PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Practice guidelines for sedation and analgesia management of critically ill children: A pilot study evaluating guideline impact and feasibility in the PICU.
AUTHORS	Keogh, Samantha; Long, Debbie; Horn, Desley

VERSION 1 - REVIEW

REVIEWER	Lyvonne Tume RN PhD Alder Hey Children's NHS FT, UK
REVIEW RETURNED	02-Sep-2014

GENERAL COMMENTS	Thank you for your interesting and relevant paper. I have a few queries and some suggestions to improve the manuscript. I think the manuscript is quite long and wordy and could be made more succinct and reduced to around 3500 words without losing the content. In the abstract it should be made clear the design is a before and after study. Initially I was quite confused about the number of patients included in a 12 month period, then it became clear that you have undertaken a power calculation which predicted 75 per group, which would have been helpful to know earlier on. I am very surprised that given a reduction in ventilation time by 21 hours (nearly a whole day) this was not statistically significant, it is certainly clinically significant and i think this should be highlighted. However if there are not people competent in extubation around when the child is 'ready' to be extubated or the nurses in your unit cannot do this, then this will influence ventilation duration and should be mentioned somewhere or included in a limitations section. Other points, throughout the paper i think you should replace 'patient' with 'child'. On P.4 line 17 you claim both under and over sedation cause agitation, well i think the main issue with over sedation is increased ventilation time, along with more dependence, tolerance and possibly withdrawal. The introduction should be a short succinct paragraph with the aim clearly stated and your separate background section could be shortened substantially, you can refer to those studies in the discussion, where there should be more reference to the literature. On p8 line 11 you state there are no normative values for ventilation time, there may not be normative values but certainly in the UK, the large audit database (PICANET) shows that across 31 PICUs the median ventilation time is 3 days - this would not be dissimilar to Australia I would imagine. This data is freely available online. There are a lot of tables and graphs, but not one of your actual guidelines, this would have been useful, because I am not clear even how often sedation, pain etc were scored. On p.10 and 11 you refer to 'weaning' please specify this as 'sedation weaning' as it could be

	confused with ventilation weaning and the 2 things are inextricably linked. On p 12 line 48, you say 'some patients'....please specify how many. On p. 14 line 21 'chart audit' might be better worded as @implementation Fidelity'. On p. 14 line 42 you mention the survey but in the methods there is no mention (I could see) of how the survey was developed, types of questions, piloted etc and who it was given to? was it just nurses or medical staff too? The discussion could be shortened and refer to more literature rather than just restating results (p. 16 line 19-23). Finally I am not sure what table 4 really adds to the paper. It would be useful and would strenghten the paper to address these issues.

REVIEWER	Yoanna Skrobik Université de Montréal Canada
REVIEW RETURNED	06-Sep-2014

GENERAL COMMENTS	This pragmatic pre-post implementation study's stated aim is the development, implementation and trial of locally developed guidelines for sedation and analgesia management in pediatric ICU patients. The authors audited charts and surveyed caregivers (nurses) for ease of use of the new guidelines. The tools described to assess the patients were the State Behaviour Scale, the Multidisciplinary Assessment of Pain Scale (MAPS) and the Opioid Benzodiazepine Withdrawal Assessment Scale (WAS). A broad variety of pharmacological interventions (varying drugs with varying half-lives in patients with very different lengths of stay) are described. A small sample of pre-implementation patients (75 patients in the pre and 63 patients in the post group) were evaluated. Study outcomes were total ventilation time (TVT), sedation doses and duration, length of stay in the PICU (LOS), and accidental extubation and readmission rates. Overall, opiate use and duration were reduced, and other outcomes were not different. The protocol was found to be feasible and acceptable to the majority of respondents (49% of the caregivers). The study is interesting and important as individualized symptom management for pain and sedation is becoming recognized as an important outcome determinant in the critically ill. The description of the protocol merits clarification. The psychometric validation of the scales applied to this pediatric population is not described, nor is caregiver evaluation performance for the individual scales. It is also not clear on whether pain and sedation levels were differentiated or prioritized (i.e. with an attempt to evaluate pain first and sedation level second), or whether targeted analgesia levels or sedation levels were any different between the pre and post groups. Finally, the variety of pharmacological interventions and the varying pharmacokinetic characteristics of the administered drugs (particularly those infused over longer periods in the patients who had very long (30-75 days) periods of mechanical ventilation or long lengths of stay) confound the interpretation of the role the protocol played in the differences between the pre and post group. Providing the 'target range' data might better answer this question.

