PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Improved diagnostics of infectious diseases in Emergency Departments – a protocol of a multifaceted multicenter diagnostic study
AUTHORS	Skjøt-Arkil, Helene; Heltborg, Anne; Lorentzen, Morten; Cartuliares, Mariana; Hertz, Mathias Amdi; Graumann, Ole; Rosenvinge, Flemming; Petersen, Eva; Østergaard, Claus; Laursen, Christian; Skovsted, Thor; Posth, Stefan; Chen, Ming; Mogensen, Christian

VERSION 1 – REVIEW

REVIEWER	Brendish, Nathan University of Southampton, Clinical & Experimental Sciences, Faculty of Medicine
REVIEW RETURNED	13-Apr-2021

GENERAL COMMENTS	Overview This is a protocol for a diagnostic accuracy study, or rather, a combined protocol for several diagnostic accuracy studies of different diagnostic tools embedded within one study. The study will recruit from three Emergency Departments in Denmark. The diagnostic tools being evaluated are primarily point-of-care tests. The scientific need for this trial is explained. While this is primarily a diagnostic accuracy set of studies, there is a randomised controlled trial of sputum diagnostics embedded within this study. The study protocol appears to conform broadly to the SPIRIT reporting guidelines for trial protocol reporting. Ethics approval has already been granted by a regional ethics committee, and funding appears already awarded. The sub-studies are prospectively registered (before the stated enrolment start-date) separately on an international trials database (clinicaltrials.gov). The sample size is appropriately justified. All patients must provide written informed consent. The inclusion and exclusion criteria for potential participants are appropriately explained. Enrolment has already commenced. The seven objectives of the study are clearly described, alongside the overarching objective to create a novel diagnostic model for ED infection management. I cannot see the appendix mentioned in the SPIRIT guidelines as part of this peer review process and so cannot comment on informed consent forms or further plans for biological specimens.

	Personally and professionally I look forward to seeing the results of the study as the potential for clinical impact and a paradigm change in how we treat patients with suspected infection is high. Major points to revise • The sponsor of the study is not mentioned (the legal rather than financial sponsor of the study) – this must be clearly documented. Additionally, the SPIRIT checklist page numbers may need updating to reflect where legal sponsor information is located. • Page 10 line 6: Please specify where the POC-PCR system (BioFire) will be located. If located in a centralised laboratory then it is not a point-of-care test and will need renaming as a rapid laboratory test, but a point-of-care laboratory sited close to patient care is likely to be perfectly acceptable. • Page 11 line 33: monitoring: monitoring in a trial usually refers to the trial processes being audited by the legal sponsor of the trial. I suggest retitling this subsection as 'Data monitoring' for clarity and also introducing a section describing the monitoring system in place for trial process auditing. • While the objectives / research questions are clear, no specific mention is made in each sub-study of the primary and secondary outcomes [excepted on page 12 for the RCT – this is not sufficiently specific though]. The primary and secondary outcomes of each of the seven sub-studies need to be clearly and precisely described for transparency and appropriate data collection. • Related to the primary and secondary outcomes, the statistical data analysis plan for each sub-study should be specified. • The WHO Trial Registration Data Set (which could be a section before the introduction), is missing – this would be a good summary of the key trial details and should be included. • As this study includes a randomised controlled trial the protocol should include mention of how the researchers will collect data about and deal with (serious) adverse events and protocol deviations/violations. Most of the 'major' points for revision are likely to be simple additions to the manuscript - much of the information appears on the clinicaltrials.gov pages (e.g. primary and secondary outcomes, most of the WHO data set information, etc). Minor points to consider revising • Page 14 line 31: Funding – consider putting the specific funding award reference numbers into this paragraph • Page 8 line 27: I would suggest removing the specified number (six) of project assistants who will recruit patients and collect data as this may cause issues if any of your project assistants leave the research group for any reason or you train more. • Page 9 line 27: "logistic system" – please clarify – this this the local IT system that lists patients attending the Emergency Department? • The 'Strengths and Limitations' section at the beginning mentions the impact of COVID-19 on trial recruitment is uncertain, yet this limitation is not mentioned anywhere in the main text. I suggest that this limitation is mentioned in the discussion and any factors that might alleviate this concern.

