PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a prospective, observational cohort study of awareness in mechanically ventilated patients admitted from the emergency department: The ED-AWARENESS Study
AUTHORS	Pappal, Ryan; Roberts, Brian; Mohr, Nicholas; Ablordeppey, Enyo; Wessman, Brian; Drewry, Anne; Yan, Yan; Kollef, Marin; Avidan, Michael; Fuller, Brian

VERSION 1 – REVIEW

REVIEWER	Jaideep J Padit Nuffield Department of Anaesthetics Oxford University Hospitals NHS Trust UK
REVIEW RETURNED	16-Aug-2019

GENERAL COMMENTS	This is a very interesting proposal/methods from a very strong and experienced team. They focus on a very relevant aspect of awareness with paralysis. Page 5, line 18: "The incidence of awareness during anesthesia with potent inhaled anesthetics in the operating room (OR) is approximately 1-2 cases/1,000" – make clear that these are Brice interview data. Other methods (eg, NAP5) yield different results (Anaesthesia. 2014 Oct;69(10):1089-101.). So this really ought to be stressed. There is no evidence that one method (Brice vs spontaneous reporting) yields a more 'accurate' incidence (see Br J Anaesth. 2015 Sep;115(3):471-2). Page 5, Line 24: "occurred for patients in the OR, this focus on awareness has yet to extend outside of that domain." – This is not true, and so I would express the logic/rationale a very different way. I would suggest that NAP5 first identified that 'accidental awareness' was possible from intubation/paralysis in the ED, and this stimulates a study into how common this problem might be (see the 'intensive care' chapter in main NAP5 report at https://www.nationalauditprojects.org.uk/NAP5report and also Anaesthesia. 2014 Oct;69(10):1089-101.) Line 30: "There is significant rationale to examine awareness in patients receiving mechanical ventilation in the emergency department (ED), as these patients have been historically managed in a way that predisposes them to experience awareness" – This is correct but only up to a point. The authors are correct to list all the interventions, none of which are directed to minimising awareness. However, the main reason why generally, the problem of awareness has not been thought relevant is that those patients requiring paralysis are thought to have low GCS state (or their

	critical illness is thought itself to make them unaware) and therefore incapable of awareness/recall. The fact that NAP5 first discovered this problem raises the intriguing possibility that even patients with low GCS can remember things that happen to them. So again, I would frame the logic/rationale in a different way for it to be more persuasive and refer to the NAP5 data as a starting point. Page 5, Line 42: "Critically ill ED patients requiring mechanical ventilation almost exclusively receive intravenous medications, and are frequently under-dosed" – This seems a circular argument. On what basis is the under-dosing already known, and to what end-point? In other words if we already know these patients are under-dosed then why do this study? Page 6. Line 10 onwards: The authors should stress the difference between the sedation literature and what they are now looking at which is general anaesthesia. Many people unfortunately use 'sedation' in a very general sense, and so this section might cause confusion unless the stress is inserted. Last line Intro: "We hypothesize that the incidence of awareness with paralysis will be approximately 1-2%." – add by what method this incidence to be measured (ie, Brice). However it is not clear whey at this point they estimate this incidence. Methods: wording around inclusion/exclusion criteria needs to be tightened. Inclusion: some patients may already be intubated by ambulance staff before arrival in ED – were these to be included? I understand the exclusion criterion around residual deficits but this needs different wording. What they need to say is that since patients need to be questioned for recall of awareness later, when they have recovered from the primary insult, some conditions make this impossible (and then list examples of those conditions). One more comment: it is not crystal clear if all of anaesthesia – paralysis – intubation are inclusion criteria independently? Or all 3 together. Some patients are intubated with no anaesthesia or paralysis. Some are intubated with only one of anaesthesia or paralysis. Some of course with all 3. However, some may rarely receive supraglottic airways (+/- anaesthesia/paralysis) or hand ventilation for periods until they recover later. I was not sure also about patients who took an overdose, then intubation for stomach washout, then extubation in ED. Are all of these to be included? I am afraid some of the wording for inclusion did not seem to encompass all the possibilities and may need re-wording or presenting with greater clarity. My apology if this is my own difficulty in reading this section. I very much liked the authors' description of how they would disentangle the origin by timing of the awareness episode. This is a novel study and I am sure that, once data are collected they may need to look at that with a different lens, and they have the experience and insight to be able to do so constructively. In this sense, this is a very challenging study to do and the authors are to be congratulated for their careful approach. We must view this plan as highly dependent upon the precise results they obtain, and it may change.