REVIEWER	Saskia N. de Wildt Pediatric intensivist, clinical pharmacologist

	Erasmus MC - Sophia Children's Hospital Rotterdam, The Netherlands
REVIEW RETURNED	16-Sep-2014

GENERAL COMMENTS	Major comments: The authors are not clear about the objectives of the study. The primary objective mentioned is 'to develop sedation and analgesia management guidelines and test their feasibility and acceptability in practice', however, in the abstract and the results they mention patient outcome data as primary result, despite small sample size. Please clarify. Overall, it took me a long time to grasp what the authors did and how they did it. The overall lack of detail on the sedation protocol and the other guidelines (the table is not very detailed), as well as the missing information on how exactly adherence was measured, make this paper hard to understand and the conclusions not very useful for extrapolation. did every patient have score list? Maybe they want to put too much in one manuscript. I would suggest a manuscript describing how they came to the protocol and how it was implemented (where nurses trained to do validated pains scores?) and another paper on the effect of implementation. There is no information on the sedation management protocol used in this study. Instead, a summary of the consensus guidelines is added in table 1. Is this how they are used in the unit, or is there an extended version, consider uploading this a supplementary file. I suggest to add the sedation protocol (flowchart?). The introduction and methods section can be significantly shortened. There is no need to discuss all studies in detail in the introduction. In the methods section, the authors discuss the consensus guidelines and 'drug cycling'. This is not appropriate in this section. In the discussion section the authors state that sedation goals were achieved quicker. However, this study shows no support of this statement. There are no scores of adequate sedation or sedation time. Please clarify. Minor comments: - Sample size calculation: it is not clear how the authors have calculated the sample size. What was the total ventilation time of the retrospective analysis? - Setting: is the study performed on a medical, surgical or mixed PICU (instead of 'a range of diagnosis'). - Study period: what was the study period? In the methods section the authors mention a study period of 6 months pre- and 6 months post-implementation, however, in the results they mention two study periods of 12 months each. - Figure 1: please mention the reasons for exclusion. - Table 2 and 3: please mention median and IQR instead of range. additional comments:

	Abstract: please specify which group the outcomes relate to (morphine dose and duration) Page 6 line 17: the fentanyl units seem wrong (doses around 500 mcg/kg/h?) Page 12 line 50: what is meant with 'deviation from study protocol or guidelines'? what is the difference between study protocol and guidelines? isn't this an outcome variable? Does this not present bias to the results? It is not clear from the methods section that parents were asked for informed consent. Asking informed consent is a bit unusual when a new treatment algorithm is introduced in practice. Page 13 2nd paragraph: the description of results is ambigue: 'a reduction … between groups'> I assume a reduction from pre to post implementation? This should be worded more clearly. 10 mcg/kg/h midazolam seems very low. Are this medians for single patients? Or is this the median of the lowest dose (e.g. at weaning) for each patient. It is insufficient to only provide median/means and p-values, also the variability e.g. SD, IQR or range for each variable should be presented. What is difference in protocol directed vs intervention group? Is this the same? Please use consistent wording throughout manuscript. It appears that a lot of effort has been put into developing these guidelines, implementing them and studying the effect, which are worth to be shared with the PICU community. As also noted above, the paper lacks in detail on methods and it should be strongly suggested to write two papers. Consider adding experts on sedation research and on implementation to your team.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Lyvonne Tume RN PhD
Institution and Country Alder Hey Children's NHS FT, UK
Please state any competing interests or state 'None declared': None declared

Dear Authors,
Thank you for your interesting and relevant paper. I have a few queries and some suggestions to improve the manuscript. I think the manuscript is quite long and wordy and could be made more succinct and reduced to around 3500 words without losing the content.
In the abstract it should be made clear the design is a before and after study.
Ok Review of litereature reviewed in background significantly reduced allowing manuscript to focus of guideline development and evaluation process.
Research design explicitly stated in abstract

Initially I was quite confused about the number of patients included in a 12 month period, then it became clear that you have undertaken a power calculation which predicted 75 per group, which would have been helpful to know earlier on.
Statement about sample was in 'participants' section of study. Subsequent advice (from both fellow reviewer and other researchers in area) the nominal power calculation was removed given focus of study not about testing hypothesis and more about evaluating absolute impact, feasibility in practice and acceptability by staff.