	• Given the extensive nature of testing the patients are receiving it would be reasonable to include a sentence if patients receive their results from POC-US etc. • I recommend removing mention of publication of results in “at least 10” journals; while likely, this cannot be foreseen. • Please consider naming the study chief investigator and the local principal investigators at each site in your protocol. • Please mention how/if public and patient involvement was included in your trial design. • Please add an expected end date for your study.

REVIEWER	McKew, Genevieve Royal Prince Alfred Hospital, Infectious Diseases and Microbiology
REVIEW RETURNED	14-May-2021

GENERAL COMMENTS	Review of bmjopen-2021-049606: “Improved diagnostics of infectious diseases in Emergency Departments – a protocol of a multifaceted multicenter diagnostic study” This is an extremely well-designed protocol for a pragmatic study aimed at improving diagnosis of common infections in emergency departments in Denmark. The aims of improving patient care and reducing use of broad spectrum antibiotics are useful. The protocol is generally well designed and explained, and I have no major criticisms. I do have some minor criticisms and clarifications. Minor points A minor point which explains why I answerd “No” to Question 12: The limitations are described, however it should be emphasised that it is only generalisable to settings where appropriately trained staff and equipment can perform bedside ultrasound, and well-resourced settings where a rapid POC sputum microbiology diagnostic service and POC-UFC is available. The gold standard will be an important part of the statistical analysis and needs to be clearly defined. In Page 5 Line 43-4 it says “In this study we define APN as a urinary tract infection with typical local symptoms and systemic affection (i.e. fever, sepsis), thus indicating ascension of infection above the bladder.” Does this refer to the patients who have SUSPECTED APN and are to be admitted to that arm? If so, should this read “we define SUSPECTED APN as…” and also what are the typical local symptoms – these need to be specified. Or is the definition of suspected APN simply that the ED physician suspects APN (this is implied later). If this is the case, I suggest removing the definition at Page 5 Line 43-4 or incorporating it into the “Reference Standard” section on page 8. Page 5 Line 52. Please justify why verified COVID-19 within the last 14 days are excluded. Does this also include patients with CAP who are included but subsequently diagnosed with COVID-19? Please clarify this. Page 5 Line 54. Please justify why pregnant women are excluded from arms that don’t include low dose CT. APN and arm C (other infections) would be diagnosed in a similar manner to non-

	pregnant patients. As there are other groups (patients under 40 years) that are excluded only from arm A for safety reasons. Page 6 Line 56 – are patient urine samples also going to be analysed by dipstick, as is common practice? This could be useful information in reporting the results. It may influence the ED physician's diagnosis and ED treatment so it should be stated whether or not it's going to be used. Page 7 Line 11: "Routine microbiology analysis of sputum (culture and PCR)." PCR needs to be defined here: will PCR be performed on sputum and/or NP swab (this would be more useful for diagnosing resp viruses which can cause up to 30% of CAP). What targets in the PCR? What modality? Will these be the same across all sites, or different? In "culture", is Gram stain going to be included? This should be specified. For example, some laboratories do not culture sputa which show large numbers of squamous epithelial cells on the Gram stain, as they are likely poor specimens from the upper respiratory tract and will not yield useful results. Some laboratories only culture sputa with polymorphs on the Gram stain. Will all sputa received in the lab be cultured, or will there be exclusions? Page 7 Line 15-6: what is the recommended action list developed by clinical microbiologists? This should be provided. Page 7 line 19: Sputum analysis. Please explain why outcome adjudicators are not blinded – is this because they will have access to the results – just state that here. Page 7 – why does the APN group get both microbiology diagnostics (POC-UFC and conventional culture) but the CAP group get randomised 1:1? This would be a lovely opportunity to analyse performance of sputum POC vs conventional culture plus PCR. Suggest considering doing both on the whole CAP group. You could still randomise to reporting only sputum POC vs reporting conventional, to be able to perform the superiority analysis proposed on Page 9. If both aren't done, this could lead to difficulties for the outcome adjudicators. For example, the patient gets only sputum culture and the conventional PCR doesn't include S. pneumoniae as a target – you would not be able to directly compare this to a patient who got Biofire and was positive for S. pneumoniae, as sputum culture may not be as sensitive. It would be good to have both results available to the expert panel defining diagnoses. Page 7 line 38 "séance" should this read "sequence"? Page 7, all sections. It states that the new radiology modalities will be reported to clinical staff immediately if clinically necessary – does this mean all scans positive for APN/CAP, or only those which require alternative interventions such as those showing hydronephrosis, thoracic diagnoses which require intervention etc. Please specify what diagnoses will/will not be notified. If all CAP/APN is notified, doesn't that undermine the premise of the study? Page 8, reference standard. This is obviously extremely important as it is going to define the success or otherwise of the interventions in this well-designed and resource-intensive study.

