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Cohort Profile of PLUTO: a perioperative biobank focusing on prediction and early diagnosis of postoperative complications

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Abstract

Purpose: Although elective surgery is generally safe, some procedures remain associated with an increased risk of complications. Improved preoperative risk stratification and earlier recognition of these complications may ameliorate postoperative recovery and improve long-term outcomes. The perioperative longitudinal study of complications and long-term outcomes (PLUTO) cohort aims to establish a comprehensive biorepository that will facilitate research in this field. In this profile paper, we will discuss its design rationale and opportunities for future studies.

Participants: Patients undergoing elective intermediate to high-risk non-cardiac surgery are eligible for enrolment. For the first 7 postoperative days, participants are subjected to daily bedside visits by dedicated observers, who adjudicate clinical events and perform non-invasive physiological measurements (including handheld spirometry and single-channel EEG). Blood samples as well as microbiome specimens are collected at preselected time points. Primary study outcomes are the postoperative occurrence of nosocomial infections, major adverse cardiac events, pulmonary complications, acute kidney injury, and delirium/acute encephalopathy. Secondary outcomes include mortality and quality of life, as well as the long-term occurrence of psychopathology, cognitive dysfunction, and chronic pain.

Findings to date: Enrolment of the first participant occurred early 2020. During the inception phase of the project (first 2 years), 431 patients were eligible of whom 297 patients consented to participate (69%). Observed event rate was 42% overall, with the most frequent complication being infection.

Future plans: The main purpose of the PLUTO biorepository is to provide a framework for research in the field of perioperative medicine and anaesthesiology, by storing high-quality clinical data and biomaterials for future studies. In addition, PLUTO aims to establish a logistical platform for conducting embedded clinical trials.

Trial registration number: NCT05331118

Strengths and limitations of this study:

- Comprehensive perioperative data- and biobank including a broad range of high-risk surgical patients.
- Prospective bedside clinical assessments during the first 7 postoperative days.
- Collection of physiological data, blood plasma and microbiome specimens at predefined timepoints.
- Broad clinical data capture allowing for extensive covariate selection in both aetiologic and prediction research.
- Robust definitions of perioperative complications and outcomes allowing for straightforward external validation of findings.
- Collection of long-term patient-centred outcomes, including cognitive and psychosocial parameters.
- Logistical framework facilitating conduct of (embedded) randomized clinical trials.
- Limitations of PLUTO relate to its single-center design, strictly non-interventional approach to data collection, and use of self-reported long term outcome measures.

Introduction

Worldwide, almost a million patients are scheduled to undergo elective surgery each day.[1] Although these procedures are generally safe, surgery is not without risk. One in six patients undergoing elective procedures in a clinical setting develop a postoperative complication.[2] As reported by a large international cohort study, infectious and cardiovascular complications – according to European Perioperative Clinical Outcome (EPCO) definitions – occur in 9% and 4.5% of patients, respectively.[2] Moreover, postoperative delirium occurs in 12-23% of patients undergoing major orthopaedic, vascular or gastro-intestinal surgery.[3,4] These complications have been associated with adverse patient outcomes, including prolonged length of hospital stay[3,4], hospital readmission[3,5], persistent postsurgical pain[6] and increased mortality[7-9]. High-risk surgical procedures, defined as procedures with an associated mortality rate of 5% or more, account for 80% of all perioperative deaths.[7,9] Therefore, improving prediction and early diagnosis of postoperative complications may particularly be rewarding in this patient group.

Biobanking initiatives provide the opportunity to collect biological samples in a structured manner and cross-reference these with clinical predictors, exposures and outcomes on a large scale, thus enabling the exploration of a wide range of aetiologic, diagnostic and prognostic research questions.[10] Although biobanks of surgical patients are not uncommon,[10-13] most are organized around specific types of procedures and have a limited focus with respect to the perioperative setting.

The perioperative longitudinal study of complications and long-term outcomes (PLUTO) cohort and its associated data- and biobank is the first initiative worldwide to include a broad range of intermediate- to high-risk surgical patients, in whom a broad list of clinical events, bedside physiological data, blood samples and microbiome specimens are prospectively collected during the entire perioperative period. Primary outcomes include the occurrence of nosocomial infections, postoperative pulmonary complications, major adverse cardiac events (MACE), acute kidney injury (AKI), delirium, acute encephalopathy, and pain. The aim is to establish a comprehensive biorepository that will facilitate research in the field of preoperative risk stratification and early diagnosis of postoperative complications. Furthermore, PLUTO will be used as a logistical framework for implementing (registry-based) randomized controlled trials.[14]

The objective of this manuscript is to report the rationale of the PLUTO cohort, describe the process by which it was established and discuss the merits of this biorepository for future (collaborative) research in the field of anaesthesiology and perioperative medicine.

Cohort description

PLUTO is a prospective data- and biobank that enrols patients undergoing intermediate- to high-risk surgery in order to establish a research platform that will be used to (1) develop, recalibrate and/or externally validate perioperative prediction models, (2) discover and/or validate novel biomarkers that enable improved risk stratification and/or early diagnosis of postoperative complications, (3) assess the relevance of delirium/acute encephalopathy for early detection of postoperative infection, (4) estimate the attributable morbidity and mortality related to selected postoperative complications and (5) estimate the incidence of (chronic) postsurgical pain with neuropathic characteristics and study its aetiology and pathophysiology. We plan to use nested case-control designs as well as advanced mathematical models to address these objectives. PLUTO was initiated by the Division of Anaesthesiology, Intensive Care and Emergency Medicine of the University Medical Center Utrecht (UMCU), the Netherlands, in close collaboration with several surgical departments and the department of medical microbiology. The project was approved by the UMCU Biobank Research Ethics Committee (TC-Bio 19-514) and was filed under Clinical Trials.gov registration number NCT05331118. The latest biobank protocol and regulations are available from the authors upon request.

A. Inclusion criteria and informed consent

All patients scheduled to undergo elective high-risk gastro-intestinal and vascular surgery (as defined by the Surgical Mortality Probability Model and ESA guidelines[15,16]) in our tertiary hospital are eligible for inclusion. Patients undergoing selected intermediate risk procedures (including gynaecological, orthopaedic, and head and neck surgeries) can also become eligible if the procedure is associated with a scheduled hospital length of stay ≥ 5 days.[16] For a complete list of included procedures, we refer to Supplementary file 1. Patients under the age of 18 years, undergoing emergency surgery (non-elective, therefore not visiting the preoperative assessment clinic), having severe anaemia (Hb < 4.5 mmol/L), or being unable to provide informed consent are ineligible for enrolment. If surgery is cancelled or terminated prematurely due to unresectable or new metastatic disease, the patient is excluded post-hoc. Based on historical data we estimate that approximately six hundred patients in our hospital will be eligible for enrolment annually.

Written informed consent is obtained by Good Clinical Practice certified study personnel during the patient's visit to the preoperative assessment clinic. This covers collection, storage and use of data and biological specimens for future scientific projects, as well as

permission to perform various bedside tests during the postoperative period (listed below). Separate permissions to query the Dutch municipality register for date of death, to query the Dutch Bureau of statistics for cause of death, to contact general practitioners for missing information, and to share data and specimens with third parties are obtained according to Dutch law.

B. Study workflow

A general overview of the PLUTO workflow is shown in Table 1 and Supplementary file 2. For data- and sample collection we distinguish five consecutive time periods: (1) the outpatient preoperative assessment clinic visit, (2) the day of surgery, (3) an active postoperative observation period until postoperative day 7, (4) a reactive postoperative surveillance period from day 7 until hospital discharge, and (5) the three- and twelve-month follow-up. In the sections below we will further discuss these phases.

C. Data collection

Clinical data and bedside observations

At the outpatient preoperative assessment clinic, information is collected on relevant comorbidities (Supplementary file 3). In addition, information on pre-existing quality of life, activities of daily living, chronic pain, cognitive functioning, and presence of psychopathology is obtained using dedicated questionnaires (discussed below).

During surgery, relevant intraoperative information – including vital parameters, anaesthetic and cardiovascular medication used, ventilatory settings, intravenous fluids, and estimated blood loss – is automatically recorded in a dedicated anaesthesia information management system (AIMS) and subsequently linked to the PLUTO database.

For the duration of the active postoperative surveillance period (see Table 1), a member of the PLUTO study team performs daily bedside follow-ups to collect information on vital parameters (including early warning score items), pain (including a neuropathic pain questionnaire), physical mobility, and incentive spirometry performance. The active surveillance period ends on postoperative day 7, or at hospital discharge, whichever comes first.

For the remainder of hospital admission (i.e., the reactive postoperative surveillance period), bedside visits will no longer be performed. However, primary and secondary outcome events will be recorded based on a daily review of hospital electronic records (listed under paragraph E).

After discharge, patients are followed up for 12-months after surgery to collect additional information, which is described in more detail below.

Physiological measurements

Data capture for routine vital signs (including heart rate, mean arterial pressure, respiratory rate, and peripheral oxygen saturation) takes place once at the preoperative assessment clinic, once per minute during surgery and three times daily during the active postoperative surveillance period. In addition, the following additional tests and measurements are performed according to the schedule as shown in Table 1.