I am very surprised that given a reduction in ventilation time by 21 hours (nearly a whole day) this was not statistically significant, it is certainly clinically significant and i think this should be highlighted. However if there are not people competent in extubation around when the child is 'ready' to be extubated or the nurses in your unit cannot do this, then this will influence ventilation duration and should be mentioned somewhere or included in a limitations section.
Given small and likely underpowered sample size it is not surprising difference in ventilation was not statistically significant. However potential for clinical significance has been enhanced as suggested. Though I am careful not to overstate findings give limitations of study.

Other points, throughout the paper i think you should replace 'patient' with 'child'.
OK changed

On P.4 line 17 you claim both under and over sedation cause agitation, well i think the main issue with over sedation is increased ventilation time, along with more dependence, tolerance and possibly withdrawal.
Yes we agree so have included in in paragraph though some already present.

The introduction should be a short succinct paragraph with the aim clearly stated and your separate background section could be shortened substantially, you can refer to those studies in the discussion, where there should be more reference to the literature.
Ok will rewrite and precis

On p8 line 11 you state there are no normative values for ventilation time, there may not be normative values but certainly in the UK, the large audit database (PICANET) shows that across 31 PICUs the median ventilation time is 3 days - this would not be dissimilar to Australia I would imagine. This data is freely available online.
Yes, thank you we also have normative national values from National reports but as mentioned previously power calculation statement now removed from manuscript.

There are a lot of tables and graphs, but not one of your actual guidelines, this would have been useful, because I am not clear even how often sedation, pain etc were scored.
Guidelines were uploaded as supplemental material on submission of manuscript and are usually offered as an appendix (as 6 pages long) to online viewers or via communication with corresponding author. You should be able to access them also. This is what was recommended in guidelines. Description and rationale for each phase was described in Guideline Development section

On p.10 and 11 you refer to 'weaning' please specify this as 'sedation weaning' as it could be confused with ventilation weaning and the 2 things are inextricably linked.
OK text added

On p 12 line 48, you say 'some patients'....please specify how many.
OK –number added in to test actual number was in Figure 2.

On p. 14 line 21 'chart audit' might be better worded as @implementation Fidelity'.
Ok added

On p. 14 line 42 you mention the survey but in the methods there is no mention (I could see) of how the survey was developed, types of questions, piloted etc and who it was given to? was it just nurses or medical staff too?
Survey was referred to in design statement and added to sample statement. Additional detail was already located in outcome variables as follows:

"Staff perceptions were ascertained through administration of a researcher developed survey with questions on ease of use, impact on practice, perceived benefit, facilitation of team management, and promotion of nurse autonomy at bedside. Staff members were also given the opportunity to comment on strengths and limitations of the guidelines. "

The discussion could be shortened and refer to more literature rather than just restating results (p. 16 line 19-23).
Soe reference to other PICU guidelines studies added. A number of other references helping to confirm or clarify results already present (e.g. medication withdrawal, guideline fidelity, staff feedback).

Finally I am not sure what table 4 really adds to the paper.
It would be useful and would strenghten the paper to address these issues.
Table 4 details responses to Staff survey

Reviewer Name Yoanna Skrobik
Institution and Country Université de Montréal
Canada
Please state any competing interests or state 'None declared': none declared

This pragmatic pre-post implementation study's stated aim is the development, implementation and trial of locally developed guidelines for sedation and analgesia management in pediatric ICU patients. The authors audited charts and surveyed caregivers (nurses) for ease of use of the new guidelines. The tools described to assess the patients were the State Behaviour Scale, the Multidisciplinary Assessment of Pain Scale (MAPS) and the Opioid Benzodiazepine Withdrawal Assessment Scale (WAS). A broad variety of pharmacological interventions (varying drugs with varying half-lives in patients with very different lengths of stay) are described. A small sample of pre-implementation patients (75 patients in the pre and 63 patients in the post group) were evaluated. Study outcomes were total ventilation time (TVT), sedation doses and duration, length of stay in the PICU (LOS), and accidental extubation and readmission rates. Overall, opiate use and duration were reduced, and other outcomes were not different. The protocol was found to be feasible and acceptable to the majority of respondents (49% of the caregivers).

The study is interesting and important as individualized symptom management for pain and sedation is becoming recognized as an important outcome determinant in the critically ill.
The description of the protocol merits clarification. The psychometric validation of the scales applied to this pediatric population is not described, nor is caregiver evaluation performance for the individual scales.
This was not the purpose of the study. The development and validity of the respective tools was conducted by the authors respectively who are duly referenced. These are now widely used in the PICU community except for the WAS tool which is known better known in revised form WAT-1. Given already lengthy state of manuscript we didn't feel paper had room or scope for this.

