PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort Profile of PLUTO: a perioperative biobank focusing on prediction and early diagnosis of postoperative complications
AUTHORS	de Mul, Nikki; Verlaan, D.; Ruurda, Jelle; van Grevenstein, Wilhelmina; Hagendoorn, J.; de Borst, Gert-Jan; Vriens, M. R.; de Bree, R; Zweemer, Ronald; Vogely, Charles; Haitsma Mulier, J.L.G.; Vernooij, Lisette; Reitsma, Johannes; de Zoete, M.R.; Top, Janetta; Kluijtmans, J.A.J.; Hoefer, Imo; Noordzij, P.; Rettig, T; Marsman, M.; de Smet, A.M.G.A.; Derde, Lennie; van Waes, Judith; Rijsdijk, M.; Schellekens, W.J.M.; Bonten, Marc; Slooter, Arjen; Cremer, Olaf

VERSION 1 – REVIEW

REVIEWER	Hemmes, Sabrine AMC, Anesthesiology
REVIEW RETURNED	12-Nov-2022

GENERAL COMMENTS	I would like to congratulate the authors on the design of this bold innovative project, that will hopefully provide for many new insights in and knowledge of the perioperative period of the high risk surgical patient. The study is very well designed and the manuscript is outstanding. Everything is clearly described. The fact that data collection and outcomes are carefully coordinated with other running trials and that outcome definitions are based on existing criteria as much as possible, is very appealing. This manuscript can be accepted as it is. I have no comments, save for two questions: - Are CXRs or other radiographic images included in the dataset? Or are they only scored within the collected outcomes, like PPCs? - How long does the PLUTO group plan to include patients?

REVIEWER	Wan, Yize Queen Mary University of London
REVIEW RETURNED	22-Dec-2022

GENERAL COMMENTS	The authors present the cohort profile of a prospective perioperative data and biobank for postoperative complications following intermediate to high-risk surgery. This will likely be a valuable resource for future research in understanding and reducing perioperative risk and improving outcomes. I would suggest the following clarifications and modifications to the manuscript to improve the precision of reporting and design for future studies. Please be specific on how you define intermediate and high-risk. You state that this is based on surgical MPM and ESA but why have you focused only on GI and vascular as high-risk surgery? Is risk stratification defined only by surgical category or will you include high-risk patients? Why have you defined intermediate-risk as

	needing a 5-day or more length of stay? How does this fit with your planned 7-day post-operative data collection? Is this pre-planned LOS or will you include those who end up having a longer LOS than expected due to complications? Clarifying your inclusion criteria and these definitions will have implications for future external validity. Please include more details in methodology. How long you intend to store the data? You state this is a single centre study but there are two hospitals, please clearly specify. During the pre-operative assessment, is data collection on comorbidities and medications based on self-reporting or coding data? If self-reporting, would coding data improve accuracy? For data collection on endpoints, you list therapies for PPC, what about treatments and interventions for other complications?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

I would like to congratulate the authors on the design of this bold innovative project, that will hopefully provide for many new insights in and knowledge of the perioperative period of the high risk surgical patient. The study is very well designed and the manuscript is outstanding. Everything is clearly described. The fact that data collection and outcomes are carefully coordinated with other running trials and that outcome definitions are based on existing criteria as much as possible, is very appealing. This manuscript can be accepted as it is. I have no comments, save for two questions:

- Are CXRs or other radiographic images included in the dataset? Or are they only scored within the collected outcomes, like PPCs?

Thank you. Concerning chest radiographs and other imaging studies: image files are currently not collected in the PLUTO database. However, each time a complication is recorded (i.e. a major adverse cardiac event, postoperative pulmonary complication, or sepsis event) we register which imaging modalities were used (and which criteria were met) to make a diagnosis. Because we also register the date of the complication onset, we can use this information in the future to search additional radiological data contained in the electronic health record. However, as this requires back-linking of pseudonymized study IDs to the original patient record, we would need to obtain prior institutional authorization for this within the constraints of a specific study objective. We have now clarified this in the manuscript.

Changes made to the manuscript:

- Tracked changes: line 402-403.
- Changes accepted: 396-397.

- How long does the PLUTO group plan to include patients?

The PLUTO cohort has no end-date. PLUTO is embedded in clinical care as much as possible and will serve as a logistical framework for intervention studies within our department for the years to come. We have added this information to the manuscript.

Changes made to the manuscript:

- Tracked changes: line 411-413.
- Changes accepted: line 405-406.

Reviewer: 2

The authors present the cohort profile of a prospective perioperative data and biobank for postoperative complications following intermediate to high-risk surgery. This will likely be a valuable resource for future research in understanding and reducing perioperative risk and improving outcomes. I would suggest the following clarifications and modifications to the manuscript to improve the precision of reporting and design for future studies.

Please be specific on how you define intermediate and high-risk. You state that this is based on surgical MPM and ESA but why have you focused only on GI and vascular as high-risk surgery?

We thank the reviewer for this feedback and we have further clarified the definition of intermediate and high-risk in the manuscript and its supplement. The high-risk category includes vascular, abdominal surgery and pulmonary surgery. Cardiac surgery is currently not included in the PLUTO cohort because of different logistics (including fast track workflows), limited length of stay in our own center (due to early transfers back to referring hospitals) and low postoperative infection risk (relative to other complication types). In addition, we now use ‘abdominal’ surgery as a more accurate term than gastro-intestinal surgery, since we do include all abdominal procedures as defined in Appendix 1a of the article by Glance et al. (Glance, Ann Surg 2012; 255:696-702). Pulmonary surgery was missing from Supplementary file 1 by mistake, we have added this information to the file. In addition, the reason for not including cardiac surgery patients is also added to Supplementary file 1.

