## Pinder, Angela (Research)

**From:** Gary H Mills <g.h.mills@sheffield.ac.uk>
**Sent:** 02 July 2015 23:00
**To:** Lambert, Dave G. (Prof.)
**Cc:** Pinder, Angela (Research)
**Subject:** Re: NIAA e-grants - Decision on Application ID WKR0-2015-0055

**Categories:** Action

Dear Dave,
This is really great news about Probese. Thanks to you and the Committee. We have ethics committee approval, so we should now be able to move forward with requesting portfolio status
Best wishes,
Gary

On 1 July 2015 at 17:48, <dgl3@leicester.ac.uk> wrote:
01-Jul-2015

YOU MAY BE RECEIVING THIS MAIL IN COPY FOR INFORMATION ONLY

Dear Dr. Mills:

The NIAA grants committee with representatives from Anaesthesia/AAGBI met yesterday to consider your application for funding. I am delighted to be able to inform you that your application was recommended for support in the sum of £10,054.

This e.mail is a formal notification of funding for which we would request an acceptance e.mail with cc to all. Please note that if we do not hear from you within two weeks of the date of this award notification then the award will be withdrawn.

For your information I attach a copy of your peer review.

Please have a look at your abstracts and let me know if there are any (small) changes that you may wish to make. These will be posted on NIAA and funding partner websites.

In order to claim the funding you (or your finance office) will need to contact AAGBI directly and for your information I copy the relevant details below. There may be some additional conditions (e.g., the need for interim/final reports) that the project funder will provide.

All funding queries (and especially finance office claims) should be directed to AAGBI and NOT NIAA.

AAGBI contact: secretariat@aagbi.org

Successful applicants should contact their CLRN as soon as the award is made and work with them to obtain NIHR portfolio approval and support.

To find out which NIAA grants are recognised for inclusion on the NIHR portfolio click here:
http://www.niaa.org.uk/article.php?newsid=877

To find out more about your local CLRN click here:
http://www.crn.nihr.ac.uk/networks/

On behalf of NIAA and its funding partners I would like to congratulate you on the quality of your application and look forward to seeing your results published.

With kind regards

Sincerely,
Prof. David Lambert
Grants Officer, NIAA e-grants
dgl3@leicester.ac.uk

Reviewer(s)' Comments to Applicant:
Reviewer: 1

Comments to the Applicant
The comments refer primarily to the text from page 18 to page 48. In the total text the same sentences reoccurs several times, the primary comments applies to all occasions where sentences convey similar information.
1. Page 18, line 35: The study population consists of patients with a BMI ≥ 35 but without a limit in the upper range. This could be troublesome as with a higher BMI probably follows an increased risk of the treatment being ineffective using a fix PEEP of 12 cm H2O in the intervention group. With very high BMI the effectiveness ot the recruitment maneuver might be less. If the treatment becomes ineffective as the BMI gets higher, sample size calculations might be inaccurate.

2. Page 26, line 34-36 and 39-40. This is somewhat ambiguous. Is it possible for the attending anestesiologist to set another goal for SpO2 than 93%? If so what is the upper limit for SpO2? Increasing oxygen concentration more than what is needed to achieve the target SpO2 (93%) will increase the risk of transforming areas in the lungs with low V/Q into atelectasis.

3. Page 26, line 38-39. During anesthesia respiratory rate is adjusted to achieve "normocapnia" , defined as an end-tidal CO2 between 45-60 mm Hg. If the anesthesia monitor displays the end-tidal CO2 as a fraction at ATPS, the desired values expressed in fractions corresponding to 45-60 mm Hg should also be specified. The relation between end-tidal CO2 and the arterial CO2 is not always straightforward, especially when there is an increase in alveolar dead space and/or atelectasis. How is the degree of this potential discrepancy checked and accounted for in the study?

4. Page 26, line 42-45. The formula given for the "Ideal Body Weight" (IBW) is mistaken for the formula used for the "Predicted body weight" (PBW). In the PROVHILO trial the PWB was used, not the IBW so it might be better to use the proper denotation PBW for the formula given?

5. Page 26, line 56. After the words "induction of anesthesia" perhaps the clarification "and immediately after intubation" could be added?

6. Page 26-27, from line 54 (page 26) to line 26 (page 27). This paragraph describes the recruitment manovere (RM) to be used, however no reference is given to prove the effectiveness of the RM. If the respiratory rate during the RM is 6 BPM the respiratory cycle is 10 sec, which means that at I:E ratio of 1:1 the inspiratory time is 5 s. Has is been proven that 3 breaths with these settings constantly open up the lungs with a plaeau
pressure between 40-50 cm H2O? For a comparison, the RM used by Reinius et al (Prevention of atelectasis in morbidly obese patients during general anesthesia and paralysis: a computerized tomography study. Anesthesiology 2009; 111:979 – 87) might be interesting. They used a inspiratory pressure of 55 cm H2O for 10 sec in their patients, BMI was 45 +/- 5 (mean +/- sd) (in the intervention group in that study). If the respiratory rate is higher than 6 BPM, the respiratory cycle will be even less, and the probability that the

RM will work will also be reduced. Also, the the length of the plateau phase could also be defined. The oxygen concentration used during the RM should be defined. Instructions for increasing the pressure in the endo-tracheal cuff during the RM might be given.

7. Page 31, line 12-13. The use of CPAP or NPPV during induction is an important factor reducing the development of atelectasis. It might cloud the interpretation of the final results. Even if the use of CPAP/NPPV becomes evenly distributed in both the control and intervention group, it might have a greater positive effect in the control group, thus increasing the risk of making a type II error.