It is also not clear on whether pain and sedation levels were differentiated or prioritized (i.e. with an attempt to evaluate pain first and sedation level second), or whether targeted analgesia levels or sedation levels were any different between the pre and post groups.
Yes, recommendation for individual patient goals determined daily as mentioned in Guideline implementation section and detailed in Guidelines, which were uploaded as supplementary material to be offered as Appendix (as is 6 page document).

Finally, the variety of pharmacological interventions and the varying pharmacokinetic characteristics of the administered drugs (particularly those infused over longer periods in the patients who had very long (30-75 days) periods of mechanical ventilation or long lengths of stay) confound the interpretation of the role the protocol played in the differences between the pre and post group. Providing the 'target range' data might better answer this question.
Yes we don't disagree with the potentially confounding influences of such a heterogeneous population; hence the 'pilot nature' of this study and the study results being considered most useful in informing the structure and outcome measures for a follow on clinical trial in this area.

Reviewer Name Saskia N. de Wildt
Institution and Country Pediatric intensivist, clinical pharmacologist
Erasmus MC - Sophia Children's Hospital
Rotterdam, The Netherlands
Please state any competing interests or state 'None declared': None declared.

Implementation of sedation protocol may improve patient outcome. The authors present the outcome of such an implementation in 2 PICUs.

Major comments:
The authors are not clear about the objectives of the study. The primary objective mentioned is 'to develop sedation and analgesia management guidelines and test their feasibility and acceptability in practice', however, in the abstract and the results they mention patient outcome data as primary result, despite small sample size. Please clarify.
Aim and objective statements through document made uniform for clarity and results reported accordingly to reflect this.

Overall, it took me a long time to grasp what the authors did and how they did it.

The overall lack of detail on the sedation protocol and the other guidelines (the table is not very detailed), as well as the missing information on how exactly adherence was measured, make this paper hard to understand and the conclusions not very useful for extrapolation. did every patient have score list?

Maybe they want to put too much in one manuscript.
I would suggest a manuscript describing how they came to the protocol and how it was implemented (where nurses trained to do validated pains scores?) and another paper on the effect of implementation.

In answer to both above statements, herein lay the challenge of reporting and writing up this study. In fact we have put significant detail about Guideline development including guiding references. The concept of two papers outlining 1. Guideline development and, 2. Short report on evaluation - was in fact rejected by previous journals! So we attempted to be as succinct yet complete describing the whole process as it occurred at the time. In essence, a truly pragmatic clinical study 'pilot testing' locally developed guidelines developed. To reduce the words I have removed the detailed summary of other guideline studies and merely referenced them.

There is no information on the sedation management protocol used in this study. Instead, a summary of the consensus guidelines is added in table 1. Is this how they are used in the unit, or is there an extended version, consider uploading this a supplementary file. I suggest to add the sedation protocol (flowchart?).
Guidelines were uploaded as supplemental material on submission of manuscript and are usually

offered as an appendix (as 6 pages long) to online viewers or via communication with corresponding author. You should be able to access them also. This is what was recommended in guidelines. Description and rationale for each phase was described in Guideline Development section.

The summary of consensus paper guiding the development of detail of the study guidelines has been brought forward to distinguish it from the body of the study.

The introduction and methods section can be significantly shortened. There is no need to discuss all studies in detail in the introduction. In the methods section, the authors discuss the consensus guidelines and 'drug cycling'. This is not appropriate in this section.
The rationale for the steps and phases of the guidelines form an essential part of the guideline implementation description.

In the discussion section the authors state that sedation goals were achieved quicker. However, this study shows no support of this statement. There are no scores of adequate sedation or sedation time. Please clarify. Ok. Acknowledged and removed. Sedation, Pain and Withdrawal scores were all captured but difficult to summarize meaningfully as a research variable. We recommended that a useful variable for follow in studies be to calculate the percentage of time each patient spent in a designated ‘zone’ and determining appropriateness and success /failure fo management accordingly. This has been added to discussion.

Minor comments:
- Sample size calculation: it is not clear how the authors have calculated the sample size. What was the total ventilation time of the retrospective analysis? ? remove
Given small and likely underpowered sample size it is not surprising difference in ventilation was not statistically significant. However potential for clinical significance has been enhanced as suggested. Though I am careful not to overstate findings give limitations of study.

