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# 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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3 58 **Abstract**

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5 59 **Purpose:** Although elective surgery is generally safe, some procedures remain associated with  
6  
7 60 an increased risk of complications. Improved preoperative risk stratification and earlier  
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9 61 recognition of these complications may ameliorate postoperative recovery and improve long-  
10  
11 62 term outcomes. The perioperative longitudinal study of complications and long-term outcomes  
12  
13 63 (PLUTO) cohort aims to establish a comprehensive biorepository that will facilitate research in  
14  
15 64 this field. In this profile paper, we will discuss its design rationale and opportunities for future  
16  
17 65 studies.

18  
19 66 **Participants:** Patients undergoing elective intermediate to high-risk non-cardiac surgery are  
20  
21 67 eligible for enrolment. For the first 7 postoperative days, participants are subjected to daily  
22  
23 68 bedside visits by dedicated observers, who adjudicate clinical events and perform non-invasive  
24  
25 69 physiological measurements (including handheld spirometry and single-channel EEG). Blood  
26  
27 70 samples as well as microbiome specimens are collected at preselected time points. Primary  
28  
29 71 study outcomes are the postoperative occurrence of nosocomial infections, major adverse  
30  
31 72 cardiac events, pulmonary complications, acute kidney injury, and delirium/acute  
32  
33 73 encephalopathy. Secondary outcomes include mortality and quality of life, as well as the long-  
34  
35 74 term occurrence of psychopathology, cognitive dysfunction, and chronic pain.

36  
37 75 **Findings to date:** Enrolment of the first participant occurred early 2020. During the inception  
38  
39 76 phase of the project (first 2 years), 431 patients were eligible of whom 297 patients consented  
40  
41 77 to participate (69%). Observed event rate was 42% overall, with the most frequent complication  
42  
43 78 being infection.

44  
45 79 **Future plans:** The main purpose of the PLUTO biorepository is to provide a framework for  
46  
47 80 research in the field of perioperative medicine and anaesthesiology, by storing high-quality  
48  
49 81 clinical data and biomaterials for future studies. In addition, PLUTO aims to establish a  
50  
51 82 logistical platform for conducting embedded clinical trials.

52  
53 83 **Trial registration number:** NCT05331118  
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3 86 **Strengths and limitations of this study:**  
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- 5 87 - Comprehensive perioperative data- and biobank including a broad range of high-risk  
6 88 surgical patients.  
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8 89 - Prospective bedside clinical assessments during the first 7 postoperative days.  
9  
10 90 - Collection of physiological data, blood plasma and microbiome specimens at predefined  
11 91 timepoints.  
12  
13 92 - Broad clinical data capture allowing for extensive covariate selection in both aetiologic  
14 93 and prediction research.  
15  
16 94 - Robust definitions of perioperative complications and outcomes allowing for  
17 95 straightforward external validation of findings.  
18  
19 96 - Collection of long-term patient-centred outcomes, including cognitive and psychosocial  
20 97 parameters.  
21  
22 98 - Logistical framework facilitating conduct of (embedded) randomized clinical trials.  
23  
24 99 - Limitations of PLUTO relate to its single-center design, strictly non-interventional  
25  
26 100 approach to data collection, and use of self-reported long term outcome measures.  
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## 102 **Introduction**

103 Worldwide, almost a million patients are scheduled to undergo elective surgery each day.<sup>1</sup>  
104 Although these procedures are generally safe, surgery is not without risk. One in six patients  
105 undergoing elective procedures in a clinical setting develop a postoperative complication.<sup>2</sup> As  
106 reported by a large international cohort study, infectious and cardiovascular complications –  
107 according to European Perioperative Clinical Outcome (EPCO) definitions – occur in 9% and  
108 4.5% of patients, respectively.<sup>2</sup> Moreover, postoperative delirium occurs in 12-23% of patients  
109 undergoing major orthopaedic, vascular or gastro-intestinal surgery.<sup>3,4</sup> These complications  
110 have been associated with adverse patient outcomes, including prolonged length of hospital  
111 stay<sup>3,4</sup>, hospital readmission<sup>3,5</sup>, persistent postsurgical pain<sup>6</sup> and increased mortality<sup>7-9</sup>. High-  
112 risk surgical procedures, defined as procedures with an associated mortality rate of 5% or more,  
113 account for 80% of all perioperative deaths.<sup>7,9</sup> Therefore, improving prediction and early  
114 diagnosis of postoperative complications may particularly be rewarding in this patient group.

115 Biobanking initiatives provide the opportunity to collect biological samples in a  
116 structured manner and cross-reference these with clinical predictors, exposures and outcomes  
117 on a large scale, thus enabling the exploration of a wide range of aetiologic, diagnostic and  
118 prognostic research questions.<sup>10</sup> Although biobanks of surgical patients are not uncommon,<sup>10-  
119 13</sup> most are organized around specific types of procedures and have a limited focus with respect  
120 to the perioperative setting.

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

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

## 135 **Cohort description**

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

151

### 152 **A. Inclusion criteria and informed consent**

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

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

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3 168 permission to perform various bedside tests during the postoperative period (listed below).  
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5 169 Separate permissions to query the Dutch municipality register for date of death, to query the  
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7 170 Dutch Bureau of statistics for cause of death, to contact general practitioners for missing  
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9 171 information, and to share data and specimens with third parties are obtained according to Dutch  
10  
11 172 law.

12 173

### 13 174 **B. Study workflow**

15  
16 175 A general overview of the PLUTO workflow is shown in Table 1 and Supplementary file 2.  
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18 176 For data- and sample collection we distinguish five consecutive time periods: (1) the outpatient  
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20 177 preoperative assessment clinic visit, (2) the day of surgery, (3) an active postoperative  
21  
22 178 observation period until postoperative day 7, (4) a reactive postoperative surveillance period  
23  
24 179 from day 7 until hospital discharge, and (5) the three- and twelve-month follow-up. In the  
25  
26 180 sections below we will further discuss these phases.

27 181

### 28 182 **C. Data collection**

#### 29 30 183 *Clinical data and bedside observations*

31  
32 184 At the outpatient preoperative assessment clinic, information is collected on relevant  
33  
34 185 comorbidities (Supplementary file 3). In addition, information on pre-existing quality of life,  
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36 186 activities of daily living, chronic pain, cognitive functioning, and presence of psychopathology  
37  
38 187 is obtained using dedicated questionnaires (discussed below).