	However, how much detail would they be able to extract form patients? I did not clearly see analysis of degree of psychological impact and how they would manage this (they could refer to the NAP5 Psychological Support Pathway – see https://www.nationalauditprojects.org.uk/NAP5-Anaesthetia-Awareness-Pathway). And would they be able to detect more nuanced experiences such as dysanaesthesia that patients might experience (Conscious Cogn. 2014 Jul;27:194-212; Anaesthesia. 2013 Oct;68(10):995-1000.)? This last may become relevant, as it is a dissociative experience with patients reporting 'floating' or 'being in another room' and in this critical illness context may overlap with the 'near-death' experiences that are anecdotal. Given the authors know about dysanaesthesia, how will they disentangle this from vivid near-death type recall? Sample size – and focus of the study. I have to admit I was a little disappointed by this aspect of the methodology. The two things – sample size and study focus are related. The authors have spent much space in justifying the sample size. I am surprised they have come to a very exact number of 383 patients. I also note they comment that they expect 2.1 patients per day – this is impossible since one can only have whole numbers of patients, either 2 or 3. They cannot expect 2.1. I understand their calculations, but would have liked to see a simpler, more of a convenience sample approach. They say there are 2 patents/day, so ~700/year, or ~1000 at 18 months. They might have said that they will aim for an 18 month study or 1000 patients, whichever the sooner, and thus obtain 10-20 cases from their incidence estimate for analysis. The higher number (20 positives) would then allow at least some conclusions about things like drug effects or monitoring etc as influential in awareness reports. Perhaps even some assessment of correlation with GCS score at time of intubation etc. However, by the very low number of 383 that they have chosen, all they will ascertain is the crude 'incidence' and even then with quite wide confidence levels (I estimate anywhere between near 0 to 8%) which may not be as meaningful as they had hoped. So I was left feeling that the group had missed an opportunity – especially as they had assembled such a strong team and made careful plans in other respects. Of course, that may be my personal interest in such data, and the desire to see such a strong team make a real impact with this study. So this is more a disappointment rather than a criticism. Very minor comment: funding – how do authors know that funders will not play a role in the future? Is that part of comment necessary? In summary this is a carefully planned study whose results I would look forward to seeing. I would like to see the text touching upon the wider aspects referred to in this report, and an updated reference list.

REVIEWER	Kalliopi Kydonaki Edinburgh Napier University Scotland
REVIEW RETURNED	02-Sep-2019

GENERAL COMMENTS	This is a protocol article for an interesting observational study of sedation depth and psychological trauma at the early stages of the care of an emergency patient. I read the manuscript and I need to declare that my expertise are in qualitative research, hence, I did not feel comfortable commenting on the statistical analysis. However, I will provide a brief review of the whole manuscript. Sample and recruitment: I felt you needed to be more explicit about the recruitment strategy and the sample of patients recruited. Will you recruit from ED or OR. Although it is mentioned on page 8, then it becomes confusing. Who will do the screening and selection of participants before the PI makes final decisions? You also need to consider selection bias in that process. With regards to ethical consideration, although the study has ethical approval, you will need to explain the process of gaining consent for accessing clinical and identifiable data. Data: you mentioned that you will collect data on sedation; you need to be more specific on the exact data, i.e. dosage, strength, duration etc. You mentioned collecting qualitative reports. You will need to explain what these reports will include, who will collect them and when, how they will be analysed. For instance, will these be collected when the questionnaires are administered and how?

VERSION 1 – AUTHOR RESPONSE

Point-by-point reply: bmjopen-2019-0333479

Note: Comments by the Editors and Reviewers are numbered. Responses appear below each comment. Text from the manuscript is indented and additions have been colored in yellow to facilitate their identification. Thank you for the opportunity to improve our manuscript with these suggestions.

Reviewer #1 comments

1. This is a very interesting proposal/methods from a very strong and experienced team. They focus on a very relevant aspect of awareness with paralysis.

Response: We thank you for the very thoughtful review of our work. It has made the work better and is very much appreciated.

