serious bacterial infection and initiating antibiotic therapy.
This is a wider brief than sepsis research.
Authors response: Changed as suggested

Reviewer #1: 143 - 144  In this consensus definition, sepsis is defined by an increase of two SOFA-points  The operational definition of sepsis is the presence of infection and a SOFA score of at least two above the baseline (which can be assumed to be zero in patients not known to have preexisting organ dysfunction).

Or, if brevity is important, and most patients triaged by GPs have baseline SOFA scores of zero:
The operational definition of sepsis is the presence of infection and a SOFA score of at least two.
Authors response: We agree that the first suggestion is the most accurate and therefore included in the manuscript.

Reviewer #1: 146 we will install three expert panels we will appoint three expert panels
Authors response: Changed as suggested

Reviewer #1: 170 the patient inclusion will be prolonged Patients will continue to be recruited
Authors response: Changed as suggested

Reviewer #1: 171 End of follow-up is 30 days after inclusion of the last patient. Does "follow-up" mean that patients were seen for the study up to 30 days after the inclusion of the last patient?
Authors response: Follow-up means collection of medical records up to 30 days after inclusion and a questionnaire at 30 days. For clarification we altered the text to "Follow-up of the patients is 30 days"
Furthermore, an additional figure shows the study procedures more clearly

Reviewer #1: 234 Using the rule of thumb of 10 events per variable Some picky reader could say that there is no good rationale for this rule of thumb

Maybe discuss this in the discussion section?
Authors response: We added the following in the discussion section “We realise the validity of rule of thumb of 10 event per variable is heavily debated.27 However, using an alternative sample size calculation suggested by van Smeden,28 results in a similar sample size of about 350 patients in case of 12 variables, an outcome rate of 0.35 and rMPSE set at 0.09”

Reviewer #1: 331 sepsis were published, which we try to implement are good as possible sepsis were published (which we try to implement) are as good as possible
Authors response: Changed into: “…sepsis were published, which we try to implement as well as possible”

Reviewer #1: 343 - 345 (increase of ≥2 points from baseline due to infection) (increase, due to infection, of ≥2 points from baseline)
Authors response: Changed as suggested

Reviewer #1: 1: Imputation of SOFA points:
Peripheral oxygen saturation (SpO2) and supplemented oxygen are used to estimate respectively the pO2 and FiO2 for calculation of the pO2/FiO2 ratio. Results from blood gas analyses are (outside the ICU) are not taken into account as the amount of oxygen supplied at the time of blood collection is unknown. For the estimation of the pO2 and FiO2, the following conversion tables are used: Replace pO2 by the conventional abbreviation, PaO2.
Authors response: This is corrected. Also the header in the table SO2, is corrected into SpO2.
Reviewer #1: The table uses PaO2 as the column header.
SOFA points are adopted from the electronic medical records from the ICU SOFA points are obtained from …
Authors response: Changed as suggested

Reviewer #2:
- CPR is commonly used acronym in healthcare for cardiopulmonary resuscitation. Suggest that the authors consider a differ acronym to avoid confusion.
Authors response: We chose not to use a different acronym, but to write “clinical prediction rule” in full throughout the paper.

Reviewer #2:
- While the title of the study includes the words diagnostic and prognostic study. The protocol describes a study which is developing models therefore it is not strictly diagnostic nor prognostic (even though the intention for these models will be to diagnose sepsis and predict admission to hospital). Further external validation would be needed to measure diagnostic and prognostic accuracy. Consider revising.
Authors response: We chose not the alter the original name of the study.

Reviewer #2:
- The TRIPOD (and potentially the STARD) checklist should be followed and all relevant changes made throughout the protocol.
Authors response: We used the TRIPOD checklist for designing of the study and writing of the manuscript.

Reviewer #2:
- It is difficult to follow the study processes from patient screening to participant follow up. A study flowchart would help the reader. A lot of the information presented in the discussion should be moved to the methods section for
Authors response: We have added a flowchart of the study processes.

Reviewer #2:
- The protocol does not adequately describe the process of data collection and follow up of the patients not referred to hospital. If these patients were subsequently referred to hospital, would this data be captured? This is important as they are false negatives in the current care pathway and so, a potential improvement over current care would be to ensure these patients were referred sooner.
Authors response: All hospital admissions in the first 30-days are captured. We added the following to the Methods section (Data-extraction): “Information from all hospital admissions in the 30-day follow-up will be retrieved, first by digital search in the local hospital and secondly by manual screening of the GP record for admissions in other hospitals”
Reviewer #2:

- Could the authors make it clear their a priori rules for the expert panel diagnosis? It is unclear what data they will be presented with when, and in which patients in order to form their diagnosis. For example, in line 343 it states that the expert panel will be instructed to use the SOFA score. The supplementary material suggested that the SOFA score will be inputted for those patients where it is not available i.e. those not admitted to hospital, is this the case. Imputation based on this data risks bias within the development of the model. In general, more clarity is needed on the analysis plan in the protocol. An appended statistical analysis plan could add strength to this protocol and aid other investigators in this complex area.

