PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a prospective, international cohort study on the Management and Outcomes of Perioperative Care among European Diabetic Patients (MOPED)
AUTHORS	buggy, Donal; Nolan, Rachel; Coburn, Mark; Columb, Malachy; Hermanides, Jeroen; Hollman, M; Zarbock, Alexander

VERSION 1 – REVIEW

REVIEWER	Park, Duk-Woo Asan Medical Center
REVIEW RETURNED	22-Oct-2020

GENERAL COMMENTS	This study is prospective, observational, international, multicentre cohort study, recruiting 5,000 patients in at least n=50 centres with diabetes undergoing elective or emergency surgery. This study is designed to evaluate the epidemiology, pattern, and the perioperative management of diabetic patients in Europe. This manuscript is relatively well-written.

REVIEWER	Lloyd, Helen University of Teesside, School of Health and Life Sciences
REVIEW RETURNED	09-Nov-2020

GENERAL COMMENTS	Thank you for the opportunity to review this interesting manuscript. I enjoyed reading the article and I think it has a valid and important contribution to make, however I have some queries around the potential for bias in the study, which I think should be addressed before the manuscript can be considered for publication. My specific comments are listed below: I commend the authors for their proposal and the presentation overall. My main concern with this paper is the potential for selection bias across the proposed study. Major comments Participant selection The proposal does not specify how participants will be selected – will this be a consecutive sample until sample size is achieved from the date of commencement or will this be at the discretion of the investigator?

In regard to the latter, and owing to some surgical patients that are optimised prior to surgery on sliding scales (such as bariatric surgery) is there not the potential for selection bias if this is not a consecutive sample?

There is the potential that those who are subsequently managed under tighter parameters could be excluded in favour of others who are not, which is therefore a risk of bias.

Minor comments

The protocol does not state the age groups to be included – is this adult, child or both?

The term 'diabetics' has been used which is not a patient first language – please consider changing this to a term such as individuals with diabetes.

Page 11, line 18 – please check the formatting of the sentence.

Page 17, line 23 – please clarify what you mean by 'some data'? What data will be collected? By whom? At what intervals?

Page 18, lines 16 -18 – the statistics regarding the number of surgeries performed and the 'perhaps 1.5million' both need a reference regardless of whether they are cited earlier or later in the document.

REVIEWER	Kerridge, Ross
	John Hunter Hospital, Anaesthetics
REVIEW RETURNED	04-Mar-2021

| GENERAL COMMENTS | Thankyou for asking me to review this protocol. The proposed study is worthwhile but I fear may be overly ambitious, particularly seeking to compare outcomes from such a wide variety of patients, procedures and settings. The organisation and content of the manuscript itself needs to be considerably improved.

I understand that it is not appropriate to suggest major changes to the study methodology. That said, there are some methodological issues of note:
• Regarding incidence and duration of use of insulin infusion therapy:- if this is to be a meaningful tertiary outcome, presumably you must separate cases where this is a planned perioperative intervention rather than 'rescue'. In resource-rich settings, planned infusions may be used in preference to 'simpler' therapies, and they may thus be a marker for resource availability. How will you account for this and for similar issues?
• As an observational study, there shall be great value in establishing a better understanding of the epidemiology of perioperative diabetes management. This will lose a great deal of validity if there is biased selection. You address this briefly but do not specify how you will avoid bias in any centre. e.g. There should be predetermined criteria and commitment to include all patients for a set time period (or similar criteria). I think you imply this at page 13 (lines 30-36), but this needs to be clarified.
• The last sentence of statistical methodology section includes mention of a 'study analysis plan' being prepared. It would be preferable if this was prepared to be read with this protocol. Much of this report is difficult to read without having a clear study plan. |

The following points focus on the manuscript rather than methodology. Overall, I think the report would be significantly improved if a reader/writer who has not been involved with the report could review the text and reorganise it, perhaps incorporating the foreshadowed Study Analysis Plan.

There are multiple minor but annoying grammatical and language errors throughout the manuscript. Most of these are simple things like missing words, inconsistent case or plurals, or ambiguous meanings. Others are simple errors of sentence construction (e.g. the second sentence in the abstract!) There are many excessively long compound sentences including multiple subject/objects. Some lists within the text become confused and could be improved by attention to grammar, or by use of formalised lists with dot points. These then need to be checked for consistency and meaning. (see page 12 objective 3d as a particularly bad example.)

1. There is an error in the listing of Authors affiliations (I suspect Buggy should be 1 &6, not just 1)

2. Page 11 paragraph 18-42 jumps from outlining sub-group analysis, goes to preoperative glycaemic control and then goes on to personalised medicine. This paragraph in particular seems to be too intellectually ambitious, and distracts from the more humble goals of this study.