2. Page 5, line 18: "The incidence of awareness during anesthesia with potent inhaled anesthetics in the operating room (OR) is approximately 1-2 cases/1,000" – make clear that these are Brice interview data. Other methods (eg, NAP5) yield different results (Anaesthesia. 2014 Oct;69(10):1089-101.). So this really ought to be stressed. There is no evidence that one method (Brice vs spontaneous reporting) yields a more 'accurate' incidence (see Br J Anaesth. 2015 Sep;115(3):471-2).

Response: This is a great point. In the first paragraph of the Introduction, we have now included:

> Different methods have been used to detect awareness events, including spontaneous reporting and the Brice questionnaire, with no compelling evidence of improved accuracy of one method versus another. As measured by the Brice questionnaire, ……

3. Page 5, Line 24: "occurred for patients in the OR, this focus on awareness has yet to extend outside of that domain." – This is not true, and so I would express the logic/rationale a very different way. I would suggest that NAP5 first identified that 'accidental awareness' was possible from intubation/paralysis in the ED, and this stimulates a study into how common this problem

might be (see the 'intensive care' chapter in main NAP5 report at https://www.nationalauditprojects.org.uk/NAP5report and also Anaesthesia. 2014 Oct;69(10):1089-101.)

Response: Thank you for bringing this up. We could have phrased this better. The intent was to draw attention to the fact that, compared to patients in the operating room, there has been much less investigation (including rigorous observational data and randomized trials) into awareness for patients in other domains. We have re-phrased that sentence to now read:

> While rigorous investigation into awareness has occurred in the OR, much less data exists for patients outside of that domain.

Also, we have modified the beginning of the 4th paragraph of the "Background and rationale" section to now include the following sentence:

This report also identified two cases of awareness in intubated ED patients, suggesting that awareness is possible from the very beginning of intubation and initiation of mechanical ventilation in the ED.

And in the 2nd sentence of the final paragraph of the "Background and rationale" section, we now state:

> Taken together, their results justify the need for studies focusing on awareness with paralysis in the critically ill mechanically ventilated ED population to assess how common this problem might be.

We hope these changes suffice in your estimation.

4. Line 30: "There is significant rationale to examine awareness in patients receiving mechanical ventilation in the emergency department (ED), as these patients have been historically managed in a way that predisposes them to experience awareness" – This is correct but only up to a point. The authors are correct to list all the interventions, none of which are directed to minimising awareness. However, the main reason why generally, the problem of awareness has not been thought relevant is that those patients requiring paralysis are thought to have low GCS state (or their critical illness is thought itself to make them unaware) and therefore incapable of awareness/recall. The fact that NAP5 first discovered this problem raises the intriguing possibility that even patients with low GCS can remember things that happen to them. So again, I would frame the logic/rationale in a different way for it to be more persuasive and refer to the NAP5 data as a starting point.

Response: Another great point that we are happy to include. The beginning of the 4th paragraph of the "Background and rationale" section now reads:

> Human factors likely play a role in the historical lack of relevance given to awareness in critically ill mechanically ventilated patients, as cardiovascular instability or an obtunded mental state may lead clinicians to believe patients are incapable of awareness recall. This may lead to the under-dosing of analgesics and sedatives. However, the 5th National Audit Project (NAP5) on accidental awareness in the United Kingdom and Ireland documented accidental awareness in critically ill and unstable patients, demonstrating that critical illness does not guarantee that memory of events will not occur

5. Page 5, Line 42: "Critically ill ED patients requiring mechanical ventilation almost exclusively receive intravenous medications, and are frequently under-dosed" – This seems a circular argument. On what basis is the under-dosing already known, and to what end-point? In other words if we already know these patients are under-dosed then why do this study?

Response: In this section, we are trying to further highlight reasons why the study should be done. Given the fact that under-dosing of anesthesia is risk factor for awareness, if this occurs in critically ill mechanically ventilated ED patients, then this puts those patients at (theoretically at least) higher risk for awareness. Several reports show that mechanically ventilated patients in the ED receive

inadequate post-intubation analgesia and sedation, including no analgesia and sedation. The Intensive Care chapter of NAP5 also reports similar, "….the Panel judged the dose of induction agent was too low."