- Capillary Refill Time (CRT) is measured by applying pressure to the nailbeds of the index and the middle fingers of each hand for three seconds to cause blanching, and then recording the time in seconds until perfusion returns.[17] Subsequently, the highest and lowest of the four measurements are excluded and the mean of the remaining two times is recorded. To further reduce interrater variability a 1 Hz metronome is used.[18] CRT is a known predictor of mortality in septic shock patients[18,19] as well as severe postoperative complications after major abdominal surgery.[17]
- Handgrip strength is assessed three times for each hand using a SAEHAN Smedley spring dynamometer.[20] Subsequently, the best of these six measurements is recorded. Muscle strength as measured by handgrip strength is a validated clinical indicator of overall condition and nutritional status.[21,22] Furthermore, preoperative handgrip strength, as well as its delayed postoperative recovery, are known predictors for the development of complications following surgery.[22-24]
- Incentive spirometry is assessed once daily (day 1-7) conform hospital protocol using the Triflow device®. Inhaled flow is registered using a 3-point scale (600-900-1200 ml/sec).
- Pulmonary function testing, including assessment of forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), is performed upon preoperative assessment and once during the active surveillance phase (on day 7 or the nearest day possible), using a hand-held spirometer (Spirostik, Geratherm Respiratory, Kissingen, Germany). To improve the interpretation of these measurements, concurrent information is gathered about patient posture and mobility, pain (see below) and Triflow performance. All raw data generated during the measurements are stored for post-hoc analysis and quality control. Test and repeatability criteria as well as contra-indications described by the European Respiratory Society (ERS) and American Thoracic Society

(ATS) guidelines are used.[25,26] Of note, these guidelines generally consider pulmonary function tests contra-indicated during the first four weeks following surgery as high intrathoracic, intra-abdominal and intracranial pressures could potentially be generated.[26] However, we performed a systematic search of the literature (unpublished data), combining the synonyms for "spirometry" and "pulmonary function tests" in combination with synonyms for "postoperative" and "postsurgical", yielding a total of 4376 studies on the topic, none of which reported safety issues or complications of spirometry specifically related to surgery. Over 500 studies reported actual applications of pulmonary function testing during the early postoperative period, although most did not include spirometry-related complications as a prespecified study outcome. Moreover, we found that peak intrathoracic pressures generated during spirometry are lower (< 200 cmH_2O) than occur during spontaneous coughing (< 400 cmH_2O).[26-29] Based on this literature review, we consider postoperative hand-held spirometry to be safe.

- The presence of acute encephalopathy that may not (yet) manifest as clinically apparent delirium is measured using single-channel electroencephalography (EEG), which is performed using a DeltaScan mobile monitor (Prolira, Utrecht, The Netherlands), measuring polymorphous delta activity (0.5-4 Hz).[30] A disposable electrode patch is used to obtain a 96 seconds single-channel recording (Fp2-Pz with reference T8). To minimize artifacts, patients are instructed to keep their eyes closed for the entire duration of measurement (approximately 4 minutes). Subsequently, the DeltaScan Monitor software algorithm provides the DeltaScan score (1-5), with higher scores indicating a higher probability of delirium.[31] All raw EEG data are saved for post-hoc analysis. Previous studies by our group have demonstrated that the EEG shows significant differences in delta-activity between patients with and patients without delirium.[31,32] Moreover, there are indications that EEG slowing is associated with the severity of delirium and that this is an independent predictor for unfavorable outcomes following surgery.[32,33] In addition to the DeltaScan measurement, the 4AT and the Confusion Assessment Method (CAM, or CAM-ICU when the patient is admitted to the Intensive Care Unit (ICU)) are recorded by the research staff to assess presence of clinically apparent delirium. These scores were shown to have the greatest validity and reliability in a recent review of delirium screening methods for postoperative patients.[34]
- The likelihood for presence of postoperative pain with neuropathic characteristics is measured using the DN4 (Douleur Neuropathique 4) questionnaire and physical

examination. This includes assessment of sensitivity to touch and pin prick, as well as presence of allodynia.[35] The examination is performed adjacent – and if possible bilaterally – to the surgical wound in affected dermatomes (except in patients having a neuraxial or plexus block). For head and neck surgery it is performed preauricular, in the masseter region. The DN4 is well-validated screening tool for neuropathic pain.[36,37] Furthermore, in a recent publication we have shown that some DN4 items (specifically presence of painful cold and itching) are predictive for chronification of postsurgical pain.[38]

Follow-up questionnaires

Participants are followed over time to assess quality of life, daily functioning, cognitive function, and psychopathology. To this end, questionnaires are distributed to participants, once at the outpatient preoperative assessment clinic (baseline assessment), once at three-month follow-up, and once approximately one year following surgery. In case of non-response, a written reminder will be sent out to the patient at first, followed by a telephone call if necessary.

Survey items include the EuroQoL-5D (EQ-5D), the WHO Disability Assessment Schedule (WHODAS2.0-12), Barthel index, Instrumental Activities of Daily Living scale (I-ADL), DN4, Hospital Anxiety and Depression Scale (HADS), and the Cognitive Failure Questionnaire (CFQ). At 1-year follow-up, the Impact of Event Scale – Revised edition (IES-R) is additionally collected, whereas at 3 months the Barthel index, I-ADL, HADS and CFQ are omitted. To this end, PLUTO coordinates closely with other large cohort studies in the Netherlands to reduce the burden on participants. This includes the 3P initiative, a nationwide collaboration of gastro-intestinal cancer cohorts, among which the Prospective Observational Cohort Study of Esophageal-gastric cancer Patients (POCOP), the Dutch Pancreatic Cancer Project (PACAP), and the Prospective Dutch ColoRectal Cancer cohort (PLCRC).[39,40]

D. Specimen collection

All biological materials are processed and stored according to standardized operating procedures established within the UMCU Biobank Regulations.[41]

Blood sampling

Specimens are collected at predetermined time points during the first week (Table 1). Additionally, sampling will be reinitiated for 7 days if an infectious event occurs during the

reactive postoperative surveillance period. Specimen collection is combined with routine blood draws whenever possible.

At each sampling time point, 6 mL EDTA plasma, 4.5 mL citrated plasma, and 3.5 mL serum are obtained. Collection tubes are centrifuged at 3000 rpm for 10 minutes before the specimens are transferred into 1 mL micronic vials (2x 900µL for EDTA and citrate, 2x 700µL for serum) and stored at -80°C in the central biobank facility of the UMCU. The maximum total timeframe for collection, processing and storage of serum and plasma samples is 4 hours.

Microbiome sampling

Oral swabs and stool samples are collected at 4 predefined timepoints (Table 1). These will be processed by next generation sequencing to identify the composition of respiratory and gut microbiota.[42] A baseline oral swab is collected at the preoperative assessment clinic by a member of the research team, whereas the baseline faecal sample is collected by the patient at home. Subsequently, faecal samples and oral swabs are collected on postoperative days 2 and 7 (or the closest timepoint feasible), with faeces being obtained once more during 1-year follow-up. The oral swabs are transferred to 1 mL cryovials that can be directly stored in the biobank, whereas stool samples are collected in 15 mL tubes by the participants themselves and kept at room temperature for a maximum of 48 hours after production. In our central biobank facility these specimens are then transferred into five 2mL tubes for 16S rRNA sequencing and shotgun metagenomics, and two 5mL tubes which are kept as backups if a later need arises to culture specific bacteria.

E. Study outcomes

Endpoints in PLUTO are recorded using a process of post-hoc adjudication, which includes a chart review as well as an inventory of available diagnostic test results (i.e., chemistry, microbiology, and radiology findings). All outcomes are defined according to strict criteria:

- Infectious complications are defined according to Centers for Disease Control and prevention (CDC) criteria and International Sepsis Forum consensus definitions.[43,44] A comprehensive list of diagnostic criteria, as well as an assessment of the interobserver agreement associated with these, has previously been published by our group.[45] In addition, all diagnostic criteria for infection are scored over five axes (clinical signs and symptoms, radiological findings, laboratory findings and microbiological findings).[46]

For all events, the post hoc probability of true infection will be categorized using a four-point scale (none, possible, probable, and definite infection).[45]

- Postoperative pulmonary complications (PPC) are defined according to the European Perioperative Clinical Outcome (EPCO) definitions and include respiratory infection, respiratory failure, pleural effusion, atelectasis, pneumothorax, bronchospasm and/or aspiration pneumonia.[16] A postoperative pulmonary complication is registered if (1) the patient has a saturation below 90% on room air or (2) the patients oxygen consumption is exceeding 5L/min or (3) the patient adheres to the EPCO definition of respiratory failure.[16] In case of PPC a record is made of the duration of the episode, its associated clinical signs and symptoms, radiology findings, instituted therapies and the final diagnosis.
- Major Adverse Cardiac Events (MACE) are defined according to the Standardized Endpoints in Perioperative medicine (StEP) criteria and include myocardial infarction, cardiac arrest, and cardiac death.[16,47] When this definition is met, extra items (some part of the EPCO definition) for MACE (i.e., clinical signs and symptoms and diagnostic modalities used, radiological and laboratory findings and the addition of the following EPCO diagnoses: arrhythmias other than atrial fibrillation, congestive heart failure, and angina) are also included in the registration. Therefore, cardiovascular complications included in both these consensus definitions can be reconstructed from the PLUTO database and easily be compared to other perioperative outcome studies.[16,47] Additionally, for every patient of 60 years and older having ≥ 1 risk factors as included in the revised cardiac risk index, daily troponine-I is obtained every morning on the first three postoperative days.
- Acute Kidney Injury (AKI) is defined according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria with creatinine criteria only as described by the renal StEP criteria.[48,49] The chart of the patients is assessed daily for creatinine/kidney function.
- Acute encephalopathy and delirium are defined as a DeltaScan score ≥ 3 and delirium as either a positive CAM(-ICU) and/or ≥4 points on the AT4.[30]
- Pain is registered as acute pain via daily scores on the Numeric Rating Scale (NRS), ranging from 0 to 10 and as pain with neuropathic characteristics as indicated by the DN4.
- Long-term quality of life (one-year following surgery) is measured by the EQ-5D and functional outcome measures using the WHODAS2.0-12-question version.[50]

- Long-term psychopathology is defined as symptoms of depression, anxiety and/or post-traumatic stress syndrome (PTSS). Symptoms of depression are defined by a score ≥ 8 on the HADS-D, and symptoms of anxiety as a score ≥ 8 on the HADS-A.[51] Symptoms of PTSS are assumed to be present in case of a mean IES-R score ≥ 1.6.[52]
- Cognitive dysfunction is assessed by the Cognitive Failure Questionnaire which will be analysed as difference in median scores.[53]
- Mortality is registered as in-hospital mortality, 30-day mortality, one-year mortality and days alive outside of the hospital in the first 30 days following surgery.[50,54]

Severity of all outcomes that occur in hospital (i.e., infectious complications, PPC, MACE, AKI and delirium) is registered according to the Clavien-Dindo classification.[55]

F. Data management

All bedside observations are entered into an electronic data capture system (Castor®, Ciwit B.V., Amsterdam, the Netherlands) and periodically paired with batchwise data extractions from the electronic hospital information system (HiX, Chipsoft, Amsterdam, the Netherlands). Additionally, pulmonary flow-volume curves and raw EEG data are saved to separate databases for post-hoc quality control. All patient-level information is pseudonymized before storage, with the key being accessible only to approved PLUTO research personnel.