39 188 During surgery, relevant intraoperative information – including vital parameters,  
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41 189 anaesthetic and cardiovascular medication used, ventilatory settings, intravenous fluids, and  
42  
43 190 estimated blood loss – is automatically recorded in a dedicated anaesthesia information  
44  
45 191 management system (AIMS) and subsequently linked to the PLUTO database.

46 192 For the duration of the active postoperative surveillance period (see Table 1), a member of  
47  
48 193 the PLUTO study team performs daily bedside follow-ups to collect information on vital  
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50 194 parameters (including early warning score items), pain (including a neuropathic pain  
51  
52 195 questionnaire), physical mobility, and incentive spirometry performance. The active  
53  
54 196 surveillance period ends on postoperative day 7, or at hospital discharge, whichever comes first.

55 197 For the remainder of hospital admission (i.e., the reactive postoperative surveillance  
56  
57 198 period), bedside visits will no longer be performed. However, primary and secondary outcome  
58  
59 199 events will be recorded based on a daily review of hospital electronic records (listed under  
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200 paragraph E).

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3 201 After discharge, patients are followed up for 12-months after surgery to collect additional  
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5 202 information, which is described in more detail below.

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8 204 *Physiological measurements*

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10 205 Data capture for routine vital signs (including heart rate, mean arterial pressure, respiratory rate,  
11  
12 206 and peripheral oxygen saturation) takes place once at the preoperative assessment clinic, once  
13  
14 207 per minute during surgery and three times daily during the active postoperative surveillance  
15  
16 208 period. In addition, the following additional tests and measurements are performed according  
17  
18 209 to the schedule as shown in Table 1.

- 19 210 - Capillary Refill Time (CRT) is measured by applying pressure to the nailbeds of the  
20  
21 211 index and the middle fingers of each hand for three seconds to cause blanching, and  
22  
23 212 then recording the time in seconds until perfusion returns.<sup>17</sup> Subsequently, the highest  
24  
25 213 and lowest of the four measurements are excluded and the mean of the remaining two  
26  
27 214 times is recorded. To further reduce interrater variability a 1 Hz metronome is used.<sup>18</sup>  
28  
29 215 CRT is a known predictor of mortality in septic shock patients<sup>18,19</sup> as well as severe  
30  
31 216 postoperative complications after major abdominal surgery.<sup>17</sup>
- 32 217 - Handgrip strength is assessed three times for each hand using a SAEHAN Smedley  
33  
34 218 spring dynamometer.<sup>20</sup> Subsequently, the best of these six measurements is recorded.  
35  
36 219 Muscle strength as measured by handgrip strength is a validated clinical indicator of  
37  
38 220 overall condition and nutritional status.<sup>21,22</sup> Furthermore, preoperative handgrip  
39  
40 221 strength, as well as its delayed postoperative recovery, are known predictors for the  
41  
42 222 development of complications following surgery.<sup>22-24</sup>
- 43 223 - Incentive spirometry is assessed once daily (day 1-7) conform hospital protocol using  
44  
45 224 the Triflow device®. Inhaled flow is registered using a 3-point scale (600-900-1200  
46  
47 225 ml/sec).
- 48 226 - Pulmonary function testing, including assessment of forced expiratory volume in 1  
49  
50 227 second (FEV<sub>1</sub>) and forced vital capacity (FVC), is performed upon preoperative  
51  
52 228 assessment and once during the active surveillance phase (on day 7 or the nearest day  
53  
54 229 possible), using a hand-held spirometer (Spirostik, Geratherm Respiratory, Kissingen,  
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56 230 Germany). To improve the interpretation of these measurements, concurrent  
57  
58 231 information is gathered about patient posture and mobility, pain (see below) and Triflow  
59  
60 232 performance. All raw data generated during the measurements are stored for post-hoc  
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234 analysis and quality control. Test and repeatability criteria as well as contra-indications  
described by the European Respiratory Society (ERS) and American Thoracic Society

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2  
3 235 (ATS) guidelines are used.<sup>25,26</sup> Of note, these guidelines generally consider pulmonary  
4 236 function tests contra-indicated during the first four weeks following surgery as high  
5 237 intrathoracic, intra-abdominal and intracranial pressures could potentially be  
6 238 generated.<sup>26</sup> However, we performed a systematic search of the literature (unpublished  
7 239 data), combining the synonyms for “spirometry” and “pulmonary function tests” in  
8 240 combination with synonyms for “postoperative” and “postsurgical”, yielding a total of  
9 241 4376 studies on the topic, none of which reported safety issues or complications of  
10 242 spirometry specifically related to surgery. Over 500 studies reported actual applications  
11 243 of pulmonary function testing during the early postoperative period, although most did  
12 244 not include spirometry-related complications as a prespecified study outcome.  
13 245 Moreover, we found that peak intrathoracic pressures generated during spirometry are  
14 246 lower (< 200 cmH<sub>2</sub>O) than occur during spontaneous coughing (< 400 cmH<sub>2</sub>O).<sup>26-29</sup>  
15 247 Based on this literature review, we consider postoperative hand-held spirometry to be  
16 248 safe.