6. Page 6. Line 10 onwards: The authors should stress the difference between the sedation literature and what they are now looking at which is general anaesthesia. Many people unfortunately use 'sedation' in a very general sense, and so this section might cause confusion unless the stress is inserted.

Response: This paragraph highlights the most recent literature on post-intubation sedation (not general anaesthesia) in the ED, as opposed to paragraph #2 of the "Background and rationale" section which highlights some older, historical practices in this cohort. We have inserted some phrases now throughout this paragraph to help clarify this point, including:

> More recent data from our research group also demonstrates some concerning practice patterns that could predispose patients to awareness during mechanical ventilation in the ED. In a single-center study on post-intubation sedation practices in the ED….
>
> To build on this single center experience, the multicenter (n= 15) ED-SED Study was a prospective cohort study conducted to examine practice patterns and clinical outcomes associated with ED-based post-intubation sedation…..
>
> This confirms that currently, despite ED-based publications regarding sedation after the initiation of mechanical ventilation……

7. Last line Intro: "We hypothesize that the incidence of awareness with paralysis will be approximately 1-2%." – add by what method this incidence to be measured (ie, Brice). However it is not clear why at this point they estimate this incidence.

Response: This has been done.

8. Methods: wording around inclusion/exclusion criteria needs to be tightened. Inclusion: some patients may already be intubated by ambulance staff before arrival in ED – were these to be included? I understand the exclusion criterion around residual deficits but this needs different wording. What they need to say is that since patients need to be questioned for recall of awareness later, when they have recovered from the primary insult, some conditions make this impossible (and then list examples of those conditions).

Response: The inclusion criteria now reads:

> Inclusion criteria are: 1) mechanical ventilation via an endotracheal tube in the ED, including patients intubated in the ED and prior to arrival (i.e. in the prehospital setting); and 2) age ≥ 18 years.
>
> The section where we explain the rationale for the exclusions has been modified to read:
>
> Furthermore, after discontinuation of mechanical ventilation, it may be impossible to accurately complete an awareness questionnaire in these patients.

9. One more comment: it is not crystal clear if all of anaesthesia – paralysis – intubation are inclusion criteria independently? Or all 3 together. Some patients are intubated with no anaesthesia or paralysis. Some are intubated with only one of anaesthesia or paralysis. Some of course with all 3. However, some may rarely receive supraglottic airways (+/- anaesthesia/paralysis) or hand ventilation for periods until they recover later. I was not sure also about patients who took an overdose, then intubation for stomach washout, then extubation in ED. Are all of these to be included? I am afraid some of the wording for inclusion did not seem to encompass all the possibilities and may need re-wording or presenting with greater clarity. My apology if this is my own difficulty in reading this section.

Response: I believe the wording of "mechanical ventilation via an endotracheal tube in the ED" does indeed capture these possibilities. Regardless of exactly how the patient ended up on the ventilator (in ED vs. prehospital; RSI vs. no meds; etc.), the end result is a patient receiving mechanical ventilation in the ED. This is our cohort of interest, as our over-arching goal is to provide generalizable evidence that will help the practicing clinician. Recognizing that this is a heterogeneous cohort of patients, we want to be inclusive and pragmatic, yielding greater external validity to our results. Our prior data also suggests that even if no paralytic is given for intubation, a significant percentage will receive paralysis at some point.

10. I very much liked the authors' description of how they would disentangle the origin by timing of the awareness episode. This is a novel study and I am sure that, once data are collected they may need to look at that with a different lens, and they have the experience and insight to be able to do so constructively. In this sense, this is a very challenging study to do and the authors are to be congratulated for their careful approach. We must view this plan as highly dependent upon the precise results they obtain, and it may change.

Response: Thank you for the kind words above, and we agree with your statement. It may indeed be quite difficult to disentangle some of the details related to awareness vs. memory, as the practice environment (and duration of sedation and mechanical ventilation) is so very different in the ED and ICU versus the operating room. We also agree that some of this may be an iterative process after the data is collected and reported. While challenging, this is not necessarily a bad thing, as it will likely allow us to refine our approach when expanding this work beyond our center. Thanks again for this comment, and we have added the following in the "Limitations" section:

> We have taken rigorous efforts to delineate memory of events from awareness, and to try and differentiate procedural awareness (i.e. of the intubation) versus awareness with paralysis while being mechanical ventilated. In reality this may prove quite challenging, requiring us to modify our approach or reporting after the data are collected.