3. 'Setting' – Paragraphs from page 13 Line 15 to Page 14 line 14. This needs to be reorganised for greater clarity. It does not 'flow' well, and parts are quite confusing (even as a native English reader). There are a number of confusing long sentences in this section. It does not appear to cover all details of organisational aspects of the study. Funding is not clarified here (or earlier) although is mentioned later on page 19.

4. 'Participants' section (and indeed most of rest of the report) could also be improved by some rewriting with some better structuring. Some details could be better presented by use of lists rather than just text. Is there a minimum duration of anaesthesia as part of inclusion criteria?

5. Bias:- As previously noted, the likelihood of selection bias seems to be ignored. Unless each centre attempts enrolment of all diabetic patients sequentially, there is a clear potential for bias. The last sentence is unwarranted.

6. 'Recruitment and screening' section includes discussion of rationale for the procedures. This should not be in this section.

7. 'Data collection' section seems incomplete and poorly structured. I note that alternate spellings (centre/center) are used.

8. 'Statistical Methodology' is difficult to interpret when the proposed analysis plan is not first described. (The protocol needs to clarify what groups will be the subject of comparing which outcomes.)

9. Pages 20-23 are generally reasonably written and appropriately detailed, but again there are 'structural' issues. The sentence at page 22 lines 11-13 does not 'fit' at this point; and the last few sentences also should be earlier in the report.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewers [in bold]

Reviewer: 1
Dr. Duk-Woo Park, Asan Medical Center
Comments to the Author:
This study is prospective, observational, international, multicentre cohort study,
recruiting 5,000 patients in at least n=50 centres with diabetes undergoing elective or
emergency surgery. This study is designed to evaluate the epidemiology, pattern, and the
perioperative management of diabetic patients in Europe. This manuscript is relatively well-written.

Thank you

Reviewer: 2
Dr. Helen Lloyd, University of Teesside
Comments to the Author:
Thank you for the opportunity to review this interesting manuscript. I enjoyed reading the article and I
think it has a valid and important contribution to make, however I have some queries around the
potential for bias in the study, which I think should be addressed before the manuscript can be
considered for publication. My specific comments are listed below:

I commend the authors for their proposal and the presentation overall. My main concern with this
paper is the potential for selection bias across the proposed study.

Major comments

Participant selection

The proposal does not specify how participants will be selected – will this be a consecutive sample
until sample size is achieved from the date of commencement or will this be at the discretion of the
investigator?
In regard to the latter, and owing to some surgical patients that are optimised prior to surgery on
sliding scales (such as bariatric surgery) is there not the potential for selection bias if this is not a
consecutive sample?
There is the potential that those who are subsequently managed under tighter parameters could be
excluded in favour of others who are not, which is therefore a risk of bias.

Thank you: Indeed we have now stated clearly that centres should enrol patients consecutively.

Minor comments

The protocol does not state the age groups to be included – is this adult, child or both?

We have clarified that adults > 18 yr only will be included.

The term 'diabetics' has been used which is not a patient first language – please consider changing
this to a term such as individuals with diabetes.

Thank you. We are using "diabetic patients" throughout.

Page 11, line 18 – please check the formatting of the sentence.

Done thank you.

Page 17, line 23 – please clarify what you mean by 'some data'? What data will be collected? By whom? At what intervals?

This has been clarified that we refer to Day 1 postoperatively, collecting specifically QoR-15 and Day of Discharge, collecting data on insulin use, glucose levels and any complications.

Page 18, lines 16 -18 – the statistics regarding the number of surgeries performed and the 'perhaps 1.5million' both need a reference regardless of whether they are cited earlier or later in the document.

Thank you, now included in Statistical Analysis Plan.

Reviewer: 3
Dr. Ross Kerridge, John Hunter Hospital
Comments to the Author:
Thank you for asking me to review this protocol. The proposed study is worthwhile but I fear may be overly ambitious, particularly seeking to compare outcomes from such a wide variety of patients, procedures and settings. The organisation and content of the manuscript itself needs to be considerably improved.

I understand that it is not appropriate to suggest major changes to the study methodology. That said, there are some methodological issues of note:
•   Regarding incidence and duration of use of insulin infusion therapy:- if this is to be a meaningful tertiary outcome, presumably you must separate cases where this is a planned perioperative intervention rather than 'rescue'. In resource-rich settings, planned infusions may be used in preference to 'simpler' therapies, and they may thus be a marker for resource availability. How will you account for this and for similar issues?