17 249 - The presence of acute encephalopathy that may not (yet) manifest as clinically apparent  
18 250 delirium is measured using single-channel electroencephalography (EEG), which is  
19 251 performed using a DeltaScan mobile monitor (Prolira, Utrecht, The Netherlands),  
20 252 measuring polymorphous delta activity (0.5-4 Hz).<sup>30</sup> A disposable electrode patch is  
21 253 used to obtain a 96 seconds single-channel recording (Fp2-Pz with reference T8). To  
22 254 minimize artifacts, patients are instructed to keep their eyes closed for the entire  
23 255 duration of measurement (approximately 4 minutes). Subsequently, the DeltaScan  
24 256 Monitor software algorithm provides the DeltaScan score (1-5), with higher scores  
25 257 indicating a higher probability of delirium.<sup>31</sup> All raw EEG data are saved for post-hoc  
26 258 analysis. Previous studies by our group have demonstrated that the EEG shows  
27 259 significant differences in delta-activity between patients with and patients without  
28 260 delirium.<sup>31,32</sup> Moreover, there are indications that EEG slowing is associated with the  
29 261 severity of delirium and that this is an independent predictor for unfavorable outcomes  
30 262 following surgery.<sup>32,33</sup> In addition to the DeltaScan measurement, the 4AT and the  
31 263 Confusion Assessment Method (CAM, or CAM-ICU when the patient is admitted to  
32 264 the Intensive Care Unit (ICU)) are recorded by the research staff to assess presence of  
33 265 clinically apparent delirium. These scores were shown to have the greatest validity and  
34 266 reliability in a recent review of delirium screening methods for postoperative patients.<sup>34</sup>  
35 267 - The likelihood for presence of postoperative pain with neuropathic characteristics is  
36 268 measured using the DN4 (Douleur Neuropathique 4) questionnaire and physical

1  
2  
3 269 examination. This includes assessment of sensitivity to touch and pin prick, as well as  
4 presence of allodynia.<sup>35</sup> The examination is performed adjacent – and if possible  
5 270 bilaterally – to the surgical wound in affected dermatomes (except in patients having a  
6 271 neuraxial or plexus block). For head and neck surgery it is performed preauricular, in  
7 272 the masseter region. The DN4 is well-validated screening tool for neuropathic pain.<sup>36,37</sup>  
8 273 Furthermore, in a recent publication we have shown that some DN4 items (specifically  
9 274 presence of painful cold and itching) are predictive for chronification of postsurgical  
10 275 pain.<sup>38</sup>  
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#### 13 278 *Follow-up questionnaires*

14 279 Participants are followed over time to assess quality of life, daily functioning, cognitive  
15 280 function, and psychopathology. To this end, questionnaires are distributed to participants, once  
16 281 at the outpatient preoperative assessment clinic (baseline assessment), once at three-month  
17 282 follow-up, and once approximately one year following surgery. In case of non-response, a  
18 283 written reminder will be sent out to the patient at first, followed by a telephone call if necessary.

19 284 Survey items include the EuroQoL-5D (EQ-5D), the WHO Disability Assessment  
20 285 Schedule (WHODAS2.0-12), Barthel index, Instrumental Activities of Daily Living scale (I-  
21 286 ADL), DN4, Hospital Anxiety and Depression Scale (HADS), and the Cognitive Failure  
22 287 Questionnaire (CFQ). At 1-year follow-up, the Impact of Event Scale – Revised edition (IES-  
23 288 R) is additionally collected, whereas at 3 months the Barthel index, I-ADL, HADS and CFQ  
24 289 are omitted. To this end, PLUTO coordinates closely with other large cohort studies in the  
25 290 Netherlands to reduce the burden on participants. This includes the 3P initiative, a nationwide  
26 291 collaboration of gastro-intestinal cancer cohorts, among which the Prospective Observational  
27 292 Cohort Study of Esophageal-gastric cancer Patients (POCOP), the Dutch Pancreatic Cancer  
28 293 Project (PACAP), and the Prospective Dutch ColoRectal Cancer cohort (PLCRC).<sup>39,40</sup>

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#### 30 295 **D. Specimen collection**

31 296 All biological materials are processed and stored according to standardized operating  
32 297 procedures established within the UMCU Biobank Regulations.<sup>41</sup>

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#### 34 299 *Blood sampling*

35 300 Specimens are collected at predetermined time points during the first week (Table 1).  
36 301 Additionally, sampling will be reinitiated for 7 days if an infectious event occurs during the



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

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

309

### 310 *Microbiome sampling*

311 Oral swabs and stool samples are collected at 4 predefined timepoints (Table 1). These will be  
312 processed by next generation sequencing to identify the composition of respiratory and gut  
313 microbiota.<sup>42</sup> A baseline oral swab is collected at the preoperative assessment clinic by a  
314 member of the research team, whereas the baseline faecal sample is collected by the patient at  
315 home. Subsequently, faecal samples and oral swabs are collected on postoperative days 2 and  
316 7 (or the closest timepoint feasible), with faeces being obtained once more during 1-year follow-  
317 up. The oral swabs are transferred to 1 mL cryovials that can be directly stored in the biobank,  
318 whereas stool samples are collected in 15 mL tubes by the participants themselves and kept at  
319 room temperature for a maximum of 48 hours after production. In our central biobank facility  
320 these specimens are then transferred into five 2mL tubes for 16S rRNA sequencing and shotgun  
321 metagenomics, and two 5mL tubes which are kept as backups if a later need arises to culture  
322 specific bacteria.

323

### 324 **E. Study outcomes**

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

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

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3 334 For all events, the post hoc probability of true infection will be categorized using a four-  
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5 335 point scale (none, possible, probable, and definite infection).<sup>45</sup>  
6  
7 336 - Postoperative pulmonary complications (PPC) are defined according to the European  
8  
9 337 Perioperative Clinical Outcome (EPCO) definitions and include respiratory infection,  
10 338 respiratory failure, pleural effusion, atelectasis, pneumothorax, bronchospasm and/or  
11 339 aspiration pneumonia.<sup>16</sup> A postoperative pulmonary complication is registered if (1) the  
12 340 patient has a saturation below 90% on room air or (2) the patients oxygen consumption  
13 341 is exceeding 5L/min or (3) the patient adheres to the EPCO definition of respiratory  
14 342 failure.<sup>16</sup> In case of PPC a record is made of the duration of the episode, its associated  
15 343 clinical signs and symptoms, radiology findings, instituted therapies and the final  
16 344 diagnosis.  
17 345 - Major Adverse Cardiac Events (MACE) are defined according to the Standardized  
18 346 Endpoints in Perioperative medicine (StEP) criteria and include myocardial infarction,  
19 347 cardiac arrest, and cardiac death.<sup>16,47</sup> When this definition is met, extra items (some part  
20 348 of the EPCO definition) for MACE (i.e., clinical signs and symptoms and diagnostic  
21 349 modalities used, radiological and laboratory findings and the addition of the following  
22 350 EPCO diagnoses: arrhythmias other than atrial fibrillation, congestive heart failure, and  
23 351 angina) are also included in the registration. Therefore, cardiovascular complications  
24 352 included in both these consensus definitions can be reconstructed from the PLUTO  
25 353 database and easily be compared to other perioperative outcome studies.<sup>16,47</sup>  
26 354 Additionally, for every patient of 60 years and older having  $\geq 1$  risk factors as included  
27 355 in the revised cardiac risk index, daily troponin-I is obtained every morning on the first  
28 356 three postoperative days.  
29 357 - Acute Kidney Injury (AKI) is defined according to the Kidney Disease Improving  
30 358 Global Outcomes (KDIGO) criteria with creatinine criteria only as described by the  
31 359 renal StEP criteria.<sup>48,49</sup> The chart of the patients is assessed daily for creatinine/kidney  
32 360 function.  
33 361 - Acute encephalopathy and delirium are defined as a DeltaScan score  $\geq 3$  and delirium  
34 362 as either a positive CAM(-ICU) and/or  $\geq 4$  points on the AT4.<sup>30</sup>  
35 363 - Pain is registered as acute pain via daily scores on the Numeric Rating Scale (NRS),  
36 364 ranging from 0 to 10 and as pain with neuropathic characteristics as indicated by the  
37 365 DN4.  
38 366 - Long-term quality of life (one-year following surgery) is measured by the EQ-5D and  
39 367 functional outcome measures using the WHODAS2.0-12-question version.<sup>50</sup>