11. However, how much detail would they be able to extract from patients? I did not clearly see analysis of degree of psychological impact and how they would manage this (they could refer to the NAP5 Psychological Support Pathway – see https://www.nationalauditprojects.org.uk/NAP5-Anaesthetia-Awareness-Pathway). And would they be able to detect more nuanced experiences such as dysanaesthesia that patients might experience (Conscious Cogn. 2014 Jul;27:194-212; Anaesthesia. 2013 Oct;68(10):995-1000.)? This last may become relevant, as it is a dissociative experience with patients reporting 'floating' or 'being in another room' and in this critical illness context may overlap with the 'near-death' experiences that are anecdotal. Given what the authors know about dysanaesthesia, how will they disentangle this from vivid near-death type recall?

Response: Some degree of psychosocial impact will be assess by questioning about perception of threat in all of the patients. Also, if awareness is detected the patients' treating clinical team will be made aware so provisions for treatment/therapy can be arranged. Your comments on dysanaesthesia are interesting. We are not quite sure how to address this at this point, getting back to your comment above regarding how the plan may change with these results. However, our questionnaire makes provisions for memory, dreams, and free text for patients' recall. If certain themes develop, then we will analyze and report these in a context that keeps the concept of dysanaesthesia in mind. Helpful comment, so thank you.

12. Sample size – and focus of the study. I have to admit I was a little disappointed by this aspect of the methodology. The two things – sample size and study focus are related. The authors have spent much space in justifying the sample size. I am surprised they have come to a very exact number of 383 patients. I also note they comment that they expect 2.1 patients per day – this is impossible since one can only have whole numbers of patients, either 2 or 3. They cannot expect 2.1. I understand their calculations, but would have liked to see a simpler, more of a convenience sample approach. They say there are 2 patents/day, so ~700/year, or ~1000 at 18 months. They might have said that they will aim for an 18 month study or 1000 patients, whichever the sooner, and thus obtain 10-20 cases from their incidence estimate for analysis.

Response: We understand and appreciate your concerns here. Regarding the sample size justification, as you are quite aware, most of the literature in this field comes from patients in the

operating room, and the reported incidence is quite low. Therefore, we anticipate that many readers could be quite skeptical when they see an awareness study of "only" 383 patients, as they may view this research strictly through the lens of the operating room data. We therefore felt compelled to spend some space in justifying our sample size to reassure the reader that a significant amount of thought was put into this aspect of the study. And it will be the largest study to date strictly focusing on awareness in mechanically ventilated ED patients.

To clarify, there are 2.1 patients per day *that will be screened for the study*, as they satisfy inclusion criteria. This was intended to reflect an average number of patients that would be screened (based on our prior work on mechanically ventilated ED patients) over the course of a year. We expect about 50% of these patients to be excluded, leaving 383 patients enrolled during the year (not ~700/year).

We have clarified this by stating:

> Over the course of a year, we expect 2.1 patients per day to fulfill inclusion criteria and be screened for the study, based on our prior work in mechanically ventilated ED patients.
>
> With an inclusion of just over one patient per day, on average, we expect to enroll 383 patients in the study during the year.

13. The higher number (20 positives) would then allow at least some conclusions about things like drug effects or monitoring etc as influential in awareness reports. Perhaps even some assessment of correlation with GCS score at time of intubation etc. However, by the very low number of 383 that they have chosen, all they will ascertain is the crude 'incidence' and even then with quite wide confidence levels (I estimate anywhere between near 0 to 8%) which may not be as meaningful as they had hoped.

Response: We also very much appreciate this comment. It also highlights why we felt the need to really justify enrolling 383 patients in the study, as we are confident that we will indeed see cases of awareness.

14. So I was left feeling that the group had missed an opportunity – especially as they had assembled such a strong team and made careful plans in other respects. Of course, that may be my personal interest in such data, and the desire to see such a strong team make a real impact with this study. So this is more a disappointment rather than a criticism.

Response: Understood, but I think your disappointment will be alleviated in the future when we expand this field beyond our center. While we very much appreciate your comments here (and largely agree!) we believe this particular study is only going to be one piece of the puzzle. If we were to spend more time (e.g. two years) conducting this study at only our center, while we would invariably have more cases, we would still only have a crude incidence *at our center*. We believe that conducting this study over a one year period will achieve the same over-arching goal of assessing awareness in this cohort. It will also provide us with better streamlined operations for doing a similar study across multiple centers, which will be even more impactful than a longer, single center study at our site only.