- Setting: is the study performed on a medical, surgical or mixed PICU (instead of 'a range of diagnosis').
Setting description changed

- Study period: what was the study period? In the methods section the authors mention a study period of 6 months pre- and 6 months post-implementation, however, in the results they mention two study periods of 12 months each.
Typo corrected to 12 month each period

- Figure 1: please mention the reasons for exclusion.
Exclusion criteria in figure and also discussed in text

- Table 2 and 3: please mention median and IQR instead of range. Changed

additional comments:
Abstract: please specify which group the outcomes relate to (morphine dose and duration) Added

Page 6 line 17: the fentanyl units seem wrong (doses around 500 mcg/kg/h?) Thanks you checked but then removed as this section précised considerably

Page 12 line 50: what is meant with ‘deviation from study protocol or guidelines’? what is the difference between study protocol and guidelines? isn’t this an outcome variable? Does this not present bias to the results?
Yes deviation from guidelines was an outcome variable as part of fidelity testing. It presents some

bias in that only per protocol analysis was conducted, but as this was largely conducted as 'pilot study' and feasibility study no causal effect is claimed or reported.

It is not clear from the methods section that parents were asked for informed consent. Asking informed consent is a bit unusual when a new treatment algorithm is introduced in practice.
Ethics approval statement with reference made. No consent was not required for this study as met conditions for low and/or neglible risk. Statement added to manuscript for clarity.

Page 13 2nd paragraph: the description of results is ambigue: 'a reduction … between groups'> I assume a reduction from pre to post implementation? This should be worded more clearly. 10 mcg/kg/h midazolam seems very low. Are this medians for single patients? Or is this the median of the lowest dose (e.g. at weaning) for each patient. It is insufficient to only provide median/means and p-values, also the variability e.g. SD, IQR or range for each variable should be presented.
Description of what each variable is i.e. median minimum or median maximum are detailed prior to reporting of actual values. IQRs added

What is difference in protocol directed vs intervention group? Is this the same? Please use consistent wording throughout manuscript.
Sorry. Inconsistencies with language corrected.

It appears that a lot of effort has been put into developing these guidelines, implementing them and studying the effect, which are worth to be shared with the PICU community.
Thank you. Yes a lot of effort went in to developing and conducting this study as well as writing it up. We realize its limitations and have reported these but sill feel it has value in revealing lessons learnt from the process and knowledge gained.

As also noted above, the paper lacks in detail on methods and it should be strongly suggested to write two papers. As mentioned previously mentioned, Editors not receptive to this suggestion.

Consider adding experts on sedation research and on implementation to your team.
This study was part of an established program in the area of sedation and analgesia management on the unit that had already included a Retrospective study on patterns of sedation and pain management practice (presented at National Meeting and served as historical control) as well as a Survey on sedation and analgesia practice across PICUs nationally (published in peer reviewed Critical Care Journal). The researchers went on to trial and evaluate a revised withdrawal assessment tool and a study comparing the outcomes of Dexmedetomidine versus Midazolam is about to commence. The study units plan to continue to use the guidelines and tools in their modified form pending the results of larger trial work recently completed in the USA.

VERSION 2 – REVIEW

REVIEWER	Tume, Lyvonne Alder Hey Children's UK
REVIEW RETURNED	10-Nov-2014

GENERAL COMMENTS	Thank you for your revised manuscript. Many of the points i have highlighted have been addressed, but a few points remain. Figure 1 has an error in it - it says 12 months before and 6 months after when you have stated in the manuscript 12 months pre and post was done. You have described a bit about the setting, but it is useful to know whether either of these PICUs do cardiac surgery because this group of children impact upon ventilation time (reduce it) - you say

	mixed medical-surgical but not if this included cardiac surgery. There is a statement non p. 9 line 56 that is unclear i guess what you mean and thus would be clearer is 'Post implementation compliance/fidelity was assessed by chart review" In the methods section you need to clearly define what level you are defining as implementation fidelity - you allude to it later on (p.16) as being 75% of the 19 points, but this needs to be in the methods section because your analysis is based on before (no) guidelines and after (guidelines) being used - but we need to know they were actually being used and your analysis is based on a yes/no (compliance or not). Other limitations not discussed are the low (45%) survey response rate - the target always being a minimum of 70%, this may introduce bias - in the people who did not respond. A further limitations is there was a nurse survey but no survey of medical staff and they are also heavily involved in sedation and analgesia prescribing etc.