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3 368 - Long-term psychopathology is defined as symptoms of depression, anxiety and/or post-  
4 369 traumatic stress syndrome (PTSS). Symptoms of depression are defined by a score  $\geq 8$   
5 370 on the HADS-D, and symptoms of anxiety as a score  $\geq 8$  on the HADS-A.<sup>51</sup> Symptoms  
6 371 of PTSS are assumed to be present in case of a mean IES-R score  $\geq 1.6$ .<sup>52</sup>  
7  
8 372 - Cognitive dysfunction is assessed by the Cognitive Failure Questionnaire which will be  
9 373 analysed as difference in median scores.<sup>53</sup>  
10  
11 374 - Mortality is registered as in-hospital mortality, 30-day mortality, one-year mortality and  
12 375 days alive outside of the hospital in the first 30 days following surgery.<sup>50,54</sup>

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17 376 Severity of all outcomes that occur in hospital (i.e., infectious complications, PPC, MACE, AKI  
18 377 and delirium) is registered according to the Clavien-Dindo classification.<sup>55</sup>  
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#### 22 23 379 **F. Data management**

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25 380 All bedside observations are entered into an electronic data capture system (Castor®, Ciwit  
26 381 B.V., Amsterdam, the Netherlands) and periodically paired with batchwise data extractions  
27 382 from the electronic hospital information system (HiX, Chipsoft, Amsterdam, the Netherlands).  
28 383 Additionally, pulmonary flow-volume curves and raw EEG data are saved to separate databases  
29 384 for post-hoc quality control. All patient-level information is pseudonymized before storage,  
30 385 with the key being accessible only to approved PLUTO research personnel.  
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#### 37 387 **Findings to date**

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39 388 During a project pilot phase which extended from February 2020 to February 2022, 431 eligible  
40 389 subjects were approached for study participation, of whom 297 (69%) provided written  
41 390 informed consent and were successfully enrolled despite several restrictions being in place due  
42 391 to the COVID-19 pandemic. Observed event rate was 42% overall, with the most frequent  
43 392 complication being infectious complications. Based on the observed inclusion rate during the  
44 393 pilot phase and the number of surgical procedures known to be eligible in our hospital each  
45 394 year, we anticipate enrolling 400-450 patients into PLUTO annually.  
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#### 52 396 **Strengths and limitations**

53 397 Biorepositories are situated at the intersection of two broader areas: big data research and the  
54 398 datafication of health.<sup>56</sup> They facilitate explorative large-scale discovery as well as provide for  
55 399 focused hypothesis testing in well-characterized (sub)groups of patients.<sup>57</sup> A particular strength  
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3 400 of the PLUTO biorepository is that it drives cooperation between various clinical and  
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5 401 preclinical specialties, thus advancing translational science and precision medicine.

6 402 PLUTO was specifically designed to enable the development and validation of  
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8 403 perioperative prediction models for risk stratification and early diagnosis of postoperative  
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10 404 complications. PLUTO will also provide a solid basis for the critical evaluation of novel  
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12 405 diagnostic and/or prognostic biomarkers. The use of robust definitions in PLUTO facilitates  
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14 406 cooperation with other studies collecting perioperative outcomes, in particular the BIG-  
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16 407 PROMISE biorepository (ClinicalTrials.gov Identifier: NCT05199025). All patients  
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18 408 undergoing high-risk surgery in two large peripheral hospitals in the Netherlands are eligible  
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20 409 and blood specimens are collected at five prespecified time points: the day before surgery, at  
21  
22 410 the end of surgery and the first 3 postoperative days. Outcome definitions and study procedures  
23  
24 411 of the PLUTO and BIG-PROMISE cohorts are carefully coordinated.

25 412 Importantly, the perioperative period represents a standardized model of systemic  
26  
27 413 inflammatory stress, with exact timing of a known surgical insult. This setting therefore also  
28  
29 414 provides unique opportunities to study the etiology of various postoperative conditions. As  
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31 415 complications develop while patients are under active surveillance, physiological responses can  
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33 416 be studied precisely at (or even before) the onset of clinical symptoms. In addition, the  
34  
35 417 comprehensive collection of symptoms and signs, biomarkers, comorbidities, and outcomes in  
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37 418 PLUTO enables extensive covariate selection as well as competing event adjustment in  
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39 419 statistical models used for causal inference. Furthermore, other designs such as case-control  
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41 420 designs or pre-post comparisons can be used.