Findings to date

During a project pilot phase which extended from February 2020 to February 2022, 431 eligible subjects were approached for study participation, of whom 297 (69%) provided written informed consent and were successfully enrolled despite several restrictions being in place due to the COVID-19 pandemic. Observed event rate was 42% overall, with the most frequent complication being infectious complications. Based on the observed inclusion rate during the pilot phase and the number of surgical procedures known to be eligible in our hospital each year, we anticipate enrolling 400-450 patients into PLUTO annually.

Strengths and limitations

Biorepositories are situated at the intersection of two broader areas: big data research and the datafication of health.[56] They facilitate explorative large-scale discovery as well as provide for focused hypothesis testing in well-characterized (sub)groups of patients.[57] A particular strength

of the PLUTO biorepository is that it drives cooperation between various clinical and preclinical specialties, thus advancing translational science and precision medicine.

PLUTO was specifically designed to enable the development and validation of perioperative prediction models for risk stratification and early diagnosis of postoperative complications. PLUTO will also provide a solid basis for the critical evaluation of novel diagnostic and/or prognostic biomarkers. The use of robust definitions in PLUTO facilitates cooperation with other studies collecting perioperative outcomes, in particular the BIG-PROMISE biorepository (ClinicalTrials.gov Identifier: NCT05199025). All patients undergoing high-risk surgery in two large peripheral hospitals in the Netherlands are eligible and blood specimens are collected at five prespecified time points: the day before surgery, at the end of surgery and the first 3 postoperative days. Outcome definitions and study procedures of the PLUTO and BIG-PROMISE cohorts are carefully coordinated.

Importantly, the perioperative period represents a standardized model of systemic inflammatory stress, with exact timing of a known surgical insult. This setting therefore also provides unique opportunities to study the etiology of various postoperative conditions. As complications develop while patients are under active surveillance, physiological responses can be studied precisely at (or even before) the onset of clinical symptoms. In addition, the comprehensive collection of symptoms and signs, biomarkers, comorbidities, and outcomes in PLUTO enables extensive covariate selection as well as competing event adjustment in statistical models used for causal inference. Furthermore, other designs such as case-control designs or pre-post comparisons can be used.

PLUTO will also serve as a logistical framework for implementation of intervention studies, including registry-based randomized clinical trials (RRCTs). Such trials are commonly considered to be highly pragmatic and offer important benefits, including the ability to enroll large numbers of patients in relatively short periods and assess comparative effectiveness of treatments in a real-world setting.[14,58] Furthermore, they are relatively inexpensive compared to conventional RCTs.[14]

A potential limitation can be that the PLUTO cohort is a strictly observational cohort and thus reliant on diagnostic workup procedures as performed during routine clinical care. In addition, long-term follow-up in PLUTO is currently performed through self-report surveys only. This makes it impossible to assess certain endpoints, such as (recovery of) handgrip strength and pulmonary function, or perform more elaborate diagnostic tests, for instance focused on the prevalence of late neuropathic pain. However, we plan to implement in-person follow-up visits for specific subgroups in the future.

Collaboration

All data and biomaterials collected in PLUTO will – in principle – be made available for future studies that fit within the scope of the project's scientific aims and informed consent provided by participants. When interested in exploring the PLUTO biorepository, the study team can be contacted via PLUTO@umcutrecht.nl. The latest version of the biobank protocol and a detailed data dictionary is also available upon request. Please note that we may seek methodological, statistical, ethical, or legal advice when evaluating your study proposal. Also, approval from the UMCU Biobank Research Ethics Committee will need to be obtained. In case data and specimens are shared with external parties, adequate pseudonymisation of subjects will be enforced and Data and/or Material Transfer Agreements with UMCU may apply.

Conclusion

In conclusion, the PLUTO cohort entails patients undergoing elective intermediate- to high-risk surgery in whom both comprehensive data/sample collection and rigorous outcome adjudication takes place throughout the perioperative period. The resulting biorepository thus supports the development of prediction models aimed at perioperative risk stratification and early diagnosis of postoperative complications, as well as etiological models based on robust methodologies for causal inference. Furthermore, PLUTO will create a local infrastructure for intervention research. Experiences in our center during the two-year initiation phase of this project indicate that PLUTO will be feasible and sustainable for the foreseeable future. \

Contributorship statement

OLC, MJMB, AJCS and WJMS conceived the idea for the PLUTO biobank, NM and OLC drafted the study protocol, which was critically reviewed by all authors. The manuscript was drafted by NM and critically revised and approved by all authors before submission.

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Competing interests

None declared.

Public and patient involvement

No patient involved

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Table 1 – PLUTO Workflow

	Baseline assessment		Surgery	Postoperative period								Three-month follow-up	One-year follow-up
				Active surveillance							Reactive surveillance		
	Preoperative assessment	Morning of surgery		POD1	POD2	POD3	POD4	POD5	POD6	POD7			
Informed consent	X												
*Preoperative visit**	X												
*Questionnaires***	X											X	X
*Postoperative visit****				X	X	X	X	X	X	X			
Handgrip strength	X			X	X	X	X	X	X	X			
*Spirometry*****	X									X			
DeltaScan EEG				X	X	X	X	X	X	X			
Delirium assessment				X	X	X	X	X	X	X			
Pain	X			X	X	X	X	X	X	X		X	X
Blood samples													
- *EDTA plasma*		X	X	X	X	X	X	X	X	X	X[a]		
- *Citrate plasma*		X	X	X	X	X	X	X	X	X	X[a]		
- *Serum*		X	X	X	X	X	X	X	X	X	X[a]		
Microbiome samples													
- *Oral swabs*	X					X			X				
- *Faeces*	X					X			X				X
Radiology	***As clinically indicated, available from the electronic health records***												
Cultures	***As clinically indicated, available from the electronic health records***												
*Standardized complication registration*****				X	X	X	X	X	X	X	X		

Table 1 – PLUTO workflow

POD = postoperative day. *Preoperative visit includes collecting the following baseline information: demographics, comorbidities, intoxications, medication use, revised cardiac risk index and measurement of the capillary refill time. **Questionnaires include the EQ-5D, HADS, Barthel index, I-ADL, WHODAS2.0-12, DN4 and CFQ on baseline and one-year follow-up. At one-year follow-up the IES-R scale is added. At three-month follow-up the EQ-5D, WHODAS2.0-12 and DN4 are obtained. ***Postoperative bedside visits include clinical assessment of the patient including a capillary refill time, collecting information on mobility, physiotherapy, incentive spirometry, early warning score and numeric rating scale. [a]Blood samples will only be obtained after the intensive follow-up of 7 days in case of an infection occurring. Sample protocol will be restarted until end of antibiotic treatment or for a maximum of 7 days. **** Spirometry is performed once in the postoperative period, on day 7 or the day closest to discharge. *****Complications registered are infectious complications, postoperative pulmonary complications, major adverse cardiac events, acute kidney injury, delirium and/or acute encephalopathy and (neuropathic) pain. Postoperative complications are registered using standardized, predefined criteria and throughout the entire hospital admission by trained research staff.

Supplementary file 1 – Included procedures

General, upper gastro-intestinal, abdominal and pancreaticohepatic surgery

- Total gastrectomy
- Subtotal gastrectomy
- Transthoracic esophageal resection
    - Either thoracoscopic, open or robot-assisted and with or without gastric sleeve reconstruction.
- Transhiatial esophageal resection.
    - Either laparoscopic, open or robot-assisted and with or without gastric sleeve reconstruction.
- Hemihepatectomy
- Robot-assisted hemihepatectomy
- Exploration Klatskin tumor
- Partial liver resection
- Robot-assistend partial liver resection
- Whipple resection
- Robot Whipple resection
- Robot distal pancreatectomy (with or without spleen)
- Total pancreatectomy
- Proctocolectomy (open)
- Fundoplication (open)
- Duodenal resection (open)
- Ileocoecal resection (open)
- Sigmoid resection (open)
- Hemicolectomy, left-sided (open)
- Hemicolectomy, right-sided (open)
- Subtotal colectomy (open)
- Entero-enterostomy (open)
- Duodenal ulcus perforation repair
- Appendectomy (open)
- Rectosigmoid resection (open)
- Choledocho-duodenostomy (open)
- Choledocho-jejunostomie (Roux-Y)
- Cholecystectomy (open)
- Correction cicatrical hernia (Open, Ramirez)
- HIPEC/cytoreduction
- Adrenalectomy (open)

Gynaecological surgery

- Radical abdominal hysterectomy (open)
- Primary hysterectomy + bilateral salpingectomy
- Debulking stage III + IV (open)
- Debulking stage II (open)

Head and Neck surgery

- Commando resection
- Laryngopharyngectomy, total laryngectomy
- Tumorresection in head and neck area including a modified bilateral radicular neck dissection