15. Very minor comment: funding – how do authors know that funders will not play a role in the future? Is that part of comment necessary?

Response: This has been deleted.

16. In summary this is a carefully planned study whose results I would look forward to seeing. I would like to see the text touching upon the wider aspects referred to in this report, and an updated reference list.

Response: We hope we have satisfied your concerns appropriately and we are looking forward to the results as well.

Reviewer #2 comments

1. This is a protocol article for an interesting observational study of sedation depth and psychological trauma at the early stages of the care of an emergency patient. I read the manuscript and I need to declare that my expertise are in qualitative research, hence, I did not feel comfortable commenting on the statistical analysis. However, I will provide a brief review of the whole manuscript.

Response: We thank you as well for taking the time to provide peer review to our manuscript.

2. Sample and recruitment: I felt you needed to be more explicit about the recruitment strategy and the sample of patients recruited. Will you recruit from ED or OR. Although it is mentioned on page 8, then it becomes confusing. Who will do the screening and selection of participants before the PI makes final decisions? You also need to consider selection bias in that process.

Response: In the "Study population" section, we state that the target population for the study is mechanically ventilated adult patients in the ED (beginning of first paragraph), and state that patients will be recruited exclusively from the ED (beginning of second paragraph in that section). In the screening and study initiation section, we discuss our automated electronic screening system. This system is what we have used for over five years now, and is a robust way to capture all consecutive mechanically ventilated patients presenting to our ED. So the screening is automatic and then study team members assess patients for inclusion and exclusion criteria. There are no final decisions, as every patient that satisfies inclusion and exclusion criteria are included in the study, avoiding selection bias. In the "Screening and study initiation" section, we have now added:

> After this automated screen, study team members will assess patients for inclusion and exclusion criteria. All patients satisfying inclusion and exclusion criteria will be enrolled in the study.

3. With regards to ethical consideration, although the study has ethical approval, you will need to explain the process of gaining consent for accessing clinical and identifiable data.

Response: This study was approved with waiver of informed consent, and we have added a statement to this effect under the "Ethics approval" section of the manuscript.

4. Data: you mentioned that you will collect data on sedation; you need to be more specific on the exact data, i.e. dosage, strength, duration etc.

Response: All sedation data from the ED will be collected, and the beginning of the 3rd paragraph under "Data" now reads:

> We will record all data (including dosage) regarding sedation in the ED will include…..

Regarding sedation data from the ICU, we will collect it during the first 48 hours of ICU care. The first sentence of the 4th paragraph now reads:

> Pertinent clinical data during the first 48 hours after admission in the ICU, including sedation depth, medications (including dosage) administered for the management of analgosedation….

5. You mentioned collecting qualitative reports. You will need to explain what these reports will include, who will collect them and when, how they will be analysed. For instance, will these be collected when the questionnaires are administered and how?

Response: Thank you for bringing this up. The qualitative reports are basically the patients' recollection and words/stories regarding their recall. These are collected routinely as part of the questionnaire administered to all patients by study team members. While the questionnaire asks for specific memories, there are also several areas for free text, which are used to document what the patient relays. These reports will not be formally analyzed, but will be provided in order to assist with adjudication of awareness events, and to provide the reader (when final results are published) a more transparent description of what these patients' experiences were. We have moved mention of this out of the "Proposed statistical methods" section. The end of the 3rd paragraph under "Outcomes" now reads:

For all patients who report memories of awareness events, we will also provide a qualitative report of the patient's subjective reported experience. These qualitative reports will essentially be the patients' stories regarding the experience, and will be collected routinely as part of the questionnaire administered to all patients by study team member. Formal analytics will not be applied to these reports; they will be provided to assist with the adjudication of awareness events, and to provide the reader a more transparent description of what the patients' experience were.

VERSION 2 – REVIEW

REVIEWER	Jaideep J Pandit Oxford, UK
REVIEW RETURNED	14-Sep-2019

GENERAL COMMENTS	The authors have carefully addressed each comment which reflects their good planning of this study. They have in particular defended the statistic aspects.