42 421 PLUTO will also serve as a logistical framework for implementation of intervention  
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44 422 studies, including registry-based randomized clinical trials (RRCTs). Such trials are commonly  
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46 423 considered to be highly pragmatic and offer important benefits, including the ability to enroll  
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48 424 large numbers of patients in relatively short periods and assess comparative effectiveness of  
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50 425 treatments in a real-world setting.<sup>14,58</sup> Furthermore, they are relatively inexpensive compared  
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52 426 to conventional RCTs.<sup>14</sup>

53 427 A potential limitation can be that the PLUTO cohort is a strictly observational cohort  
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55 428 and thus reliant on diagnostic workup procedures as performed during routine clinical care. In  
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57 429 addition, long-term follow-up in PLUTO is currently performed through self-report surveys  
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59 430 only. This makes it impossible to assess certain endpoints, such as (recovery of) handgrip  
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431 strength and pulmonary function, or perform more elaborate diagnostic tests, for instance  
432 focused on the prevalence of late neuropathic pain. However, we plan to implement in-person  
433 follow-up visits for specific subgroups in the future.

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3 4344  
5 4356 436 **Collaboration**

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8 437 All data and biomaterials collected in PLUTO will – in principle – be made available for future  
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10 438 studies that fit within the scope of the project’s scientific aims and informed consent provided  
11  
12 439 by participants. When interested in exploring the PLUTO biorepository, the study team can be  
13  
14 440 contacted via [PLUTO@umcutrecht.nl](mailto:PLUTO@umcutrecht.nl). The latest version of the biobank protocol and a detailed  
15  
16 441 data dictionary is also available upon request. Please note that we may seek methodological,  
17  
18 442 statistical, ethical, or legal advice when evaluating your study proposal. Also, approval from  
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20 443 the UMCU Biobank Research Ethics Committee will need to be obtained. In case data and  
21  
22 444 specimens are shared with external parties, adequate pseudonymisation of subjects will be  
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24 445 enforced and Data and/or Material Transfer Agreements with UMCU may apply.

25 446

26 447 **Conclusion**

27 448 In conclusion, the PLUTO cohort entails patients undergoing elective intermediate- to high-risk  
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29 449 surgery in whom both comprehensive data/sample collection and rigorous outcome  
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31 450 adjudication takes place throughout the perioperative period. The resulting biorepository thus  
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33 451 supports the development of prediction models aimed at perioperative risk stratification and  
34  
35 452 early diagnosis of postoperative complications, as well as etiological models based on robust  
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37 453 methodologies for causal inference. Furthermore, PLUTO will create a local infrastructure for  
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39 454 intervention research. Experiences in our center during the two-year initiation phase of this  
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41 455 project indicate that PLUTO will be feasible and sustainable for the foreseeable future. \

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3 458 **Contributorship statement**

4  
5 459 OLC, MJMB, AJCS and WJMS conceived the idea for the PLUTO biobank, NM and OLC  
6  
7 460 drafted the study protocol, which was critically reviewed by all authors. The manuscript was  
8  
9 461 drafted by NM and critically revised and approved by all authors before submission.

10 462

11  
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14  
15 465 public, commercial or not-for-profit sectors.

16  
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18  
19 467 **Competing interests**

20 468 None declared.

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24 470 **Public and patient involvement**

25 471 No patient involved  
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**Table 1 – PLUTO Workflow**

	<u>Baseline assessment</u>		<u>Surgery</u>	<u>Postoperative period</u>							<u>Reactive surveillance</u>	<u>Three-month follow-up</u>	<u>One-year follow-up</u>
	<u>Preoperative assessment</u>	<u>Morning of surgery</u>		<u>Active surveillance</u>									
				<u>POD1</u>	<u>POD2</u>	<u>POD3</u>	<u>POD4</u>	<u>POD5</u>	<u>POD6</u>	<u>POD7</u>			
<i>Informed consent</i>	X												
<i>Preoperative visit*</i>	X												
<i>Questionnaires**</i>	X											X	X
<i>Postoperative visit***</i>				X	X	X	X	X	X	X			
<i>Handgrip strength</i>	X			X	X	X	X	X	X	X			
<i>Spirometry****</i>	X									X			
<i>DeltaScan EEG</i>				X	X	X	X	X	X	X			
<i>Delirium assessment</i>				X	X	X	X	X	X	X			
<i>Pain</i>	X			X	X	X	X	X	X	X		X	X
<i>Blood samples</i>													
- EDTA plasma		X	X	X	X	X	X	X	X	X	X <sup>a</sup>		
- Citrate plasma		X	X	X	X	X	X	X	X	X	X <sup>a</sup>		
- Serum		X	X	X	X	X	X	X	X	X	X <sup>a</sup>		
<i>Microbiome samples</i>													
- Oral swabs	X					X				X			
- Faeces	X					X				X			X
<i>Radiology</i>	<i>As clinically indicated, available from the electronic health records</i>												
<i>Cultures</i>	<i>As clinically indicated, available from the electronic health records</i>												
<i>Standardized complication registration*****</i>				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. <sup>a</sup>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.
- Transhiatal 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-assisted partial liver resection
- Whipple resection
- Robot Whipple resection
- Robot distal pancreatectomy (with or without spleen)
- Total pancreatectomy
- Proctocolectomy (open)
- Fundoplication (open)
- Duodenal resection (open)
- Ileocolic resection (open)
- Sigmoid resection (open)
- Hemicolectomy, left-sided (open)
- Hemicolectomy, right-sided (open)
- Subtotal colectomy (open)
- Entero-enterostomy (open)
- Duodenal ulcer perforation repair
- Appendectomy (open)
- Rectosigmoid resection (open)
- Choledocho-duodenostomy (open)
- Choledocho-jejunostomy (Roux-Y)
- Cholecystectomy (open)
- Correction cicatricial 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
- Tumoresection in head and neck area including a modified bilateral radical neck dissection