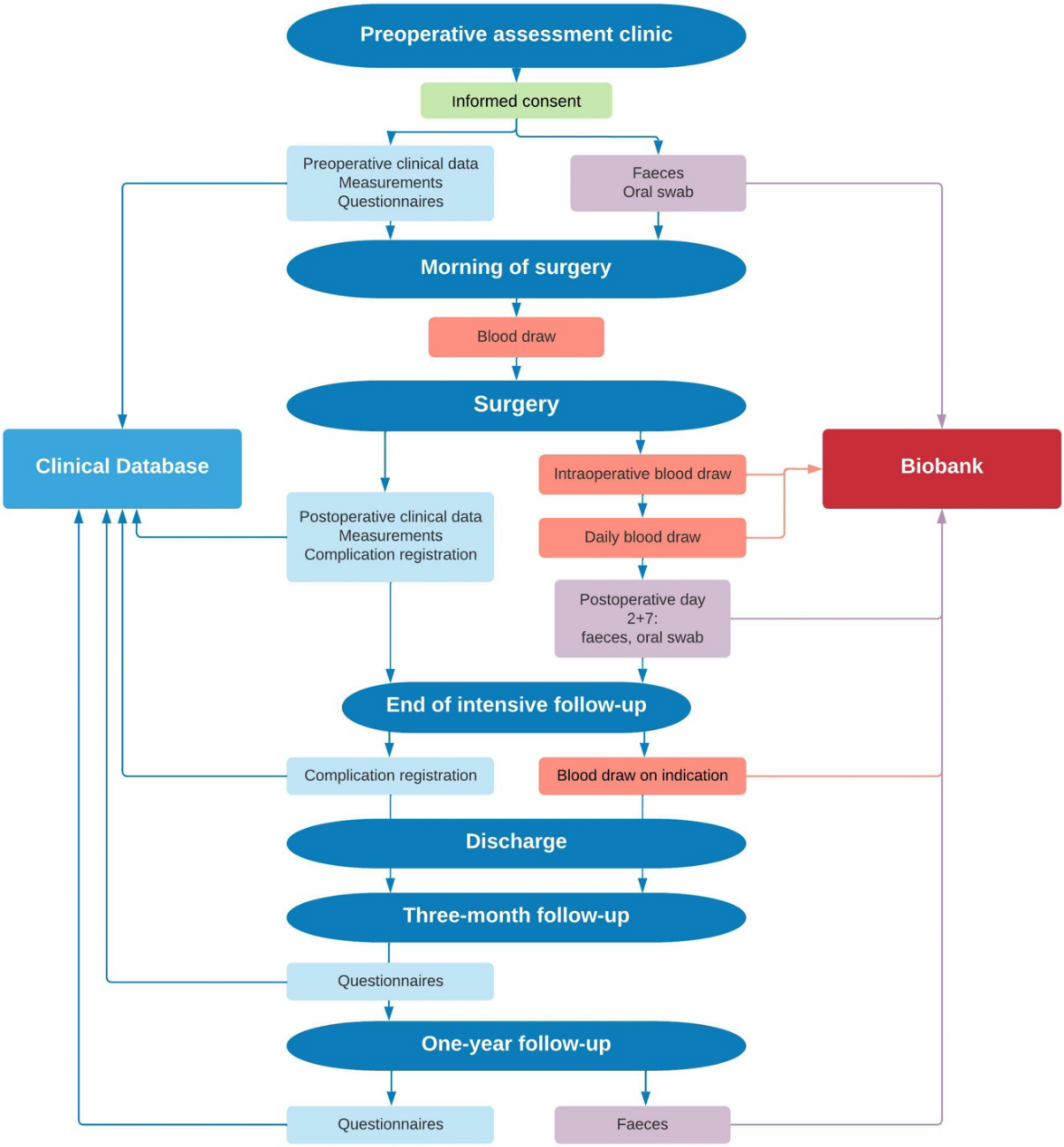
Orthopedic surgery

- Spondylodesis ≥ 4 segments (thoracic)

Vascular surgery

- Abdominal aortic repair (open)
- Nefrectomy

Supplementary file 2 – PLUTO flowchart



Supplementary file 2 – Flowchart of the PLUTO cohort.
Patients are included at the preoperative assessment clinic. Intensive follow-up lasts 7 days or until discharge and includes daily visits by PLUTO study personnel who perform additional bedside measurements. Measurements at the preoperative assessment clinic include hand grip strength, capillary refill time, handheld spirometry and screening for neuropathic pain using the Douleur Neuropathique 4 questionnaire and examination (DN4). These measurements are repeated daily in the 7-day intensive follow-up period, expect for spirometry which is performed on day 7 (or the day closest to discharge) only. In addition, one-channel EEG (DeltaScan) measurements are performed daily in the intensive follow-up period. Blood draws consist of 6mL EDTA plasma, 4.5 mL citrate plasma and 3.5 mL serum. Complications registered include infectious complications, postoperative pulmonary complications, major adverse cardiac events, acute kidney injury, delirium and/or acute encephalopathy and (neuropathic) pain. Questionnaires include the EQ-5D, WHODAS2.0-12, Barthel index, I-ADL, HADS (Hospital Anxiety and Depression Scale) and CFQ (Cognitive Failure Questionnaire) and DN4 at baseline and one-year follow-up, with addition of the IES-R (Impact of Event Scale, revised) at one-year follow-up. At three-month follow-up the EQ-5D, WHODAS2.0-12 and DN4 are collected.

Supplementary file 3 – List of included comorbidities and medication registration

Comorbidities

Severe coronary disease	Severe cardiovascular insufficiency. Angina or dyspnea in rest or minimal exercise (NYHA IV), or based on severe valvular disease.
Chronic ulcera/cellulitis	Decubitus, chronic venous insufficiency, chronic ulcera (all skin defects or open wounds existing > 1 month).
Asplenia	Congenital, acquired or functional asplenia.
Depression / bipolar disorder	Chronic (>1 month pre-admission) use of antidepressants or documented episode of depression in the patients' history up to 5 years before admission.
Myocardial infarction	Myocardial infarction > 1 week before admission; must be diagnosed based on ECG-abnormalities and/or enzyme abnormalities.
Heart failure	Documented chronic NYHA II-IV heart failure or patients with ejection fraction below 45% (documented on echocardiography < 2 years prior to admission) or orthopnea (for which chronic prescription of diuretic medication).
Peripheral vascular disease	Patients with intermittent claudication, patients treated with PTA/bypass surgery because of arterial insufficiency or gangrene and patients with a thoracic or abdominal aneurysms of more than 6 cm or dissection, unless atherosclerosis is not the main problem.
Hypertension	Chronic (>1 month) known hypertension and/or patients using antihypertensive medication.
Severe pulmonary disease	Chronic restrictive, obstructive or vascular pulmonary disease resulting in severe functional limitations.
COPD	Use of bronchodilators and/or corticosteroids because of chronic obstructive pulmonary disease (> 6 months).
Chronic O_2 therapy	Continuous or intermittent oxygen use in extramural setting
Chronic home mechanical ventilation	All forms of chronic mechanical ventilation in an extramural setting (both intermittent CPAP and continuous tracheal ventilation).
Cerebrovascular disease	Transient ischemic attack, cerebrovascular accident or subarachnoid hemorrhage.
Hemiplegia	Irreversible paresis of arm and leg with severe handicap or decreased mobility caused by a cerebrovascular accident.
Dementia	Dementia diagnosed by geriatrician or neurologist prior to admission.
Renal insufficiency	Increased serum creatinine > 177 µmol/L and documented as chronic renal failure/insufficiency prior to admission.

Dialysis dependent	Chronic dialysis patient, either hemodialysis or peritoneal dialysis for more than 1 month prior to admission.
Liver cirrhosis	Portal hypertension with positive liver biopsy and/or episode of upper gastro-intestinal bleeding caused by portal hypertension and/or episode of hepatic encephalopathy / coma due to liver failure.
Non-metastasized tumor	Neoplasm without metastases confirmed by pathology and/or clinically evident prior to admission. Hematological malignancies do not classify into this definition.
Metastasized tumor	Neoplasm with metastases (stage IV) confirmed by pathology and/or clinically evident prior to admission.
Hematological malignancy	Diagnosis of lymphoma, leukemia, or multiple myeloma (M Kahler) prior to admission.
Connective tissue disease / rheumatological disease	Diagnosis of rheumatological disease (SLE, MCTD, polymyalgia, rheumatoid artritis and polymyositis, vasculitis such as M. Wegener for example, diagnosed by internal specialist or rheumatologist.
Dyspepsia and/or ulcus disease	Treatment for chronic gastric ulcer diagnosed in the previous 5 years prior to admission.
Immunodeficiency	Use of immunosuppressants at the time of admission, and/or chemo/radiotherapy in the year prior to admission, and/or documented humoral or cellular deficiency.
HIV-infection	Documented HIV-seropositivity prior to admission or treatment with antiretroviral medication (with or without detectable viral load, with or without AIDS).
AIDS	HIV infection with CD4 < 200 and/or clinical complications.
Diabetes	Use of insulin and/or oral antidiabetics in the period prior to admission.
Diabetic end-organ damage	Diabetes mellitus and end-organ damage prior to admission. A clear link to diabetes does not have to be proven.
Thyroid or other endocrine disease	Hypothyroidism, hyperthyroidism and/or other endocrine disease.
Nursing home	Patient lives in a home where permanent care and support of activities of daily living is provided.
Alcohol- or drugs addiction	Suspicion of negative influence on daily functioning in patients with recent (<1 year) alcohol or drugs misuse that is evident from documentation or use of more than 4 glasses of alcohol a day or use of drugs apparent from patient history.
Current alcoholabusus	Current use of more than 3 glasses of alcohol a day, document in medical history but no direct negative consequences for daily functioning.
Current smoker	Current smoker documented in medical history.

Medication use

We register the following medication used at home:

- Beta blockers
- Other anti-arithmics
- Diuretics
- Calcium antagonists
- ACE inhibitors, angiotensin receptor blockers
- Statins
- Other lipid lowering drugs
- Thrombocyte aggregation inhibitors
- Anticoagulants
- NSAIDs / COX2 inhibitors
- Proton pump inhibitors, H2 antagonists
- Corticosteroids
- Other immunosuppressants
- Bronchodilators
- Cytostatics
- Oral antidiabetics
- Insulin
- Antirheumatic medication
- Benzodiazepines
- Anti-epileptics
- Antipsychotics
- Antiparkinson medication
- Migraine medication
- Antimicrobial medication
- Opioids
- No medication use (for validation)

BMJ Open

Cohort Profile of PLUTO: a perioperative biobank focusing on prediction and early diagnosis of postoperative complications

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Cohort Profile of PLUTO: a perioperative biobank focusing on prediction and early diagnosis of postoperative complications

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Abstract

Purpose: Although elective surgery is generally safe, some procedures remain associated with an increased risk of complications. Improved preoperative risk stratification and earlier recognition of these complications may ameliorate postoperative recovery and improve long-term outcomes. The perioperative longitudinal study of complications and long-term outcomes (PLUTO) cohort aims to establish a comprehensive biorepository that will facilitate research in this field. In this profile paper, we will discuss its design rationale and opportunities for future studies.