Thank you. We have clarified that a continuous glucose/insulin infusion is regarded as planned, whereas any insulin boluses on top of this infusion will be deemed rescue or "additional". This has been added to the text.

•   As an observational study, there shall be great value in establishing a better understanding of the epidemiology of perioperative diabetes management. This will lose a great deal of validity if there is biased selection. You address this briefly but do not specify how you will avoid bias in any centre. e.g. There should be predetermined criteria and commitment to include all patients for a set time period (or similar criteria). I think you imply this at page 13 (lines 30-36), but this needs to be clarified.

Thank you. We have clarified that centres will enrol patients consecutively and for a period of up to 18 months.
•   The last sentence of statistical methodology section includes mention of a 'study analysis plan' being prepared. It would be preferable if this was prepared to be read with this protocol. Much of this report is difficult to read without having a clear study plan.

Thank you. The Statistical Analysis Plan is now included in the text.

The following points focus on the manuscript rather than methodology. Overall, I think the report would be significantly improved if a reader/writer who has not been involved with the report could review the text and reorganise it, perhaps incorporating the foreshadowed Study Analysis Plan.

There are multiple minor but annoying grammatical and language errors throughout the manuscript. Most of these are simple things like missing words, inconsistent case or plurals, or ambiguous meanings. Others are simple errors of sentence construction (e.g. the second sentence in the abstract!) There are many excessively long compound sentences including multiple subject/objects. Some lists within the text become confused and could be improved by attention to grammar, or by use of formalised lists with dot points. These then need to be checked for consistency and meaning. (see page 12 objective 3d as a particularly bad example.)
1.   There is an error in the listing of Authors affiliations (I suspect Buggy should be 1 &6, not just 1)

Thank you, corrected.
2.   Page 11 paragraph 18-42 jumps from outlining sub-group analysis, goes to preoperative glycaemic control and then goes on to personalised medicine. This paragraph in particular seems to be too intellectually ambitious, and distracts from the more humble goals of this study.

Thank you. We request that the thrust of this paragraph be retained, although its tone is now modified and it is shortened. Please allow us to dream of a little idealism!
3.   'Setting' – Paragraphs from page 13 Line 15 to Page 14 line 14.   This needs to be reorganised for greater clarity. It does not 'flow' well, and parts are quite confusing (even as a native English reader). There are a number of confusing long sentences in this section. It does not appear to cover all details of organisational aspects of the study. Funding is not clarified here (or earlier) although is mentioned later on page 19.

Thank you: This has been rewritten with shorter, clearer sentences.
4.   'Participants' section (and indeed most of rest of the report) could also be improved by some rewriting with some better structuring. Some details could be better presented by use of lists rather than just text.

Thank you: we have taken this on board here.

Is there a minimum duration of anaesthesia as part of inclusion criteria?

No
5.   Bias:- As previously noted, the likelihood of selection bias seems to be ignored. Unless each centre attempts enrolment of all diabetic patients sequentially, there is a clear potential for bias. The last sentence is unwarranted.

We have now stipulated the need for consecutive enrolment as outlined above.
6.   'Recruitment and screening' section includes discussion of rationale for the procedures. This should not be in this section.

Thank you, noted.
7.   'Data collection' section seems incomplete and poorly structured. I note that alternate spellings (centre/center) are used.

We have attempted to rewrite and improve this.
8.   'Statistical Methodology' is difficult to interpret when the proposed analysis plan is not first

described. (The protocol needs to clarify what groups will be the subject of comparing which outcomes.)

Analysis plan now added.

9.   Pages 20-23 are generally reasonably written and appropriately detailed, but again there are 'structural' issues. The sentence at page 22 lines 11-13 does not 'fit' at this point; and the last few sentences also should be earlier in the report.

We have removed some sentences and positioned them earlier as suggested, thank you again.

VERSION 2 – REVIEW

REVIEWER	Lloyd, Helen
	University of Teesside, School of Health and Life Sciences
REVIEW RETURNED	08-Apr-2021

GENERAL COMMENTS	Thank you for your re-submission and addressing the specific major revision previously highlighted.

REVIEWER	Kerridge, Ross
	John Hunter Hospital, Anaesthetics
REVIEW RETURNED	30-Mar-2021

GENERAL COMMENTS	I think this manuscript has improved considerably. I am reassured that inclusion criteria have been revised to include consecutive patients from each centre, although remain concerned that this will be difficult to assure in the 'real world', and may remain a source of inadvertent bias. I suggest that the trial coordinators work actively with all participating centres to minimise selection bias occurring.