	Please further define the expert group (see next comment). Please attach the standardized template for review. It can be quite difficult to definitively differentiate bacterial from viral pneumonia, or from viral infection with a secondary bacterial pneumonia vs a viral pneumonia. Please include the template and the parameters the expert group will be using for review. Page 8, reference standard. Please state if the expert group is going to attribute the causative pathogen in the CAP group – as the "appropriate antibiotics" outcome in the CAP group is going to depend on the causation. I would suggest this requires expert respiratory medicine and/or clinical microbiology input, as microbiology results don't always match causation for CAP. E.g. patients with COPD may be colonised with Haemophilus and grow Haemophilus, but the cause of their exacerbation may be RSV. Or bronchiectatic patients may grow Pseudomonas as they are colonised, but this is not the cause of CAP. Such patients aren't excluded. Page 9 Line 2 – 4. Urine culture is going to be used as a reference standard for POC-UFC; what CFU/mL of a uropathogen will be used?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Nathan Brendish, University of Southampton Comments to the Author:

Overview:
This is a protocol for a diagnostic accuracy study, or rather, a combined protocol for several diagnostic accuracy studies of different diagnostic tools embedded within one study. The study will recruit from three Emergency Departments in Denmark. The diagnostic tools being evaluated are primarily point-of-care tests. The scientific need for this trial is explained.

While this is primarily a diagnostic accuracy set of studies, there is a randomised controlled trial of sputum diagnostics embedded within this study.

The study protocol appears to conform broadly to the SPIRIT reporting guidelines for trial protocol reporting. Ethics approval has already been granted by a regional ethics committee, and funding appears already awarded. The sub-studies are prospectively registered (before the stated enrolment start-date) separately on an international trials database (clinicaltrials.gov). The sample size is appropriately justified. All patients must provide written informed consent. The inclusion and exclusion criteria for potential participants are appropriately explained. Enrolment has already commenced.

The seven objectives of the study are clearly described, alongside the overarching objective to create a novel diagnostic model for ED infection management.

I cannot see the appendix mentioned in the SPIRIT guidelines as part of this peer review process and so cannot comment on informed consent forms or further plans for biological specimens.
ANSWER: We are sorry for that. I have tried to add it to the submission again and hope this time it will be visible

Personally and professionally I look forward to seeing the results of the study as the potential for clinical impact and a paradigm change in how we treat patients with suspected infection is high.
ANSWER: Thank you so much for this comment - it motivates.

Major points to revise:

- The sponsor of the study is not mentioned (the legal rather than financial sponsor of the study) – this must be clearly documented. Additionally, the SPIRIT checklist page numbers may need updating to reflect where legal sponsor information is located.

ANSWER: We have added the study sponsor under declaration.

- Page 10 line 6: Please specify where the POC-PCR system (BioFire) will be located. If located in a centralised laboratory then it is not a point-of-care test and will need renaming as a rapid laboratory test, but a point-of-care laboratory sited close to patient care is likely to be perfectly acceptable.

ANSWER: We have added this sentence to the method section: “The study assistants or laboratory technicians will perform the POC-PCR analysis in a point-of-care laboratory at the ED or close to the department to which the transport time is less than 10 minutes”.
For the description of POC-UFC we have added a similar sentence, as it was not explained her as well.

- Page 11 line 33: monitoring: monitoring in a trial usually refers to the trial processes being audited by the legal sponsor of the trial. I suggest retitling this subsection as ‘Data monitoring’ for clarity and also introducing a section describing the monitoring system in place for trial process auditing.

ANSWER: Thank you for this clarification. We have changed it to ‘Data monitoring’ and added a section about auditing

- While the objectives / research questions are clear, no specific mention is made in each sub-study of the primary and secondary outcomes [excepted on page 12 for the RCT – this is not sufficiently specific though]. The primary and secondary outcomes of each of the seven sub-studies need to be clearly and precisely described for transparency and appropriate data collection.