Changes made to the manuscript:

- Tracked changes: line 156.
- Changes accepted: line 154.

Is risk stratification defined only by surgical category or will you include high-risk patients?

We have defined risk stratification by surgical category only because we deliberately aim to enroll subjects across a wide range of patient-specific risk factors. This will enable us to study perioperative biomarkers for risk stratification and develop prognostic models for specific procedure types. The PLUTO study domain is therefore defined by consecutive patients undergoing high-risk as well as a selection of intermediate risk surgeries. We have now clarified this in the manuscript.

Changes made to the manuscript:

- Tracked changes: line 154-155.
- Changes accepted: 152-153.

Why have you defined intermediate-risk as needing a 5-day or more length of stay? How does this fit with your planned 7-day post-operative data collection?

Since the group of patients undergoing intermediate risk surgical procedures is potentially very large, we had to apply further selection criteria in order to keep the PLUTO project feasible. As length of stay generally shows good correlation with postoperative complication risk, we therefore decided to limit enrollment to intermediate-risk procedures associated with a planned length of stay ≥ 5 days.

Although bedside visits are scheduled to take place until day 7, there will obviously be patients who are discharged earlier if they are clinically well. However, by limiting PLUTO to procedures associated with a prolonged (scheduled) length-of-stay, we expect to have at least 5 days of bedside visits for most patients. Analysis of the first 297 enrolments (of whom 286 completed postoperative follow-up at that time) indeed shows 87% and 64% of included patients completing at least 5 or 7 days of follow-up, respectively. We have elaborated on this decision in Supplementary file 1 on included procedures.

Is this pre-planned LOS or will you include those who end up having a longer LOS than expected due to complications? Clarifying your inclusion criteria and these definitions will have implications for future external validity.

Enrolment is indeed based on expected (not actual) LOS, since we define our cohort on the basis of preoperative characteristics only. Furthermore, expected LOS itself is entirely defined by procedure type and (in principle) not on patient characteristics.

In addition, please note that including patients who unexpectedly end up having a prolonged stay might introduce selection bias (i.e. implying that we would then only include patients with a complicated course, and not those with an uneventful course undergoing the same procedure). We have clarified these decisions in the supplementary file in the paragraph on included procedure types.

Please include more details in methodology. How long you intend to store the data?

We thank the reviewer for pointing out that our data storage policy needs soms clarification. Since PLUTO has been designed as a perpetual observation study (POS) that has no set end-date storage of data will be maintained for a duration of at least 15 years following enrolment of the last patient. This is in compliance with regulation on data storage for research that is conducted under Dutch law (i.e. the "Wet Medisch Wetenschappelijk Onderzoek met mensen" (WMO)) but does not involve IMP testing. In addition, informed consent forms for PLUTO will be archived for the same period. Of note, Dutch GDPR regulations simply specify that data must be destroyed 'if there is no use case for further storage' which in our opinion also provides justification for the above time frames.

We have clarified this in the manuscript. Changes made to the manuscript:

- Tracked changes: line 411-413.
- Changes accepted: line 405-406.

You state this is a single centre study but there are two hospitals, please clearly specify.

The reviewer is right that PLUTO is a single centre study. However, we do collaborate closely with the BIG-PROMISE cohort (which itself enrolls patients across two non-academic Dutch hospitals), yet there are some significant differences between both cohorts. Most notably, BIG-PROMISE is an industry-sponsored cohort that includes large numbers of cardiac surgery patients, does not perform daily bedside visits, and entails more limited sample collection. Nonetheless, both determinant and outcome definitions were aligned as much as possible between PLUTO and BIG-PROMISE. We have clarified this in the manuscript.

Changes made to the manuscript:

- Tracked changes: line 438-445.
- Changes accepted: line 430-433.

During the pre-operative assessment, is data collection on comorbidities and medications based on self-reporting or coding data? If self-reporting, would coding data improve accuracy?

The data on comorbidity and medication is collected by using the preoperative anaesthesia screening questionnaires and clarifying any missing or discrepant information with the patient him/herself at the preoperative outpatient visit. Furthermore, a pharmacy assistant specifically checks all preoperative chronic medication use with the patient use and a validated list is then registered in the PLUTO database. We have clarified this in the manuscript.

Changes made to the manuscript:

- Tracked changes: line 200-202.
- Changes accepted: line 197-199.

For data collection on endpoints, you list therapies for PPC, what about treatments and interventions for other complications?

We thank the reviewer for pointing out that this was not clearly described in the manuscript. For each in-hospital endpoint (i.e. including all complications other than PPC) collected within PLUTO, the most relevant therapies given are registered in the case record form. This includes antibiotics and source control (infectious complications), antiplatelet drugs, anticoagulants, systemtic thrombolysis, antihypertensive drugs, percutaneous coronary intervetion (PCI), coronary artery bypass grafting (CABG), intra-aortal balloonpump/assist device implantation and anti-arrythmic medication (major adverse cardiac events), type of oxygen suppletion, high-flow nasal canula / non-invasive ventilation / intubation, prone positioning, furosemide, antibiotics, corticosteroids, bronchodilators and thoracic drain placement (postoperative pulmonary complications), diuretics, potassium lowering drugs and dialysis (acute kidney injury) and pain medications prescribed specifically for acute or neuropathic pain (pain). We have included this (summarized) in this section of the manuscript.

Changes made to the manuscript:

- Tracked changes: line 355-356, line 371, line 382, line 384-385, line 388-389.
- Changes accepted: line 352-353, line 368, line 377, line 379-380, line 382-384.

VERSION 2 – REVIEW

REVIEWER	Wan, Yize Queen Mary University of London
REVIEW RETURNED	05-Feb-2023

GENERAL COMMENTS	Thank you for revising the protocol following review. I have no further comments.