Participants: Patients undergoing elective intermediate to high-risk non-cardiac surgery are eligible for enrolment. For the first 7 postoperative days, participants are subjected to daily bedside visits by dedicated observers, who adjudicate clinical events and perform non-invasive physiological measurements (including handheld spirometry and single-channel EEG). Blood samples as well as microbiome specimens are collected at preselected time points. Primary study outcomes are the postoperative occurrence of nosocomial infections, major adverse cardiac events, pulmonary complications, acute kidney injury, and delirium/acute encephalopathy. Secondary outcomes include mortality and quality of life, as well as the long-term occurrence of psychopathology, cognitive dysfunction, and chronic pain.

Findings to date: Enrolment of the first participant occurred early 2020. During the inception phase of the project (first 2 years), 431 patients were eligible of whom 297 patients consented to participate (69%). Observed event rate was 42% overall, with the most frequent complication being infection.

Future plans: The main purpose of the PLUTO biorepository is to provide a framework for research in the field of perioperative medicine and anaesthesiology, by storing high-quality clinical data and biomaterials for future studies. In addition, PLUTO aims to establish a logistical platform for conducting embedded clinical trials.

Trial registration number: NCT05331118

Strengths and limitations of this study:

- Comprehensive perioperative data- and biobank including a broad range of high-risk surgical patients in whom prospective bedside clinical assessments take place during the first 7 postoperative days, including collection of physiological data, blood plasma and microbiome specimens at predefined timepoints.
- Broad clinical data capture allowing for extensive covariate selection in both aetiologic and prediction research and the use of robust definitions of perioperative complications and outcomes allowing for straightforward external validation of findings.
- Collection of long-term patient-centred outcomes, including cognitive and psychosocial parameters.
- Logistical framework facilitating conduct of (embedded) randomized clinical trials.
- Limitations of PLUTO relate to its single-center design, strictly non-interventional approach to data collection, and use of self-reported long term outcome measures.

Introduction

Worldwide, almost a million patients are scheduled to undergo elective surgery each day.[1] Although these procedures are generally safe, surgery is not without risk. One in six patients undergoing elective procedures in a clinical setting develop a postoperative complication.[2] As reported by a large international cohort study, infectious and cardiovascular complications – according to European Perioperative Clinical Outcome (EPCO) definitions – occur in 9% and 4.5% of patients, respectively.[2] Moreover, postoperative delirium occurs in 12-23% of patients undergoing major orthopaedic, vascular or gastro-intestinal surgery.[3, 4] These complications have been associated with adverse patient outcomes, including prolonged length of hospital stay[3, 4], hospital readmission[3, 5], persistent postsurgical pain[6] and increased mortality[7-9]. High-risk surgical procedures, defined as procedures with an associated mortality rate of 5% or more, account for 80% of all perioperative deaths[7, 9]. Therefore, improving prediction and early diagnosis of postoperative complications may particularly be rewarding in this patient group.

Biobanking initiatives provide the opportunity to collect biological samples in a structured manner and cross-reference these with clinical predictors, exposures and outcomes on a large scale, thus enabling the exploration of a wide range of aetiologic, diagnostic and prognostic research questions.[10] Although biobanks of surgical patients are not uncommon,[10-13] most are organized around specific types of procedures and have a limited focus with respect to the perioperative setting.

The perioperative longitudinal study of complications and long-term outcomes (PLUTO) cohort and its associated data- and biobank is the first initiative worldwide to include a broad range of intermediate- to high-risk surgical patients, in whom a broad list of clinical events, bedside physiological data, blood samples and microbiome specimens are prospectively collected during the entire perioperative period. Primary outcomes include the occurrence of nosocomial infections, postoperative pulmonary complications, major adverse cardiac events (MACE), acute kidney injury (AKI), delirium, acute encephalopathy, and pain. The aim is to establish a comprehensive biorepository that will facilitate research in the field of preoperative risk stratification and early diagnosis of postoperative complications. Furthermore, PLUTO will be used as a logistical framework for implementing (registry-based) randomized controlled trials.[14]

The objective of this manuscript is to report the rationale of the PLUTO cohort, describe the process by which it was established and discuss the merits of this biorepository for future (collaborative) research in the field of anaesthesiology and perioperative medicine.

Cohort description

PLUTO is a prospective data- and biobank that enrols patients undergoing intermediate- to high-risk surgery in order to establish a research platform that will be used to (1) develop, recalibrate and/or externally validate perioperative prediction models, (2) discover and/or validate novel biomarkers that enable improved risk stratification and/or early diagnosis of postoperative complications, (3) assess the relevance of delirium/acute encephalopathy for early detection of postoperative infection, (4) estimate the attributable morbidity and mortality related to selected postoperative complications and (5) estimate the incidence of (chronic) postsurgical pain with neuropathic characteristics and study its aetiology and pathophysiology. We plan to use nested case-control designs as well as advanced mathematical models to address these objectives. PLUTO was initiated by the Division of Anaesthesiology, Intensive Care and Emergency Medicine of the University Medical Center Utrecht (UMCU), the Netherlands, in close collaboration with several surgical departments and the department of medical microbiology. The project was approved by the UMCU Biobank Research Ethics Committee (TC-Bio 19-514) and was filed under Clinical Trials.gov registration number NCT05331118. The latest biobank protocol and regulations are available from the authors upon request.

A. Inclusion criteria and informed consent

Recruitment into PLUTO is based on procedural risk alone, as we explicitly aim to enrol subjects across a wide range of patient-specific risk factors. All patients scheduled to undergo elective high-risk abdominal, pulmonary and vascular surgery (as defined by the Surgical Mortality Probability Model and ESA guidelines[15, 16]) in our tertiary hospital are eligible for inclusion. Patients undergoing selected intermediate risk procedures (including gynaecological, orthopaedic, and head and neck surgeries) can also become eligible if the procedure is associated with a scheduled hospital length of stay ≥ 5 days.[16] For a complete list of included procedures, we refer to Supplementary file 1. Patients under the age of 18 years, undergoing emergency surgery (non-elective, therefore not visiting the preoperative assessment clinic), having severe anaemia (Hb < 4.5 mmol/L), or being unable to provide informed consent are ineligible for enrolment. If surgery is cancelled or terminated prematurely due to unresectable or new metastatic disease, the patient is excluded post-hoc. Based on historical data we estimate that approximately six hundred patients in our hospital will be eligible for enrolment annually.

Written informed consent is obtained by Good Clinical Practice certified study personnel during the patient's visit to the preoperative assessment clinic. This covers collection, storage and use of data and biological specimens for future scientific projects, as well as permission to perform various bedside tests during the postoperative period (listed below). Separate permissions to query the Dutch municipality register for date of death, to query the Dutch Bureau of statistics for cause of death, to contact general practitioners for missing information, and to share data and specimens with third parties are obtained according to Dutch law.

B. Study workflow

A general overview of the PLUTO workflow is shown in Table 1 and Supplementary file 2. For data- and sample collection we distinguish five consecutive time periods: (1) the outpatient preoperative assessment clinic visit, (2) the day of surgery, (3) an active postoperative observation period until postoperative day 7, (4) a reactive postoperative surveillance period from day 7 until hospital discharge, and (5) the three- and twelve-month follow-up. In the sections below we will further discuss these phases.

Table 1 – PLUTO Workflow

	Baseline assessment		Surgery	Postoperative period								Three-month follow-up	One-year follow-up
				Active surveillance							Reactive surveillance		
	Preoperative assessment	Morning of surgery		POD1	POD2	POD3	POD4	POD5	POD6	POD7			
Informed consent	X												
*Preoperative visit**	X												
*Questionnaires***	X											X	X
*Postoperative visit****				X	X	X	X	X	X	X			
Handgrip strength	X			X	X	X	X	X	X	X			
*Spirometry*****	X									X			
DeltaScan EEG				X	X	X	X	X	X	X			
Delirium assessment				X	X	X	X	X	X	X			
Pain	X			X	X	X	X	X	X	X		X	X
Blood samples													
- *EDTA plasma*		X	X	X	X	X	X	X	X	X	X[a]		
- *Citrate plasma*		X	X	X	X	X	X	X	X	X	X[a]		
- *Serum*		X	X	X	X	X	X	X	X	X	X[a]		
Microbiome samples													
- *Oral swabs*	X					X			X				
- *Faeces*	X					X			X				X
Radiology	*As clinically indicated, available from the electronic health records*												
Cultures	*As clinically indicated, available from the electronic health records*												
*Standardized complication registration*****				X	X	X	X	X	X	X	X		

Table 1 – PLUTO workflow

POD = postoperative day. *Preoperative visit includes collecting the following baseline information: demographics, comorbidities, intoxications, medication use, revised cardiac risk index and measurement of the capillary refill time. **Questionnaires include the EQ-5D, HADS, Barthel index, I-ADL, WHODAS2.0-12, DN4 and CFQ on baseline and one-year follow-up. At one-year follow-up the IES-R scale is added. At three-month follow-up the EQ-5D, WHODAS2.0-12 and DN4 are obtained. ***Postoperative bedside visits include clinical assessment of the patient including a capillary refill time, collecting information on mobility, physiotherapy, incentive spirometry, early warning score and numeric rating scale. [a]Blood samples will only be obtained after the intensive follow-up of 7 days in case of an infection occurring. Sample protocol will be restarted until end of antibiotic treatment or for a maximum of 7 days. **** Spirometry is performed once in the postoperative period, on day 7 or the day closest to discharge. *****Complications registered are infectious complications, postoperative pulmonary complications, major adverse cardiac events, acute kidney injury, delirium and/or acute encephalopathy and (neuropathic) pain. Postoperative complications are registered using standardized, predefined criteria and throughout the entire hospital admission by trained research staff.

C. Data collection

Clinical data and bedside observations

At the outpatient preoperative assessment clinic, information is prospectively collected on relevant comorbidities and preoperative medication use (verified by the pharmacy-assistant) (Supplementary file 3). In addition, information on pre-existing quality of life, activities of daily living, chronic pain, cognitive functioning, and presence of psychopathology is obtained using dedicated questionnaires (discussed below).

During surgery, relevant intraoperative information – including vital parameters, anaesthetic and cardiovascular medication used, ventilatory settings, intravenous fluids, and estimated blood loss – is automatically recorded in a dedicated anaesthesia information management system (AIMS) and subsequently linked to the PLUTO database.