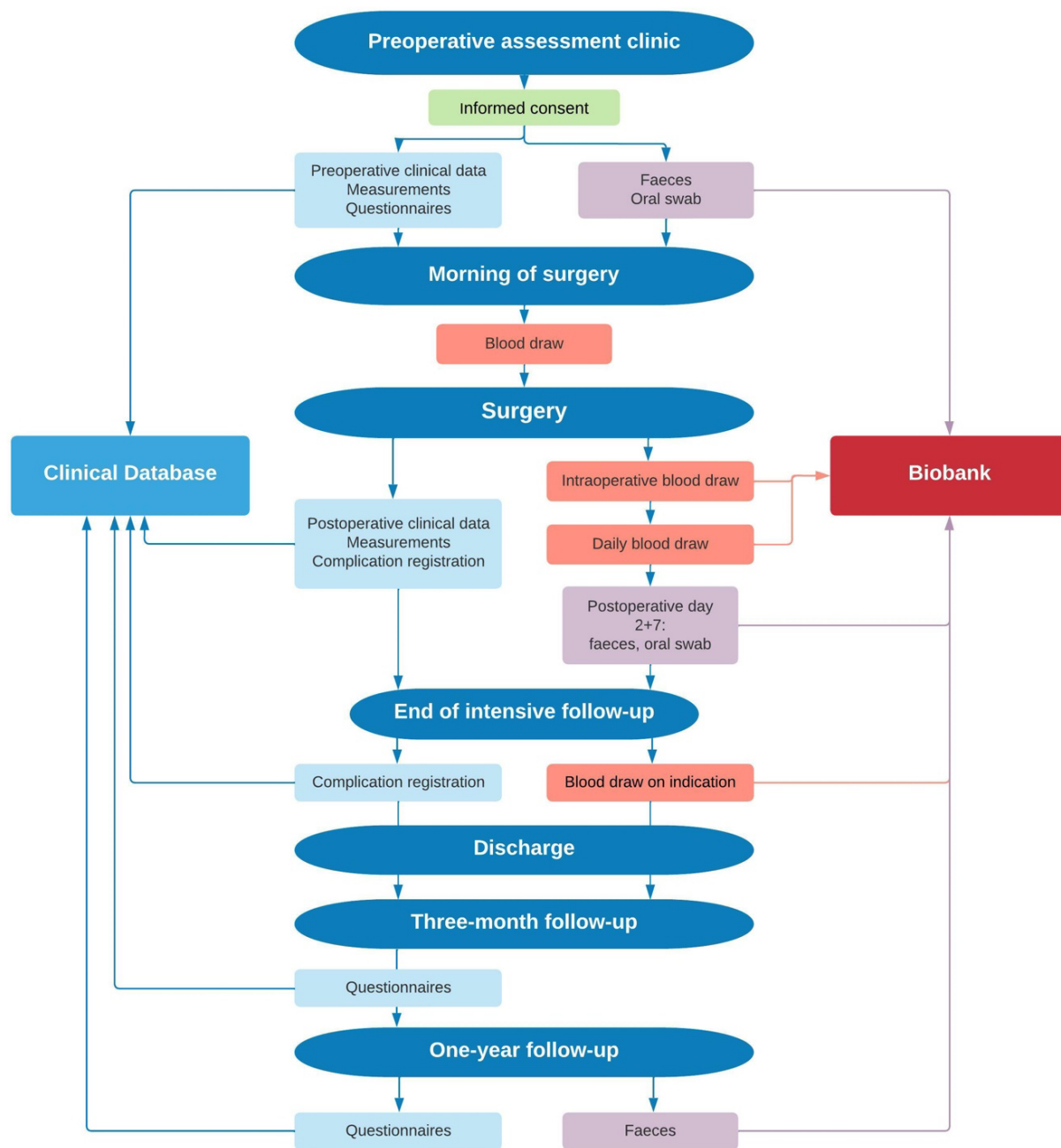
## Orthopedic surgery

- Spondylodesis  $\geq$  4 segments (thoracic)

## Vascular surgery

- Abdominal aortic repair (open)
- Nephrectomy

## 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, except 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 <sub>2</sub> 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 arthritis and polymyositis, vasculitis such as M. Wegener for example, diagnosed by internal specialist or rheumatologist.
Dyspepsia and/or ulcer 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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3 58 **Abstract**

4 59 **Purpose:** Although elective surgery is generally safe, some procedures remain associated with  
5 an increased risk of complications. Improved preoperative risk stratification and earlier  
6 60 recognition of these complications may ameliorate postoperative recovery and improve long-  
7 61 term outcomes. The perioperative longitudinal study of complications and long-term outcomes  
8 62 (PLUTO) cohort aims to establish a comprehensive biorepository that will facilitate research in  
9 63 this field. In this profile paper, we will discuss its design rationale and opportunities for future  
10 64 studies.  
11 65

12 66 **Participants:** Patients undergoing elective intermediate to high-risk non-cardiac surgery are  
13 67 eligible for enrolment. For the first 7 postoperative days, participants are subjected to daily  
14 68 bedside visits by dedicated observers, who adjudicate clinical events and perform non-invasive  
15 69 physiological measurements (including handheld spirometry and single-channel EEG). Blood  
16 70 samples as well as microbiome specimens are collected at preselected time points. Primary  
17 71 study outcomes are the postoperative occurrence of nosocomial infections, major adverse  
18 72 cardiac events, pulmonary complications, acute kidney injury, and delirium/acute  
19 73 encephalopathy. Secondary outcomes include mortality and quality of life, as well as the long-  
20 74 term occurrence of psychopathology, cognitive dysfunction, and chronic pain.

21 75 **Findings to date:** Enrolment of the first participant occurred early 2020. During the inception  
22 76 phase of the project (first 2 years), 431 patients were eligible of whom 297 patients consented  
23 77 to participate (69%). Observed event rate was 42% overall, with the most frequent complication  
24 78 being infection.

25 79 **Future plans:** The main purpose of the PLUTO biorepository is to provide a framework for  
26 80 research in the field of perioperative medicine and anaesthesiology, by storing high-quality  
27 81 clinical data and biomaterials for future studies. In addition, PLUTO aims to establish a  
28 82 logistical platform for conducting embedded clinical trials.