ANSWER: The primary and secondary outcomes have been added for each sub study

- Related to the primary and secondary outcomes, the statistical data analysis plan for each sub-study should be specified.

ANSWER: We have added the statistical analysis plan for each sub-study

- The WHO Trial Registration Data Set (which could be a section before the introduction), is missing – this would be a good summary of the key trial details and should be included.

ANSWER: A section including the WHO Trial Registration Data Set has been added before the introduction, as suggested.

- As this study includes a randomised controlled trial the protocol should include mention of how the researchers will collect data about and deal with (serious) adverse events and protocol deviations/violations.

ANSWER: We have added the following to Data monitoring section: “Overall risk for the participants in the randomized trial (POC-PCR sputum analysis) is minimal, as sputum collection is part of the standard care, and it will not affect the following diagnostic work-up. However the POC-PCR results may inform the clinician in a favorable way before onset of patient treatment. Any protocol deviation and/or unknown/unexpected adverse event, will be reported in RedCap, evaluated continuously by the steering committee, and reported to the treating physician and patient.”

Most of the 'major' points for revision are likely to be simple additions to the manuscript - much of the information appears on the clinicaltrials.gov pages (e.g. primary and secondary outcomes, most of the WHO data set information, etc).

Minor points to consider revising:

- Page 14 line 31: Funding – consider putting the specific funding award reference numbers into this paragraph

ANSWER: When receiving funding from the Region, Hospital, and University we did not receive a funding award reference number

- Page 8 line 27: I would suggest removing the specified number (six) of project assistants who will recruit patients and collect data as this may cause issues if any of your project assistants leave the research group for any reason or you train more.
ANSWER: Thank you for the advice – the numbers have been removed

- Page 9 line 27: "logistic system" – please clarify – this this the local IT system that lists patients attending the Emergency Department?
ANSWER: We have clarified this in the text

- The 'Strengths and Limitations' section at the beginning mentions the impact of COVID-19 on trial recruitment is uncertain, yet this limitation is not mentioned anywhere in the main text. I suggest that this limitation is mentioned in the discussion and any factors that might alleviate this concern.
ANSWER: We have added the following paragraph to de beginning of the discussion section: "COVID-19 and the consequent societal lockdown might affect trial recruitment and patient distribution. This might lead to an extended recruitment period, as patients suspected of an infectious not related to COVID-19 will be admitted to other departments than the ED, so the ED will be able to handle the many COVID-19 patients. The lockdown may also reduce the number of infections in the society, so fewer patient will visit the hospital, and the distribution of the infections might differ since e.g. the airborne transmitted infections will be reduced. This challenge will especially sub-study 1 be aware of when presenting the results"

- Given the extensive nature of testing the patients are receiving, it would be reasonable to include a sentence if patients receive their results from POC-US etc.
ANSWER: A sentence has been added to the procedure section. We have also added the sentence "The treating staff informs the patients about relevant test results. All medical records including laboratory and imaging can be assessed by the patient via the Danish public healthcare web portal (www.sundhed.dk)" to the Ethics and dissemination section.

- I recommend removing mention of publication of results in "at least 10" journals; while likely, this cannot be foreseen.
ANSWER: Thank you for the advice – we have deleted the 'at least ten'.

- Please consider naming the study chief investigator and the local principal investigators at each site in your protocol.
ANSWER: We have added this information under 'Roles and responsibilities' in the Declaration section

- Please mention how/if public and patient involvement was included in your trial design.
ANSWER: In the Declaration section the text says: "Patient and Public Involvement: The patients or public were not involved in the development of the research question or the study design."

- Please add an expected end date for your study.
ANSWER: This is part of the WHO Trial Registration Data Set, so it has been added here.

Reviewer: 2
Dr. Genevieve McKew, Royal Prince Alfred Hospital, Concord Hospital Comments to the Author:
Review of bmjopen-2021-049606: "Improved diagnostics of infectious diseases in Emergency Departments – a protocol of a multifaceted multicenter diagnostic study"

This is an extremely well-designed protocol for a pragmatic study aimed at improving diagnosis of common infections in emergency departments in Denmark. The aims of improving patient care and reducing use of broad spectrum antibiotics are useful.