For the duration of the active postoperative surveillance period (see Table 1), a member of the PLUTO study team performs daily bedside follow-ups to collect information on vital parameters (including early warning score items), pain (including a neuropathic pain questionnaire), physical mobility, and incentive spirometry performance. The active surveillance period ends on postoperative day 7, or at hospital discharge, whichever comes first.

For the remainder of hospital admission (i.e., the reactive postoperative surveillance period), bedside visits will no longer be performed. However, primary and secondary outcome events will be recorded based on a daily review of hospital electronic records (listed under paragraph E).

After discharge, patients are followed up for 12-months after surgery to collect additional information, which is described in more detail below.

Physiological measurements

Data capture for routine vital signs (including heart rate, mean arterial pressure, respiratory rate, and peripheral oxygen saturation) takes place once at the preoperative assessment clinic, once per minute during surgery and three times daily during the active postoperative surveillance period. In addition, the following additional tests and measurements are performed according to the schedule as shown in Table 1.

- Capillary Refill Time (CRT) is measured by applying pressure to the nailbeds of the index and the middle fingers of each hand for three seconds to cause blanching, and then recording the time in seconds until perfusion returns.[17] Subsequently, the highest and lowest of the four measurements are excluded and the mean of the remaining two

times is recorded. To further reduce interrater variability a 1 Hz metronome is used.[18] CRT is a known predictor of mortality in septic shock patients[18, 19] as well as severe postoperative complications after major abdominal surgery.[17]

- Handgrip strength is assessed three times for each hand using a SAEHAN Smedley spring dynamometer.[20] Subsequently, the best of these six measurements is recorded. Muscle strength as measured by handgrip strength is a validated clinical indicator of overall condition and nutritional status.[21, 22] Furthermore, preoperative handgrip strength, as well as its delayed postoperative recovery, are known predictors for the development of complications following surgery.[22-24]
- Incentive spirometry is assessed once daily (day 1-7) conform hospital protocol using the Triflow device®. Inhaled flow is registered using a 3-point scale (600-900-1200 ml/sec).
- Pulmonary function testing, including assessment of forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), is performed upon preoperative assessment and once during the active surveillance phase (on day 7 or the nearest day possible), using a hand-held spirometer (Spirostik, Geratherm Respiratory, Kissingen, Germany). To improve the interpretation of these measurements, concurrent information is gathered about patient posture and mobility, pain (see below) and Triflow performance. All raw data generated during the measurements are stored for post-hoc analysis and quality control. Test and repeatability criteria as well as contra-indications described by the European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines are used.[25, 26] Of note, these guidelines generally consider pulmonary function tests contra-indicated during the first four weeks following surgery as high intrathoracic, intra-abdominal and intracranial pressures could potentially be generated.[26] However, we performed a systematic search of the literature (unpublished data), combining the synonyms for "spirometry" and "pulmonary function tests" in combination with synonyms for "postoperative" and "postsurgical", yielding a total of 4376 studies on the topic, none of which reported safety issues or complications of spirometry specifically related to surgery. Over 500 studies reported actual applications of pulmonary function testing during the early postoperative period, although most did not include spirometry-related complications as a prespecified study outcome. Moreover, we found that peak intrathoracic pressures generated during spirometry are lower (< 200 cmH_2O) than occur during spontaneous coughing (< 400

cmH_2O).[26-29] Based on this literature review, we consider postoperative hand-held spirometry to be safe.

- The presence of acute encephalopathy that may not (yet) manifest as clinically apparent delirium is measured using single-channel electroencephalography (EEG), which is performed using a DeltaScan mobile monitor (Prolira, Utrecht, The Netherlands), measuring polymorphous delta activity (0.5-4 Hz).[30] A disposable electrode patch is used to obtain a 96 seconds single-channel recording (Fp2-Pz with reference T8). To minimize artifacts, patients are instructed to keep their eyes closed for the entire duration of measurement (approximately 4 minutes). Subsequently, the DeltaScan Monitor software algorithm provides the DeltaScan score (1-5), with higher scores indicating a higher probability of delirium.[31] All raw EEG data are saved for post-hoc analysis. Previous studies by our group have demonstrated that the EEG shows significant differences in delta-activity between patients with and patients without delirium.[31, 32] Moreover, there are indications that EEG slowing is associated with the severity of delirium and that this is an independent predictor for unfavorable outcomes following surgery.[32, 33] In addition to the DeltaScan measurement, the 4AT and the Confusion Assessment Method (CAM, or CAM-ICU when the patient is admitted to the Intensive Care Unit (ICU)) are recorded by the research staff to assess presence of clinically apparent delirium. These scores were shown to have the greatest validity and reliability in a recent review of delirium screening methods for postoperative patients.[34]
- The likelihood for presence of postoperative pain with neuropathic characteristics is measured using the DN4 (Douleur Neuropathique 4) questionnaire and physical examination. This includes assessment of sensitivity to touch and pin prick, as well as presence of allodynia.[35] The examination is performed adjacent – and if possible bilaterally – to the surgical wound in affected dermatomes (except in patients having a neuraxial or plexus block). For head and neck surgery it is performed preauricular, in the masseter region. The DN4 is well-validated screening tool for neuropathic pain.[36, 37] Furthermore, in a recent publication we have shown that some DN4 items (specifically presence of painful cold and itching) are predictive for chronification of postsurgical pain.[38]

Follow-up questionnaires

Participants are followed over time to assess quality of life, daily functioning, cognitive function, and psychopathology. To this end, questionnaires are distributed to participants, once at the outpatient preoperative assessment clinic (baseline assessment), once at three-month follow-up, and once approximately one year following surgery. In case of non-response, a written reminder will be sent out to the patient at first, followed by a telephone call if necessary.

Survey items include the EuroQoL-5D (EQ-5D), the WHO Disability Assessment Schedule (WHODAS2.0-12), Barthel index, Instrumental Activities of Daily Living scale (I-ADL), DN4, Hospital Anxiety and Depression Scale (HADS), and the Cognitive Failure Questionnaire (CFQ). At 1-year follow-up, the Impact of Event Scale – Revised edition (IES-R) is additionally collected, whereas at 3 months the Barthel index, I-ADL, HADS and CFQ are omitted. To this end, PLUTO coordinates closely with other large cohort studies in the Netherlands to reduce the burden on participants. This includes the 3P initiative, a nationwide collaboration of gastro-intestinal cancer cohorts, among which the Prospective Observational Cohort Study of Esophageal-gastric cancer Patients (POCOP), the Dutch Pancreatic Cancer Project (PACAP), and the Prospective Dutch ColoRectal Cancer cohort (PLCRC).[39, 40]

D. *Specimen collection*

All biological materials are processed and stored according to standardized operating procedures established within the UMCU Biobank Regulations.[41]

Blood sampling

Specimens are collected at predetermined time points during the first week (Table 1). Additionally, sampling will be reinitiated for 7 days if an infectious event occurs during the reactive postoperative surveillance period. Specimen collection is combined with routine blood draws whenever possible.

At each sampling time point, 6 mL EDTA plasma, 4.5 mL citrated plasma, and 3.5 mL serum are obtained. Collection tubes are centrifuged at 3000 rpm for 10 minutes before the specimens are transferred into 1 mL micronic vials (2x 900µL for EDTA and citrate, 2x 700µL for serum) and stored at -80°C in the central biobank facility of the UMCU. The maximum total timeframe for collection, processing and storage of serum and plasma samples is 4 hours.

Microbiome sampling

Oral swabs and stool samples are collected at 4 predefined timepoints (Table 1). These will be processed by next generation sequencing to identify the composition of respiratory and gut microbiota.[42] A baseline oral swab is collected at the preoperative assessment clinic by a member of the research team, whereas the baseline faecal sample is collected by the patient at home. Subsequently, faecal samples and oral swabs are collected on postoperative days 2 and 7 (or the closest timepoint feasible), with faeces being obtained once more during 1-year follow-up. The oral swabs are transferred to 1 mL cryovials that can be directly stored in the biobank, whereas stool samples are collected in 15 mL tubes by the participants themselves and kept at room temperature for a maximum of 48 hours after production. In our central biobank facility these specimens are then transferred into five 2mL tubes for 16S rRNA sequencing and shotgun metagenomics, and two 5mL tubes which are kept as backups if a later need arises to culture specific bacteria.

E. Study outcomes

Endpoints in PLUTO are recorded using a process of post-hoc adjudication, which includes a chart review as well as an inventory of available diagnostic test results (i.e., chemistry, microbiology, and radiology findings). All outcomes are defined according to strict criteria:

- Infectious complications are defined according to Centers for Disease Control and prevention (CDC) criteria and International Sepsis Forum consensus definitions.[43, 44] A comprehensive list of diagnostic criteria, as well as an assessment of the interobserver agreement associated with these, has previously been published by our group.[45] In addition, all diagnostic criteria for infection are scored over five axes (clinical signs and symptoms, radiological findings, laboratory findings and microbiological findings).[46] For all events, the post hoc probability of true infection will be categorized using a four-point scale (none, possible, probable, and definite infection).[45] Treatment, including antibiotics and source control, is prospectively registered.
- Postoperative pulmonary complications (PPC) are defined according to the European Perioperative Clinical Outcome (EPCO) definitions and include respiratory infection, respiratory failure, pleural effusion, atelectasis, pneumothorax, bronchospasm and/or aspiration pneumonia.[16] A postoperative pulmonary complication is registered if (1)

the patient has a saturation below 90% on room air or (2) the patients oxygen consumption is exceeding 5L/min or (3) the patient adheres to the EPCO definition of respiratory failure.[16] In case of PPC a record is made of the duration of the episode, its associated clinical signs and symptoms, radiology findings, instituted therapies and the final diagnosis.