29 83 **Trial registration number:** NCT05331118  
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3 86 **Strengths and limitations of this study:**  
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- 5 87 - Comprehensive perioperative data- and biobank including a broad range of high-risk  
6 88 surgical patients in whom prospective bedside clinical assessments take place during  
7 89 the first 7 postoperative days, including collection of physiological data, blood plasma  
8 90 and microbiome specimens at predefined timepoints.  
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11 91 - Broad clinical data capture allowing for extensive covariate selection in both aetiologic  
12 92 and prediction research and the use of robust definitions of perioperative complications  
13 93 and outcomes allowing for straightforward external validation of findings.  
14  
15 94 - Collection of long-term patient-centred outcomes, including cognitive and psychosocial  
16 95 parameters.  
17  
18 96 - Logistical framework facilitating conduct of (embedded) randomized clinical trials.  
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20 97 - Limitations of PLUTO relate to its single-center design, strictly non-interventional  
21 98 approach to data collection, and use of self-reported long term outcome measures.  
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## 100 **Introduction**

101 Worldwide, almost a million patients are scheduled to undergo elective surgery each day.[1]  
102 Although these procedures are generally safe, surgery is not without risk. One in six patients  
103 undergoing elective procedures in a clinical setting develop a postoperative complication.[2]  
104 As reported by a large international cohort study, infectious and cardiovascular complications  
105 – according to European Perioperative Clinical Outcome (EPCO) definitions – occur in 9% and  
106 4.5% of patients, respectively.[2] Moreover, postoperative delirium occurs in 12-23% of  
107 patients undergoing major orthopaedic, vascular or gastro-intestinal surgery.[3, 4] These  
108 complications have been associated with adverse patient outcomes, including prolonged length  
109 of hospital stay[3, 4], hospital readmission[3, 5], persistent postsurgical pain[6] and increased  
110 mortality[7-9]. High-risk surgical procedures, defined as procedures with an associated  
111 mortality rate of 5% or more, account for 80% of all perioperative deaths[7, 9]. Therefore,  
112 improving prediction and early diagnosis of postoperative complications may particularly be  
113 rewarding in this patient group.

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

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

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

## 134 **Cohort description**

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

150

### 151 **A. Inclusion criteria and informed consent**

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

1  
2  
3 166 Written informed consent is obtained by Good Clinical Practice certified study  
4  
5 167 personnel during the patient's visit to the preoperative assessment clinic. This covers collection,  
6  
7 168 storage and use of data and biological specimens for future scientific projects, as well as  
8  
9 169 permission to perform various bedside tests during the postoperative period (listed below).  
10  
11 170 Separate permissions to query the Dutch municipality register for date of death, to query the  
12  
13 171 Dutch Bureau of statistics for cause of death, to contact general practitioners for missing  
14  
15 172 information, and to share data and specimens with third parties are obtained according to Dutch  
16  
17 173 law.

174

### 175 **B. Study workflow**

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



182 **Table 1 – PLUTO Workflow**

183

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

184

185 **Table 1 – PLUTO workflow**

186 POD = postoperative day. \*Preoperative visit includes collecting the following baseline information: demographics, comorbidities, intoxications, medication use, revised cardiac risk index and  
 187 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  
 188 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  
 189 including a capillary refill time, collecting information on mobility, physiotherapy, incentive spirometry, early warning score and numeric rating scale. <sup>a</sup>Blood samples will only be obtained after  
 190 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  
 191 once in the postoperative period, on day 7 or the day closest to discharge. \*\*\*\*\*Complications registered are infectious complications, postoperative pulmonary complications, major adverse  
 192 cardiac events, acute kidney injury, delirium and/or acute encephalopathy and (neuropathic) pain. Postoperative complications are registered using standardized, predefined criteria and  
 193 throughout the entire hospital admission by trained research staff.

194

195

### 196 **C. Data collection**

#### 197 *Clinical data and bedside observations*

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

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

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

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

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

#### 219 *Physiological measurements*

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

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

1  
2  
3 229 times is recorded. To further reduce interrater variability a 1 Hz metronome is used.[18]  
4  
5 230 CRT is a known predictor of mortality in septic shock patients[18, 19] as well as severe  
6  
7 231 postoperative complications after major abdominal surgery.[17]  
8  
9 232 - Handgrip strength is assessed three times for each hand using a SAEHAN Smedley  
10 233 spring dynamometer.[20] Subsequently, the best of these six measurements is recorded.  
11  
12 234 Muscle strength as measured by handgrip strength is a validated clinical indicator of  
13  
14 235 overall condition and nutritional status.[21, 22] Furthermore, preoperative handgrip  
15  
16 236 strength, as well as its delayed postoperative recovery, are known predictors for the  
17  
18 237 development of complications following surgery.[22-24]  
19  
20 238 - Incentive spirometry is assessed once daily (day 1-7) conform hospital protocol using  
21  
22 239 the Triflow device®. Inhaled flow is registered using a 3-point scale (600-900-1200  
23  
24 240 ml/sec).  
25  
26 241 - Pulmonary function testing, including assessment of forced expiratory volume in 1  
27  
28 242 second (FEV<sub>1</sub>) and forced vital capacity (FVC), is performed upon preoperative  
29  
30 243 assessment and once during the active surveillance phase (on day 7 or the nearest day  
31  
32 244 possible), using a hand-held spirometer (Spirostik, Geratherm Respiratory, Kissingen,  
33  
34 245 Germany). To improve the interpretation of these measurements, concurrent  
35  
36 246 information is gathered about patient posture and mobility, pain (see below) and Triflow  
37  
38 247 performance. All raw data generated during the measurements are stored for post-hoc  
39  
40 248 analysis and quality control. Test and repeatability criteria as well as contra-indications  
41  
42 249 described by the European Respiratory Society (ERS) and American Thoracic Society  
43  
44 250 (ATS) guidelines are used.[25, 26] Of note, these guidelines generally consider  
45  
46 251 pulmonary function tests contra-indicated during the first four weeks following surgery  
47  
48 252 as high intrathoracic, intra-abdominal and intracranial pressures could potentially be  
49  
50 253 generated.[26] However, we performed a systematic search of the literature  
51  
52 254 (unpublished data), combining the synonyms for “spirometry” and “pulmonary function  
53  
54 255 tests” in combination with synonyms for “postoperative” and “postsurgical”, yielding a  
55  
56 256 total of 4376 studies on the topic, none of which reported safety issues or complications  
57  
58 257 of spirometry specifically related to surgery. Over 500 studies reported actual  
59  
60 258 applications of pulmonary function testing during the early postoperative period,  
259  
260 although most did not include spirometry-related complications as a prespecified study  
261  
262 outcome. Moreover, we found that peak intrathoracic pressures generated during  
spirometry are lower (< 200 cmH<sub>2</sub>O) than occur during spontaneous coughing (< 400