Authors response: Additional file 1 is extended with more detailed information what information is presented to the expert panel and how the SOFA scores are calculated.

Reviewer #2:

- Within the data cleaning section (lines 251 - 255): the explanation of removal of outliers 'more than three standard deviations from the mean' is worrying as it could lead to selection bias. By nature of sepsis, these patients may have extremely high or extremely low clinical test results. A more appropriate plan would be to look for statistical outliers and explore whether these are data recording errors. If so, they could be removed. If not, they should be included as they may represent the most important data of all. Failure to include these data points could results in selection bias. Please see reference: Rousséeuw, P.J. and Hubert, M. (2011), Robust statistics for outlier detection. WIREs Data Mining Knowl Discov, 1: 73-79. doi:10.1002/widm.2

Authors response: We agree it would not be appropriate to remove all outliers. Therefore, this is not our suggested method. We describe that outliers more than three standard deviations from the mean are discussed. We clarified this in the text: “.will be discussed and corrected or removed in case of data recording error”

Reviewer #2:

- Do you have a health economic evaluation plan? If so, please add to the supplementary material as it will be useful for other researchers.

Authors response: The complete health economic evaluation plan is provided as a separate supplemental file.

Reviewer #2:

- Presentation of the inclusion and exclusion criteria could be improved and separated on individual lines to help the reader. Further clarity could be added to also help the reader from other countries understand the exact patient group which are eligible.

Authors response: The in- and exclusion criteria are represented in separated lines as suggested.

Reviewer #2:

- The protocol is inconsistent in the description of the QoL instrument (EQ-5D or EQ-5D-5L) which will be used. Please choose appropriate tool and make consistent.

Authors response: This is corrected to consistent using of EQ5D-5L.
Reviewer #2:
- How the data regarding confidence in diagnosis was going to be analysis was not clear. Please clarify analysis plan.
Authors response: For the construction of the clinical prediction rule, only the consensus diagnosis of sepsis is used. The confidence in the diagnosis will be reported as additional background information.

Reviewer #2:
- Line 89: propose changing diagnosis to recognise…
Authors response: We believe the term “diagnose” is more correct in this context.

Reviewer #2:
- Line 155: Change "in" to "into".
Authors response: This is corrected.

Reviewer #2:
- Lines 186-188: there is an apparent time delay in taking blood samples from those patients who are referred to hospital and now. Will this be accounted for in the analysis?
Authors response: In both cases the blood samples are taken about 30-60 minutes after inclusion. In the final paper we will show the time difference between the groups.

Reviewer #2:
- Lines 213-214: Asking patients to complete an EQ-5D-5L questionnaire from recall for the worst day they remember from their recent sepsis episode is going to produce results of questionable accuracy. A symptom of sepsis is acute confusion, and this, coupled with the duration of time from their sepsis episode to the end of follow-up when they are asked to complete the questionnaire (30 days), would lead to poor accuracy of recall in this largely elderly population. This should be discussed as a limitation.
Authors response: We agree with this limitation although we believe the clinical prediction rule is not compromised. We added the following lines in the discussion section: “For the cost-effectiveness analysis, patients will receive a questionnaire at day 30 measuring EQ5D-5L. The results may be biased due to selective response and poor recall due to sepsis- or age-related cognitive impairment”

Reviewer #2:
- Line 226: EMV not defined.
Authors response: Although “EMV score” is most widely known by clinicians in The Netherland, we realize for readers not familiar with this abbreviation “Glasgow Coma Score” is more clear. This is corrected.

Reviewer #2:
- Lines 232-234: It is important to note the evidence advocating 10 events per variable in binary logistic regression analysis is weak. Further explanation should be provided why you are using this rule. The authors may find this paper helpful: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6710621/pdf/10.1177_0962280218784726.pdf
Authors response: We added the following in the discussion section “We realise the validity of rule of thumb of 10 event per variable is heavily debated.27 However, using an alternative sample size calculation suggested by van Smeden,28 results in a similar sample size of about 350 patients in case of 12 variables, an outcome rate of 0.35 and rMPSE set at 0.09”
Reviewer #2:
- Line 248: primary outcome should read "sepsis within 72 hours"
Authors response: “sepsis within 72 hours of inclusion” is changed to “sepsis within 72 hours” throughout the paper.

Reviewer #2:
- Table 1 - add references to the sources in order to future proof this publication.
Authors response: References are added in Table 1.

Reviewer #2:
- Line 289 - Using AUROC to compare between different models should be used with caution, please see reference: https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-11-13
Authors response: Difference in model performance will be evaluated based on the whole body of evidence of calibration and discrimination. No single measure will be used to determine model superiority over another.

Reviewer #2:
- Line 331 - try to implement as good as possible: reword to ' try to implement as much/well as possible'
Authors response: This is altered in “as well as possible”

Reviewer #2:
- Line 360 - change retroactive to retrospective.
Authors response: Changed as suggested

Reviewer #2:
- Are the investigators planning to make the data available for other investigators? It would add strength to make their intentions clear in like 367.
Authors response: Data will be made available and this is added under the subheading “Availability of data and materials”.