8. There is no mention of the oxygen concentration used during induction of or emergence from anesthesia in the protocol. Is there a assumption that 100% O2 will be used in every patient in accordance with standard care? The oxygen concentration during induction and emergence is of great importance for the effect of CPAP/PEEP used perioperatively. Without CPAP/NIV during induction there will be widespread atelectasis in both groups immediately after intubation with 100% O2. Using a suboptimal RM might not fully re-expand the lungs in the control group. Also, if 100 % oxygen is used during emergence and extubation, most of the effect of the RM performed at "end of surgery" will be lost (as was found in normal weight patient in "The Effect of Increased FIO2 Before Tracheal Extubation on Postoperative Atelectasis", Benoit et al, Anesth Analg 2002;95:1777–81 and also shown by Lumb et al in Lung recruitment and positive airway pressure before extubation does not improve oxygenation in the post-anaesthesia care unit: a randomized clinical trial; British Journal of Anaesthesia 104 (5): 643–7 (2010).

Reviewer: 2

Comments to the Applicant
1. Clarity of hypotheses, aims and/or objectives: This study has the clear objective of comparing the composite incidence of postoperative pulmonary complications after high and low PEEP ventilation in obese patients. This is a logical extension of the Provhilo trial in a patient group likely to show significant benefit.
2. Strengths & weaknesses of project: The ventilation and rescue protocol is quite clear and should be easy for the investigators to follow. Anesthetic management is otherwise left up to the clinician. My one concern is with the postoperative data collection. CXR, for example, is optional, yet many of the PPC as defined rely on a CXR or other imaging to establish the diagnosis. I understand that this trial is already underway elsewhere. How will you account for centers having different thresholds for obtaining postoperative testing? i.e. how do you avoid overdiagnosis of mild PPC such as atelectasis in some centers versus others?
3. Feasibility of work programme & relevant track-record of applicant: Dr. Mills has a long track-record of work in ventilation and successful participation in several multi-center studies
4. For clinical projects have all NHS research costs been met?: The applicant has requested funding for 1 research nurse (5000 GBP x 2 yrs). A more detailed job description/budget would be useful in order to determine if this funding level is appropriate.
5. For clinical projects benefit to the NHS (including priorities): As the number of patients with obesity continues to increase, this work will assist in defining the best anesthetic care and ideally reduce postoperative pulmonary complications.
6. Cost effectiveness: Primary expense is patient recruitment and data collection. The protocol should not require any additional operative time or expenditure.

Reviewer: 3

Comments to the Applicant
Two comments are raised by this project :
- why obese patients between 30 to 35 kg/m2 are not included in this study. Do the applicants could provide the difference in sample size calculation to assess clearly the cost/benefit ratio not to include these obese patients ?
- the financial summary needs clarification : Salaries of 7 research nurses are mentioned, but where will be the nurses in this multi center study? How they will work together ?...In addition, we need some explanations about the other expenses related to this project even there is no funding from the NIAA.

minor comment : why Provihlo study (Lancet. 2014 9;384:495-503) is not mentioned in references ?

Reviewer: 4

Comments to the Applicant
This proposal aims to test two different ventilatory strategies on pulmonary and extra-pulmonary outcome measures after general anesthesia for surgery. Of particular note it is designed to test two ventilatory strategies in a group of patients at higher risk for intraoperative and postoperative atelectasis. Atelectasis that develops during surgery is a possible predisposing factor for postoperative pulmonary complications, although this remains to date a hypothesis. The investigators correctly point out the lack of representation of obesity in currently published trials.

The study aims to test higher levels of PEEP with recruitment maneuvers (which are likely to prevent or resolve atelectasis) compared with lower levels of PEEP without recruitment maneuvers. Tidal volume in both groups will be set to 7 ml/kg IBW.

The primary outcome is postoperative pulmonary complications, for which there are detailed definitions. There are several secondary outcomes, including intraoperative complications, (e.g. low SpO2, hypotension during recruitment maneuvers), need for postoperative ventilatory support, unexpected ICU admission, hospital readmission within 30 days, hospital-free days and mortality at day 90, postoperative extrapulmonary complications and wound healing. Some markers of lung injury/sepsis will be measured, including angiopoietin-2 and surfactant proteins A and D, as well as markers of kidney injury: cystatin C and NGAL. It appears that interpretation of the relevant parameters will occur by investigators blinded to the intraoperative ventilation strategy. Power analysis has been performed appropriately. There are detailed and practical protocols for treatment of low SpO2 and protocol deviations. The plan for statistical analysis has been outlined.

The main weaknesses of the proposal relate to what might be called lost opportunities for examining mechanisms. The ongoing discussion about the effects of ‘volutrauma’ and ‘atelectrauma’ are thus far theoretical, with no means currently available to measure them in humans. While testing of one specific ventilatory strategy based on plausible rationale vs. another is appropriate, a better strategy might be one in which indices of atelectasis or stretch are measured so that a medical practitioner can make adjustments to the ventilatory strategy in real time. In this regard the proposed study makes no attempt to develop parameters that might be useful in this regard. It might also be fruitful to investigate some parameters consistently rather than ad hoc. Examples might include routine bedside spirometry, continuous postoperative pulse oximetry (with recording of supplemental oxygen administration). Radiographic imaging to detect atelectasis immediately after surgery, perhaps in a randomly selected subset of patients in both groups, might provide some mechanistic insight.

In summary, this is a well-articulated study that is likely to fulfil its purpose of further defining best-practice for intraoperative ventilatory management.

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Gary Mills
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