PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Pain Predict Genetics: Protocol for a prospective observational study of clinical and genetic factors to predict the development of postoperative pain.
AUTHORS	LI, SONG; van Boekel, Regina L.M.; van den Heuvel, Sandra; Coenen, Marieke J.H.; Vissers, Kris

VERSION 1 – REVIEW

REVIEWER	Mitra, Sukanya Govt Med Coll
REVIEW RETURNED	24-Jul-2022

GENERAL COMMENTS	This is a very ambitious study, aimed to span at least 10 years and recruit 10,000 participants to enable a properly powered GWAS and further replication in independent samples. It has important potential implications for prediction and hence control of postoperative pain. My queries are related to the more precise definitions of both "acute" and "chronic" postoperative pain, which I find missing from the manuscript. Acute pain is almost ubiquitous (though in varying intensity and duration, depending on a multitude of factors) in the immediate postoperative pain. So what the authors trying to predict in the acute phase? If it refers to moderate or severe pain (as it would appear from the section on sample size calculation), then it has to be explicitly mentioned, detected operationally, and measured. Similar considerations apply for the important variable of chronic pain (threshold for diagnosis, assessment).

REVIEWER	WEBER , STEFAN Krankenhaus Koln-Merheim
REVIEW RETURNED	30-Jul-2022

GENERAL COMMENTS	Dear authors, you have launched a bold effort to construct an extensive database with the potential to gain insight in the development of post surgical pain. 1) secondary objectives: (abstract): "to build a databank enabling researches to identify other risk factors". In the "objectives" section you state 4 separate objectives. Please specify in the abstract. Will the database be exploredby your group or will it be open to other researchers? 2) COVID caused temporary stop of recrution an subsequent conversion into a multicentric study. Is the change of protocol covered by the ethics committee ? Does the change of protocol need to be indicated at clinicalTrials.gov? 3) Funding: You name departmental fundig only. Is there also funding for the other centers of the multicentric study?

	x) spelling: "incudion" line 380 4) Appendix c: Physical activities, question: you give the options 0-10 as well as "yes/no", please specify 5) Strega guidelines checklist: I did not find information to item #7b on page 16. Please add

VERSION 1 – AUTHOR RESPONSE

Comments from Reviewer 1:
This is a very ambitious study, aimed to span at least 10 years and recruit 10,000 participants to enable a properly powered GWAS and further replication in independent samples. It has important potential implications for prediction and hence control of postoperative pain.
My queries are related to the more precise definitions of both "acute" and "chronic" postoperative pain, which I find missing from the manuscript. Acute pain is almost ubiquitous (though in varying intensity and duration, depending on a multitude of factors) in the immediate postoperative pain. So what the authors trying to predict in the acute phase? If it refers to moderate or severe pain (as it would appear from the section on sample size calculation), then it has to be explicitly mentioned, detected operationally, and measured. Similar considerations apply for the important variable of chronic pain (threshold for diagnosis, assessment).
Authors: We added a paragraph to illustrate the definition, measurement, and threshold for the outcome measures of both acute and chronic postoperative pain. Please find it on page 18, lines 304-316.
The prediction model will be used to predict moderate to severe acute and chronic postoperative pain according to the definitions set. We clarified this point on page 20, line 352.

Comments from Reviewer 2:
Dear authors, you have launched a bold effort to construct an extensive database with the potential to gain insight in the development of post surgical pain.
1) secondary objectives:
(abstract): "to build a databank enabling researches to identify other risk factors". In the "objectives" section you state 4 separate objectives. Please specify in the abstract. Will the database be explored by your group or will it be open to other researchers?
Authors: The secondary objectives are followed by the primary objective in the abstract. Please see page 3 line 42 – 45.
The databank will be publicly available with an access fee to cover the cost of databank maintenance. Reasonable requests will be discussed in the research group before approval. We have added this information in the objectives on page 9 line 154-156.

2) COVID caused temporary stop of recrution an subsequent conversion into a multicentric study. Is the change of protocol covered by the ethics committee ? Does the change of protocol need to be indicated at clinicalTrials.gov?
Authors: The recruiting procedure was suspended because patients who underwent surgery were decreased during COVID. We did not suspend the recruiting process actively. Therefore, no protocol change is involved.
Regarding conversion into a multicenter study, the only protocol changes is to increase patients by adding more hospitals. The multicenter protocol is in preparation alongside with the negotiations of the hospitals involved.The ethics committee will first review this for approval and after that clinicaltrial.gov will be updated.

3) Funding: You name departmental fundig only. Is there also funding for the other centers of the multicentric study?

Authors: As patient data collection is integrated into clinical practice, other centers will run this project by departmental funding as well. Besides departmental funding, we aim to apply for extra grants to cover the potential cost of including more patients and the cost of databank maintenance. Please see page 24, line 442-444.

x) spelling: "incudion" line 380
Authors: This typo has been changed.

4) Appendix c: Physical activities, question: you give the options 0-10 as well as "yes/no", please specify
Authors: We have fixed the error. Only "yes/no" is kept as the only option.

5) Strega guidelines checklist: I did not find information to item #7b on page 16. Please add
Authors: Regarding item #7b “clearly define genetic exposures (genetic variants)”, this is covered for our study as we will use the screening array from Illumina and imputation from 1000 Genomes reference panel. Therefore, all SNPs that we identify will be reported on previously with e.g. RS numbers (RSID), and there is no need to define new genetic variants.
Regarding “identify variables likely to be associated with population stratification (confounding by ethnic origin)”. We have added a sentence on page 20, line 339, to clarify how to adjust the confounding caused by population stratification.

VERSION 2 – REVIEW

REVIEWER	WEBER , STEFAN Krankenhaus Koln-Merheim
REVIEW RETURNED	03-Oct-2022

GENERAL COMMENTS	All concerns were answered properly.