The protocol is generally well designed and explained, and I have no major criticisms. I do have some minor criticisms and clarifications.
ANSWER: Thank you for the kind words

Minor points:

A minor point which explains why I answerd “No” to Question 12: The limitations are described, however it should be emphasised that it is only generalisable to settings where appropriately trained staff and equipment can perform bedside ultrasound, and well-resourced settings where a rapid POC sputum microbiology diagnostic service and POC-UFC is available.
ANSWER: We agree with you. We have added a paragraph in the discussions section discussing this: “The study is only generalisable to settings where appropriately trained staff and equipment can perform POC-US, and well-resourced settings where a rapid POC-PCR and POC-UFC service is available.” In the abstract under ‘Strengths and limitations of the study’ we have added “The study is only generalizable to settings with a similar technological context and trained staff”.

The gold standard will be an important part of the statistical analysis and needs to be clearly defined. In Page 5 Line 43-4 it says “In this study we define APN as a urinary tract infection with typical local symptoms and systemic affection (i.e. fever, sepsis), thus indicating ascension of infection above the bladder.” Does this refer to the patients who have SUSPECTED APN and are to be admitted to that arm? If so, should this read “we define SUSPECTED APN as…” and also what are the typical local symptoms – these need to be specified.
Or is the definition of suspected APN simply that the ED physician suspects APN (this is implied later). If this is the case, I suggest removing the definition at Page 5 Line 43-4 or incorporating it into the “Reference Standard” section on page 8.
ANSWER: Thank you for noticing this. It is the last definition, so we have deleted the definition on page 5.

Page 5 Line 52. Please justify why verified COVID-19 within the last 14 days are excluded. Does this also include patients with CAP who are included but subsequently diagnosed with COVID-19? Please clarify this.
ANSWER: We have added the sentence “Verified COVID-19 disease within 14 days before admission to avoid a skewed population consisting of COVID-19 patients instead of CAP patients. Patients suspected of COVID-19, at the time of recruitment, will not be excluded – nor if subsequently tested positive.” to the exclusion criteria

Page 5 Line 54. Please justify why pregnant women are excluded from arms that don’t include low dose CT. APN and arm C (other infections) would be diagnosed in a similar manner to non-pregnant patients. As there are other groups (patients under 40 years) that are excluded only from arm A for safety reasons.
ANSWER: We have added this explanation: “…this to uniform all the studies. At the participating EDs the pregnant women represent a very small patient group, as they are admitted directly to the ward.”

Page 6 Line 56 – are patient urine samples also going to be analysed by dipstick, as is common practice? This could be useful information in reporting the results. It may influence the ED physician’s diagnosis and ED treatment so it should be stated whether or not it’s going to be used.
ANSWER: We have added that the urine will be analysed by dipstick and added the sentence: “The results of the dipstick analysis and the urine culturing will be available to the treating physician as part of the usual procedure (within one hour for dipstick and after up to several days for culturing).”

Page 7 Line 11: “Routine microbiology analysis of sputum (culture and PCR).” PCR needs to be defined here: will PCR be performed on sputum and/or NP swab (this would be more useful for diagnosing resp viruses which can cause up to 30% of CAP). What targets in the PCR? What modality? Will these be the same across all sites, or different?
ANSWER: We have added the sentences: “Expectorated sputum or tracheal secretions will be used for the analysis.” and “The used POC-PCR targets 27 of the most common pathogens involved in lower respiratory tract infections (see appendix IV).”

In “culture”, is Gram stain going to be included? This should be specified. For example, some laboratories do not culture sputa which show large numbers of squamous epithelial cells on the Gram stain, as they are likely poor specimens from the upper respiratory tract and will not yield useful results. Some laboratories only culture sputa with polymorphs on the Gram stain. Will all sputa received in the lab be cultured, or will there be exclusions?
ANSWER: We have added the sentence: “All sputum samples will be cultured. Gram stain and microscopy are not included in the analysis”.

Page 7 Line 15-6: what is the recommended action list developed by clinical microbiologists? This should be provided.
ANSWER: The list has been added to appendix V.

Page 7 line 19: Sputum analysis. Please explain why outcome adjudicators are not blinded – is this because they will have access to the results – just state that here.
ANSWER: It is because one of the 6 project assistants is also responsible for data collection at one site and analyses of the RCT. The others are blinded for the analyses.