- Major Adverse Cardiac Events (MACE) are defined according to the Standardized Endpoints in Perioperative medicine (StEP) criteria and include myocardial infarction, cardiac arrest, and cardiac death.[16, 47] When this definition is met, extra items (some part of the EPCO definition for MACE) are included in the registration, including clinical signs and symptoms, diagnostic modalities used, radiological and laboratory findings, instituted treatments and the presence of congestive heart failure and arrhythmias other than atrial fibrillation. Therefore, cardiovascular complications included in both these consensus definitions can be reconstructed from the PLUTO database and easily be compared to other perioperative outcome studies.[16, 47] Additionally, for every patient of 60 years and older having ≥ 1 risk factors as included in the revised cardiac risk index, daily troponine-I is obtained every morning on the first three postoperative days.
- Acute Kidney Injury (AKI) is defined according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria with creatinine criteria only as described by the renal StEP criteria.[48, 49] The chart of the patients is assessed daily for creatinine/kidney function. Use of diuretics and hemodialysis or -filtration is also registered.
- Acute encephalopathy and delirium are defined as a DeltaScan score ≥ 3 and delirium as either a positive CAM(-ICU) and/or ≥4 points on the 4AT.[30] Medications used to treat delirium are extracted from the electronic health records.
- Acute pain is registered using daily scoring on the Numeric Rating Scale (NRS), ranging from 0 to 10. Neuropathic characteristics are assessed by the DN4 questionnaire. Use of pain medications is prospectively registered daily during the active surveillance period.
- Long-term quality of life (one-year following surgery) is measured by the EQ-5D and functional outcome measures using the WHODAS2.0-12-question version.[50]
- Long-term psychopathology is defined as symptoms of depression, anxiety and/or post-traumatic stress syndrome (PTSS). Symptoms of depression are defined by a score ≥ 8

on the HADS-D, and symptoms of anxiety as a score ≥ 8 on the HADS-A.[51] Symptoms of PTSS are assumed to be present in case of a mean IES-R score ≥ 1.6.[52]

- Cognitive dysfunction is assessed by the Cognitive Failure Questionnaire which will be analysed as difference in median scores.[53]
- Mortality is registered as in-hospital mortality, 30-day mortality, one-year mortality and days alive outside of the hospital in the first 30 days following surgery.[50, 54]

Severity of all outcomes that occur in hospital (i.e., infectious complications, PPC, MACE, AKI and delirium) is registered according to the Clavien-Dindo classification.[55] For all in-hospital complications the diagnostic modalities used are recorded.

F. Data management

All bedside observations are entered into an electronic data capture system (Castor®, Ciwit B.V., Amsterdam, the Netherlands) and periodically paired with batchwise data extractions from the electronic hospital information system (HiX, Chipsoft, Amsterdam, the Netherlands). Additionally, pulmonary flow-volume curves and raw EEG data are saved to separate databases for post-hoc quality control. All patient-level information is pseudonymized before storage, with the key being accessible only to authorized personnel. The PLUTO cohort has no set end-date and data will be stored for a minimum of 15 years after termination.

G. Public and patient involvement

During the design of this study we did not involve patient organisations.

Findings to date

During a project pilot phase which extended from February 2020 to February 2022, 431 eligible subjects were approached for study participation, of whom 297 (69%) provided written informed consent and were successfully enrolled despite several restrictions being in place due to the COVID-19 pandemic. Observed event rate was 42% overall, with the most frequent complication being infectious complications. Based on the observed inclusion rate during the pilot phase and the number of surgical procedures known to be eligible in our hospital each year, we anticipate enrolling 400-450 patients into PLUTO annually.

Strengths and limitations

Biorepositories are situated at the intersection of two broader areas: big data research and the datafication of health.[56] They facilitate explorative large-scale discovery as well as provide for focused hypothesis testing in well-characterized (sub)groups of patients.[57] A particular strength of the PLUTO biorepository is that it drives cooperation between various clinical and preclinical specialties, thus advancing translational science and precision medicine.

PLUTO was specifically designed to enable the development and validation of perioperative prediction models for risk stratification and early diagnosis of postoperative complications. PLUTO will also provide a solid basis for the critical evaluation of novel diagnostic and/or prognostic biomarkers. The use of robust definitions in PLUTO facilitates cooperation with other studies collecting perioperative outcomes, in particular the BIG-PROMISE biorepository of two partner hospitals in the Netherlands (ClinicalTrials.gov Identifier: NCT05199025), which enrolls patients undergoing major surgery and collects blood specimens are collected at five prespecified time points. Outcome definitions and study procedures of the PLUTO and BIG-PROMISE cohorts are carefully coordinated.

Importantly, the perioperative period represents a standardized model of systemic inflammatory stress, with exact timing of a known surgical insult. This setting therefore also provides unique opportunities to study the etiology of various postoperative conditions. As complications develop while patients are under active surveillance, physiological responses can be studied precisely at (or even before) the onset of clinical symptoms. In addition, the comprehensive collection of symptoms and signs, biomarkers, comorbidities, and outcomes in PLUTO enables extensive covariate selection as well as competing event adjustment in statistical models used for causal inference. Furthermore, other designs such as case-control designs or pre-post comparisons can be used.

PLUTO will also serve as a logistical framework for implementation of intervention studies, including registry-based randomized clinical trials (RRCTs). Such trials are commonly considered to be highly pragmatic and offer important benefits, including the ability to enroll large numbers of patients in relatively short periods and assess comparative effectiveness of treatments in a real-world setting.[14, 58] Furthermore, they are relatively inexpensive compared to conventional RCTs.[14]

A potential limitation can be that the PLUTO cohort is a strictly observational cohort and thus reliant on diagnostic workup procedures as performed during routine clinical care. In addition, long-term follow-up in PLUTO is currently performed through self-report surveys only. This makes it impossible to assess certain endpoints, such as (recovery of) handgrip

strength and pulmonary function, or perform more elaborate diagnostic tests, for instance focused on the prevalence of late neuropathic pain. However, we plan to implement in-person follow-up visits for specific subgroups in the future.

Collaboration

All data and biomaterials collected in PLUTO will – in principle – be made available for future studies that fit within the scope of the project's scientific aims and informed consent provided by participants. When interested in exploring the PLUTO biorepository, the study team can be contacted via PLUTO@umcutrecht.nl. The latest version of the biobank protocol and a detailed data dictionary is also available upon request. Please note that we may seek methodological, statistical, ethical, or legal advice when evaluating your study proposal. Also, approval from the UMCU Biobank Research Ethics Committee will need to be obtained. In case data and specimens are shared with external parties, adequate pseudonymisation of subjects will be enforced and Data and/or Material Transfer Agreements with UMCU may apply.

Conclusion

In conclusion, the PLUTO cohort entails patients undergoing elective intermediate- to high-risk surgery in whom both comprehensive data/sample collection and rigorous outcome adjudication takes place throughout the perioperative period. The resulting biorepository thus supports the development of prediction models aimed at perioperative risk stratification and early diagnosis of postoperative complications, as well as etiological models based on robust methodologies for causal inference. Furthermore, PLUTO will create a local infrastructure for intervention research. Experiences in our center during the two-year initiation phase of this project indicate that PLUTO will be feasible and sustainable for the foreseeable future.

Contributorship statement

OLC, MJMB, AJCS and WJMS conceived the idea for the PLUTO biobank, NM and OLC drafted the study protocol, which was critically reviewed by all authors. The manuscript was drafted by NM and critically revised and approved by DV, JPR, WMUG, JH, GJB, MRV, RB, RPZ, HCV, JLGHM, LMV, JBR, MRZ, JT,, JAJK, IEH, PN, TR, MM, AMGAS, LPGD, JARW, MR, WJMS, MJMB, AJCS and OLC before submission.

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Competing interests

None declared.

Data sharing statement

Not applicable.

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Supplementary file 1 – Included procedures

Recruitment into PLUTO is based on procedural risk alone, as we explicitly aim to enrol subjects across a wide range of patient-specific risk factors. All patients scheduled to undergo elective high-risk abdominal and vascular surgery (as defined by the Surgical Mortality Probability Model and ESA guidelines[1,2]) in our tertiary hospital are eligible for inclusion. Patients undergoing selected intermediate risk procedures (including gynaecological, orthopaedic, and head and neck surgeries) can also become eligible if the procedure is associated with a scheduled hospital length of stay ≥ 5 days.[2] 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).
Bedside visits in PLUTO take place until day 7, or until discharge, whichever comes first. 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.

General, upper gastro-intestinal, abdominal and pancreaticohepatic surgery

- Total gastrectomy
- Subtotal gastrectomy
- Transthoracic esophageal resection
    - Either thoracoscopic, open or robot-assisted and with or without gastric sleeve reconstruction.
- Transhiatial esophageal resection.
    - Either laparoscopic, open or robot-assisted and with or without gastric sleeve reconstruction.
- Hemihepatectomy
- Robot-assisted hemihepatectomy
- Exploration Klatskin tumor
- Partial liver resection
- Robot-assistend partial liver resection
- Whipple resection
- Robot Whipple resection
- Robot distal pancreatectomy (with or without spleen)
- Total pancreatectomy
- Proctocolectomy (open)
- Fundoplication (open)
- Duodenal resection (open)
- Ileocoecal resection (open)
- Sigmoid resection (open)
- Hemicolectomy, left-sided (open)

- Hemicolectomy, right-sided (open)
- Subtotal colectomy (open)
- Entero-enterostomy (open)
- Duodenal ulcus perforation repair
- Appendectomy (open)
- Rectosigmoid resection (open)
- Choledocho-duodenostomy (open)
- Choledocho-jejunostomie (Roux-Y)
- Cholecystectomy (open)
- Correction cicatrical hernia (Open, Ramirez)
- HIPEC/cytoreduction
- Adrenalectomy (open)

Gynaecological surgery

- Radical abdominal hysterectomy (open)
- Primary hysterectomy + bilateral salpingectomy
- Debulking stage III + IV (open)
- Debulking stage II (open)

Head and Neck surgery

- Commando resection
- Laryngopharyngectomy, total laryngectomy
- Tumorresection in head and neck area including a modified bilateral radicular neck dissection

Orthopedic surgery

- Spondylodesis ≥ 4 segments (thoracic)

Vascular surgery

- Abdominal aortic repair (open)
- Nefrectomy

Pulmonary surgery

- Bilobectomy (open procedure)
- Pneumectomy (open procedure)