REVIEWER	Saskia N. de Wildt Pediatric intensivist, clinical pharmacologist Erasmus MC - Sophia Children's Hospital Rotterdam, The Netherlands
REVIEW RETURNED	14-Nov-2014

GENERAL COMMENTS	We acknowledge and appreciate the significant effort that the authors have put into improving the article, and it shows. But, to my opinion, the article still lacks in clarity/clear structure. A more focused organization of the paper is still needed. For example, the authors still mention different aims in the article, which is confusing. In the abstract, the aim is feasibility next to outcome variables, while the authors in the introduction mention 'develop, implement and evauate sedation guidelines' as primary aim. Consequently, at the end of the background the aim is develop guidelines based on the consensus guidelines and in the methods section (sample and participants) the main aim is feasibility. This all is confusing when reading the article. Furthermore, because of the different aims, the methods and result section is also not straight forward. Study design depends on the primary aim, which is not clear now. Overall, the methods and results section need to be structured. In the methods section the same subheadings needs to be addressed as in the results section. For example, implementation fidelity needs to be described in the methods section and after describing guideline development in the methods section, in the results section this guideline must be showed. Furthermore, the results section mainly describes patient outcomes, while this is not the primary aim. I have not gone into evaluating each answer of their letter, as this may change again after a better structure.

VERSION 2 – AUTHOR RESPONSE

Response to Reviewer 1
Apologies for continued typographical/formatting errors with this figure. Hopefully this is firmly corrected now.

No, neither of the study sites at the time of the study looked after patients post cardiac surgery. This has changed relatively recently. The description of population further clarified

Yes, an arbitrary number of 75% was chosen but the point of the audit was to evaluate the level of guideline uptake and/or adherence to elements of the same whatever they were.

Thank you. These points were not raised in the first review, however they are valid criticisms. A statement acknowledgment limitation of survey due to small response rate and single population has been added.

Response to Reviewer 2

The aims for respective sections copied and pasted below to check for consistency or inconsistency. While there are slight wording changes to minimize repetitiveness we believe we have been consistent with aims across stated sections. The evaluation of outcomes variables are consistently stated as including patient outcomes (for impact as well as quality and safety), feasibility and acceptability of guidelines in practice and staff acceptance. The results of the analyses of all these variables yielded valuable information that informed ongoing practice and research.

Title
Practice guidelines for sedation and analgesia management of critically ill children: A pre and post test study evaluating of impact and feasibility in the PICU.

Abstract
Objectives: The aim of this study was to develop, implement and evaluate guidelines for sedation and analgesia management in the paediatric intensive care unit (PICU).
Primary and secondary outcome measures: In addition to key outcome variables (ventilation time, medication dose and duration, length of stay), feasibility outcomes data (recruitment, data collection, safety) were evaluated.

Introduction
The aim of this study was to develop, implement and evaluate guidelines for sedation and analgesia management in the PICU as a part of program of research in this area and as a prelude to future trial work.

Background
The aim of this study was to develop sedation and analgesia management guidelines based on the 2006 consensus recommendation and test their feasibility and acceptability in practice as a prelude to rigorous trial evaluation of guidelines in practice.

Method
The main aim of this study was to develop, implement and evaluate locally developed guidelines for sedation and analgesia management on patient outcomes. Secondary aims were to evaluate the feasibility and acceptability of the guidelines in practice.

We believe the paper is structured logically, consistently and in accordance with standard research paper layout as follows:
Methods
Aims and Objectives of Study
Study design
Setting
Sample and participants

Guideline development
Guideline are submitted as supplementary material for inclusion in document as an appendix due to size of file. These are then available through embedded link for all on line readers and as hard copy by request.
Guideline implementation
Outcome variables
Description of variables of interest including patient outcomes, feasibility outcomes, guideline fidelity and staff perceptions.
Statistical analysis

Results
1. Initial paragraph and figure details participant recruitment and characteristics
2. Following paragraphs detail the impact the guidelines had on medication use and administration. The analysis of the patient and medication outcomes is in line with stated aims. Measuring and describing these was essential to (a) demonstrate equivalence across study groups and (b) serve as quality and safety measure i.e. that guidelines did not unnecessarily prolong actual or likelihood of ventilation or be associated with accidental/premature extubation, (c) confirm guidelines had desired impact on medication practice.
3. Results for implementation fidelity
4. Results from staff survey

The Discussion of the results is laid out similarly.
Some additional text discussing feasibility of participant eligibility, recruitment and data collection time has been added for clarification of feasibility outcomes.