Page 7 – why does the APN group get both microbiology diagnostics (POC-UFC and conventional culture) but the CAP group get randomised 1:1? This would be a lovely opportunity to analyse performance of sputum POC vs conventional culture plus PCR. Suggest considering doing both on the whole CAP group. You could still randomise to reporting only sputum POC vs reporting conventional, to be able to perform the superiority analysis proposed on Page 9. If both aren't done, this could lead to difficulties for the outcome adjudicators. For example, the patient gets only sputum culture and the conventional PCR doesn't include S. pneumoniae as a target – you would not be able to directly compare this to a patient who got Biofire and was positive for S. pneumoniae, as sputum culture may not be as sensitive. It would be good to have both results available to the expert panel defining diagnoses.
ANSWER: For the CAP-group we are interesting in the importance of the antibiotic treatment of adding POC-PCR to the diagnostics – not primarily examining FilmArrays analytical precision. However a secondary analysis is POC-PCR vs conventional culture plus PCR. We have added the sentence "A reliability analysis for POC-PCR and routine culturing will be performed as secondary analysis calculating the Intra-class correlation coefficient". In the 'Statistical analysis and plan' section we have described the primary and secondary outcome more specific.

Page 7 line 38 "séance" should this read "sequence"?
ANSWER: yes – it has been corrected

Page 7, all sections. It states that the new radiology modalities will be reported to clinical staff immediately if clinically necessary – does this mean all scans positive for APN/CAP, or only those which require alternative interventions such as those showing hydronephrosis, thoracic diagnoses which require intervention etc. Please specify what diagnoses will/will not be notified. If all CAP/APN is notified, doesn't that undermine the premise of the study?
ANSWER: Thank you for this relevant question. We have tried to clarify this by added the following sentences:

- POC-US of kidney: "The result will not be available to the treating physician since the patient is examined by a radiologist immediately after, and the results from this examination is reported to the clinician according to standard care"
- POC-US of lung: "The FLUS result will not be available to the treating physician unless. If a the result requires immediate action (pneumothorax or large pleural effusions)"
- ULDCT: "If a result requires immediate action, the clinician will be contacted directly by the examiner (pneumothorax and large pleural effusions), according to standard care."
- CEUS: "The non-experimental results of the scans will be available to the treating physician within a week. If a result requires immediate action (suspicion of pyonephrosis or renal abcess), the clinician will be contacted directly by the examiner, according to standard care"

Page 8, reference standard. This is obviously extremely important as it is going to define the success or otherwise of the interventions in this well-designed and resource-intensive study. Please further define the expert group (see next comment). Please attach the standardized template for review. It can be quite difficult to definitively differentiate bacterial from viral pneumonia, or from viral infection with a secondary bacterial pneumonia vs a viral pneumonia. Please include the template and the parameters the expert group will be using for review.
ANSWER: We have described it by adding this paragraph: "The final diagnosis will be based on information available within the first week after admission. A standardized template in RedCap will be used, and the experts will register if the patient has an infectious disease, if the focus of infection is the lungs, kidneys or other, and specify the infection by adding an ICD-10 diagnosis code. If the patient has two focal diagnoses e.g. pneumonia and APN, the assessment will be based on what is

the most probable cause of infection and on the patient's condition at admission." The template has been added as Appendix VI.

Page 8, reference standard. Please state if the expert group is going to attribute the causative pathogen in the CAP group – as the "appropriate antibiotics" outcome in the CAP group is going to depend on the causation. I would suggest this requires expert respiratory medicine and/or clinical microbiology input, as microbiology results don't always match causation for CAP. E.g. patients with COPD may be colonised with Haemophilus and grow Haemophilus, but the cause of their exacerbation may be RSV. Or bronchiectatic patients may grow Pseudomonas as they are colonised, but this is not the cause of CAP. Such patients aren't excluded.
ANSWER: You are right, that it is probably almost impossible to be 100% certain to determine the causality at case level. This is why we do not investigate whether we have identified the right agent at case level, but whether the implementation of a rapid microbiological screening leads to a changed antibiotic consumption. In appendix VII we have added the algorithm which is going to be used to register if the antibiotic treatment of CAP-patients is targeted or non-targeted.