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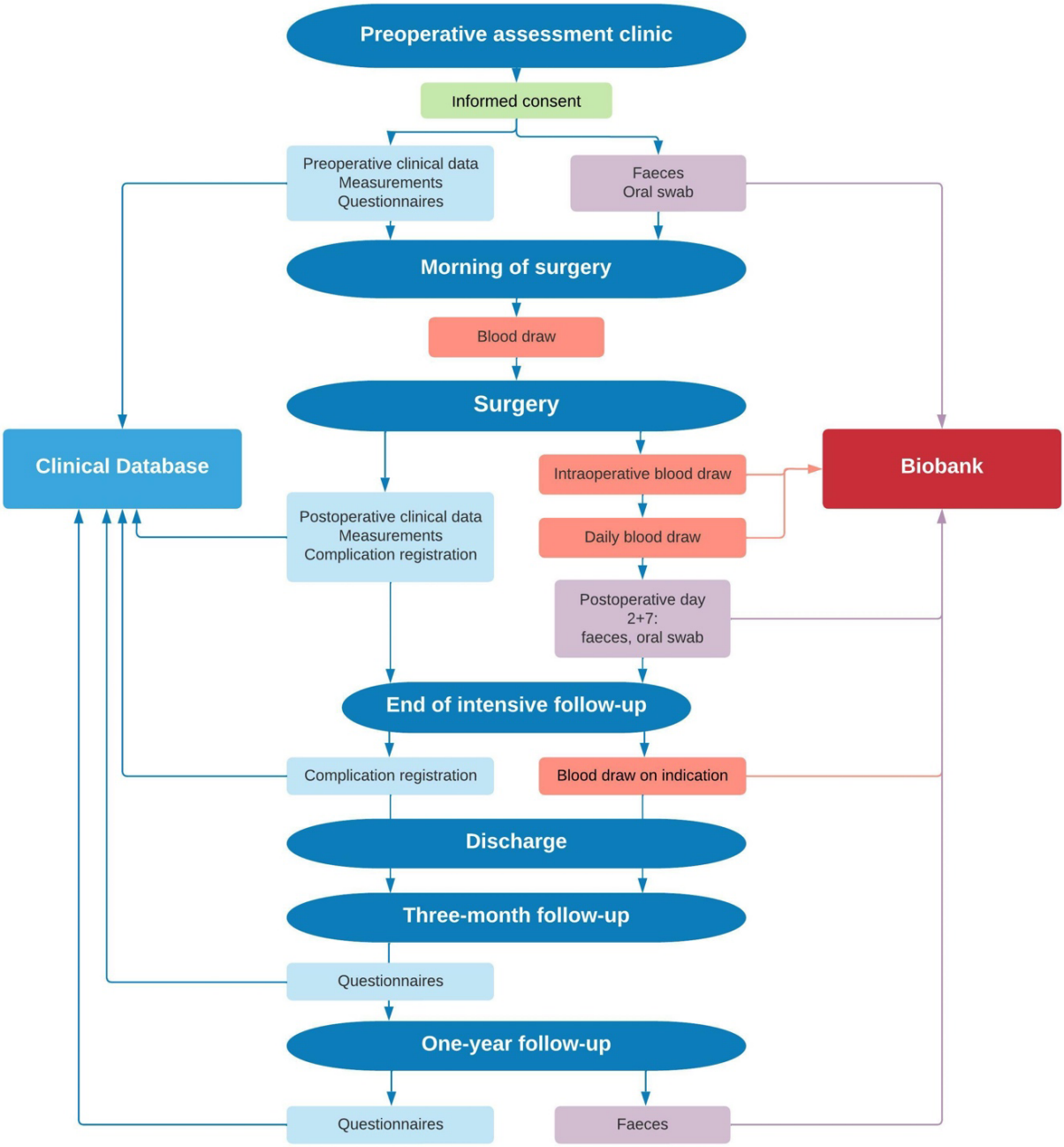
Supplementary file 2 – PLUTO flowchart



Supplementary file 2 – Flowchart of the PLUTO cohort.
Patients are included at the preoperative assessment clinic. Intensive follow-up lasts 7 days or until discharge and includes daily visits by PLUTO study personnel who perform additional bedside measurements. Measurements at the preoperative assessment clinic include hand grip strength, capillary refill time, handheld spirometry and screening for neuropathic pain using the Douleur Neuropathique 4 questionnaire and examination (DN4). These measurements are repeated daily in the 7-day intensive follow-up period, expect for spirometry which is performed on day 7 (or the day closest to discharge) only. In addition, one-channel EEG (DeltaScan) measurements are performed daily in the intensive follow-up period. Blood draws consist of 6mL EDTA plasma, 4.5 mL citrate plasma and 3.5 mL serum. Complications registered include infectious complications, postoperative pulmonary complications, major adverse cardiac events, acute kidney injury, delirium and/or acute encephalopathy and (neuropathic) pain. Questionnaires include the EQ-5D, WHODAS2.0-12, Barthel index, I-ADL, HADS (Hospital Anxiety and Depression Scale) and CFQ (Cognitive Failure Questionnaire) and DN4 at baseline and one-year follow-up, with addition of the IES-R (Impact of Event Scale, revised) at one-year follow-up. At three-month follow-up the EQ-5D, WHODAS2.0-12 and DN4 are collected.

Supplementary file 3 – List of included comorbidities and medication registration

Comorbidities

Severe coronary disease	Severe cardiovascular insufficiency. Angina or dyspnea in rest or minimal exercise (NYHA IV), or based on severe valvular disease.
Chronic ulcera/cellulitis	Decubitus, chronic venous insufficiency, chronic ulcera (all skin defects or open wounds existing > 1 month).
Asplenia	Congenital, acquired or functional asplenia.
Depression / bipolar disorder	Chronic (>1 month pre-admission) use of antidepressants or documented episode of depression in the patients' history up to 5 years before admission.
Myocardial infarction	Myocardial infarction > 1 week before admission; must be diagnosed based on ECG-abnormalities and/or enzyme abnormalities.
Heart failure	Documented chronic NYHA II-IV heart failure or patients with ejection fraction below 45% (documented on echocardiography < 2 years prior to admission) or orthopnea (for which chronic prescription of diuretic medication).
Peripheral vascular disease	Patients with intermittent claudication, patients treated with PTA/bypass surgery because of arterial insufficiency or gangrene and patients with a thoracic or abdominal aneurysms of more than 6 cm or dissection, unless atherosclerosis is not the main problem.
Hypertension	Chronic (>1 month) known hypertension and/or patients using antihypertensive medication.
Severe pulmonary disease	Chronic restrictive, obstructive or vascular pulmonary disease resulting in severe functional limitations.
COPD	Use of bronchodilators and/or corticosteroids because of chronic obstructive pulmonary disease (> 6 months).
Chronic O_2 therapy	Continuous or intermittent oxygen use in extramural setting
Chronic home mechanical ventilation	All forms of chronic mechanical ventilation in an extramural setting (both intermittent CPAP and continuous tracheal ventilation).
Cerebrovascular disease	Transient ischemic attack, cerebrovascular accident or subarachnoid hemorrhage.
Hemiplegia	Irreversible paresis of arm and leg with severe handicap or decreased mobility caused by a cerebrovascular accident.
Dementia	Dementia diagnosed by geriatrician or neurologist prior to admission.
Renal insufficiency	Increased serum creatinine > 177 µmol/L and documented as chronic renal failure/insufficiency prior to admission.

Dialysis dependent	Chronic dialysis patient, either hemodialysis or peritoneal dialysis for more than 1 month prior to admission.
Liver cirrhosis	Portal hypertension with positive liver biopsy and/or episode of upper gastro-intestinal bleeding caused by portal hypertension and/or episode of hepatic encephalopathy / coma due to liver failure.
Non-metastasized tumor	Neoplasm without metastases confirmed by pathology and/or clinically evident prior to admission. Hematological malignancies do not classify into this definition.
Metastasized tumor	Neoplasm with metastases (stage IV) confirmed by pathology and/or clinically evident prior to admission.
Hematological malignancy	Diagnosis of lymphoma, leukemia, or multiple myeloma (M Kahler) prior to admission.
Connective tissue disease / rheumatological disease	Diagnosis of rheumatological disease (SLE, MCTD, polymyalgia, rheumatoid artritis and polymyositis, vasculitis such as M. Wegener for example, diagnosed by internal specialist or rheumatologist.
Dyspepsia and/or ulcus disease	Treatment for chronic gastric ulcer diagnosed in the previous 5 years prior to admission.
Immunodeficiency	Use of immunosuppressants at the time of admission, and/or chemo/radiotherapy in the year prior to admission, and/or documented humoral or cellular deficiency.
HIV-infection	Documented HIV-seropositivity prior to admission or treatment with antiretroviral medication (with or without detectable viral load, with or without AIDS).
AIDS	HIV infection with CD4 < 200 and/or clinical complications.
Diabetes	Use of insulin and/or oral antidiabetics in the period prior to admission.
Diabetic end-organ damage	Diabetes mellitus and end-organ damage prior to admission. A clear link to diabetes does not have to be proven.
Thyroid or other endocrine disease	Hypothyroidism, hyperthyroidism and/or other endocrine disease.
Nursing home	Patient lives in a home where permanent care and support of activities of daily living is provided.
Alcohol- or drugs addiction	Suspicion of negative influence on daily functioning in patients with recent (<1 year) alcohol or drugs misuse that is evident from documentation or use of more than 4 glasses of alcohol a day or use of drugs apparent from patient history.
Current alcoholabusus	Current use of more than 3 glasses of alcohol a day, document in medical history but no direct negative consequences for daily functioning.
Current smoker	Current smoker documented in medical history.

Medication use

We register the following medication used at home:

- Beta blockers
- Other anti-arithmics
- Diuretics
- Calcium antagonists
- ACE inhibitors, angiotensin receptor blockers
- Statins
- Other lipid lowering drugs
- Thrombocyte aggregation inhibitors
- Anticoagulants
- NSAIDs / COX2 inhibitors
- Proton pump inhibitors, H2 antagonists
- Corticosteroids
- Other immunosuppressants
- Bronchodilators
- Cytostatics
- Oral antidiabetics
- Insulin
- Antirheumatic medication
- Benzodiazepines
- Anti-epileptics
- Antipsychotics
- Antiparkinson medication
- Migraine medication
- Antimicrobial medication
- Opioids
- No medication use (for validation)