Page 9 Line 2 – 4. Urine culture is going to be used as a reference standard for POC-UFC; what CFU/mL of a uropathogen will be used?
ANSWER: We have added the sentence: "A urine culture will be considered positive with a cut-off of > 1000 CFU/ml for uropathogens and >10.000 CFU/ml for others"

VERSION 2 – REVIEW

REVIEWER	Brendish, Nathan University of Southampton, Clinical & Experimental Sciences, Faculty of Medicine
REVIEW RETURNED	04-Sep-2021

GENERAL COMMENTS	The manuscript has been improved by the authors, and most of the points raised in peer-review have been appropriately actioned or otherwise responded to appropriately. I suggest: - page 2 - abstract - suggest removing "results will be presented in ten peer-reviewed journals" - the precise number may be likely, but not definite, and therefore it may be better to remove "in ten". - page 18 - the legal sponsor of the trial is typically the organisation taking responsibility for the trial in that country (usually a hospital or university or company). It can be an individual but in my experience this is uncommon. Professor CBM is listed here - please check who is the legal sponsor and change if needed. As before, I look forward to seeing the trial results in due course.

REVIEWER	McKew, Genevieve Royal Prince Alfred Hospital, Infectious Diseases and Microbiology
REVIEW RETURNED	02-Sep-2021

GENERAL COMMENTS	This revision of the study protocol has addressed all the points I made in the previous review. The recommended action list for patients diagnosed with CAP based on the Biofire panel is straightforward and clear, and should be easy for emergency medicine physicians to action. I note that penicillins have been included in the "Penicillin-allergy" box in the table on page 53, and

	these should be removed. There are also some minor typographical errors in the table on page 49.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2
Dr. Genevieve McKew, Royal Prince Alfred Hospital, Concord Hospital Comments to the Author:
This revision of the study protocol has addressed all the points I made in the previous review. The recommended action list for patients diagnosed with CAP based on the Biofire panel is straightforward and clear, and should be easy for emergency medicine physicians to action. I note that penicillins have been included in the "Penicillin-allergy" box in the table on page 53, and these should be removed.
ANSWER: The predictive value of reported penicillin allergy is extremely low, so some patients will get penicillin anyway - typically because the doctor overlooks or actively ignores the information. If there is no penicillin in the penicillin allergy column, then we can not classify these patients. We have added ‘reported’ to the column header. Hope this solution will be satisfying.

There are also some minor typographical errors in the table on page 49.
ANSWER: Thank you for noticing these errors. We have corrected them.

Reviewer: 1
Dr. Nathan Brendish, University of Southampton Comments to the Author:
The manuscript has been improved by the authors, and most of the points raised in peer-review have been appropriately actioned or otherwise responded to appropriately.

I suggest:

- page 2 - abstract - suggest removing "results will be presented in ten peer-reviewed journals" - the precise number may be likely, but not definite, and therefore it may be better to remove "in ten".
ANSWER: Thank you for noticing, that we forgot to change it in the abstract. ‘ten’ has been removed

- page 18 - the legal sponsor of the trial is typically the organisation taking responsibility for the trial in that country (usually a hospital or university or company). It can be an individual but in my experience this is uncommon. Professor CBM is listed here - please check who is the legal sponsor and change if needed.
ANSWER: We have changed the legal sponsor to ‘University Hospital of Southern Denmark’, as suggested

As before, I look forward to seeing the trial results in due course.

Answers to email dated 07-sep-2021 from BMJ Open Editorial Office

1. Funding Information: You have indicated a funder/s for your paper. Please ensure to provide an award/grant number for your funder/s in the main document file and in ScholarOne.

ANSWER: This has been added

2. Appendix 1-2 citation missing: The in-text citation for “Appendix 1-2” is missing in the main text of your main document file. Please amend accordingly.

ANSWER: This has been added

VERSION 3 – REVIEW

REVIEWER	Brendish, Nathan University of Southampton, Clinical & Experimental Sciences, Faculty of Medicine
REVIEW RETURNED	14-Sep-2021

GENERAL COMMENTS	Nil to add.

REVIEWER	McKew, Genevieve Royal Prince Alfred Hospital, Infectious Diseases and Microbiology
REVIEW RETURNED	16-Sep-2021

GENERAL COMMENTS	Thank you, the minor revision of the penicillin-allergy table is sensible.