1  
2  
3 262 cmH<sub>2</sub>O).[26-29] Based on this literature review, we consider postoperative hand-held  
4  
5 263 spirometry to be safe.  
6  
7 264 - The presence of acute encephalopathy that may not (yet) manifest as clinically apparent  
8  
9 265 delirium is measured using single-channel electroencephalography (EEG), which is  
10  
11 266 performed using a DeltaScan mobile monitor (Prolira, Utrecht, The Netherlands),  
12  
13 267 measuring polymorphous delta activity (0.5-4 Hz).[30] A disposable electrode patch is  
14  
15 268 used to obtain a 96 seconds single-channel recording (Fp2-Pz with reference T8). To  
16  
17 269 minimize artifacts, patients are instructed to keep their eyes closed for the entire  
18  
19 270 duration of measurement (approximately 4 minutes). Subsequently, the DeltaScan  
20  
21 271 Monitor software algorithm provides the DeltaScan score (1-5), with higher scores  
22  
23 272 indicating a higher probability of delirium.[31] All raw EEG data are saved for post-  
24  
25 273 hoc analysis. Previous studies by our group have demonstrated that the EEG shows  
26  
27 274 significant differences in delta-activity between patients with and patients without  
28  
29 275 delirium.[31, 32] Moreover, there are indications that EEG slowing is associated with  
30  
31 276 the severity of delirium and that this is an independent predictor for unfavorable  
32  
33 277 outcomes following surgery.[32, 33] In addition to the DeltaScan measurement, the  
34  
35 278 4AT and the Confusion Assessment Method (CAM, or CAM-ICU when the patient is  
36  
37 279 admitted to the Intensive Care Unit (ICU)) are recorded by the research staff to assess  
38  
39 280 presence of clinically apparent delirium. These scores were shown to have the greatest  
40  
41 281 validity and reliability in a recent review of delirium screening methods for  
42  
43 282 postoperative patients.[34]  
44  
45 283 - The likelihood for presence of postoperative pain with neuropathic characteristics is  
46  
47 284 measured using the DN4 (Douleur Neuropathique 4) questionnaire and physical  
48  
49 285 examination. This includes assessment of sensitivity to touch and pin prick, as well as  
50  
51 286 presence of allodynia.[35] The examination is performed adjacent – and if possible  
52  
53 287 bilaterally – to the surgical wound in affected dermatomes (except in patients having a  
54  
55 288 neuraxial or plexus block). For head and neck surgery it is performed preauricular, in  
56  
57 289 the masseter region. The DN4 is well-validated screening tool for neuropathic pain.[36,  
58  
59 290 37] Furthermore, in a recent publication we have shown that some DN4 items  
60  
291 (specifically presence of painful cold and itching) are predictive for chronification of  
292 postsurgical pain.[38]

1  
2  
3 2954  
5 296 *Follow-up questionnaires*

6 297 Participants are followed over time to assess quality of life, daily functioning, cognitive  
7 298 function, and psychopathology. To this end, questionnaires are distributed to participants, once  
8 299 at the outpatient preoperative assessment clinic (baseline assessment), once at three-month  
9 300 follow-up, and once approximately one year following surgery. In case of non-response, a  
10 301 written reminder will be sent out to the patient at first, followed by a telephone call if necessary.

11 302 Survey items include the EuroQoL-5D (EQ-5D), the WHO Disability Assessment  
12 303 Schedule (WHODAS2.0-12), Barthel index, Instrumental Activities of Daily Living scale (I-  
13 304 ADL), DN4, Hospital Anxiety and Depression Scale (HADS), and the Cognitive Failure  
14 305 Questionnaire (CFQ). At 1-year follow-up, the Impact of Event Scale – Revised edition (IES-  
15 306 R) is additionally collected, whereas at 3 months the Barthel index, I-ADL, HADS and CFQ  
16 307 are omitted. To this end, PLUTO coordinates closely with other large cohort studies in the  
17 308 Netherlands to reduce the burden on participants. This includes the 3P initiative, a nationwide  
18 309 collaboration of gastro-intestinal cancer cohorts, among which the Prospective Observational  
19 310 Cohort Study of Esophageal-gastric cancer Patients (POCOP), the Dutch Pancreatic Cancer  
20 311 Project (PACAP), and the Prospective Dutch ColoRectal Cancer cohort (PLCRC).[39, 40]

21 312

22 313 **D. Specimen collection**

23 314 All biological materials are processed and stored according to standardized operating  
24 315 procedures established within the UMCU Biobank Regulations.[41]

25 316

26 317 *Blood sampling*

27 318 Specimens are collected at predetermined time points during the first week (Table 1).  
28 319 Additionally, sampling will be reinitiated for 7 days if an infectious event occurs during the  
29 320 reactive postoperative surveillance period. Specimen collection is combined with routine blood  
30 321 draws whenever possible.

31 322 At each sampling time point, 6 mL EDTA plasma, 4.5 mL citrated plasma, and 3.5 mL  
32 323 serum are obtained. Collection tubes are centrifuged at 3000 rpm for 10 minutes before the  
33 324 specimens are transferred into 1 mL micronic vials (2x 900µL for EDTA and citrate, 2x 700µL  
34 325 for serum) and stored at -80°C in the central biobank facility of the UMCU. The maximum total  
35 326 timeframe for collection, processing and storage of serum and plasma samples is 4 hours.

36 327

1  
2  
3 328  
4  
5 329 *Microbiome sampling*  
6  
7 330 Oral swabs and stool samples are collected at 4 predefined timepoints (Table 1). These will be  
8  
9 331 processed by next generation sequencing to identify the composition of respiratory and gut  
10  
11 332 microbiota.[42] A baseline oral swab is collected at the preoperative assessment clinic by a  
12  
13 333 member of the research team, whereas the baseline faecal sample is collected by the patient at  
14  
15 334 home. Subsequently, faecal samples and oral swabs are collected on postoperative days 2 and  
16  
17 335 7 (or the closest timepoint feasible), with faeces being obtained once more during 1-year follow-  
18  
19 336 up. The oral swabs are transferred to 1 mL cryovials that can be directly stored in the biobank,  
20  
21 337 whereas stool samples are collected in 15 mL tubes by the participants themselves and kept at  
22  
23 338 room temperature for a maximum of 48 hours after production. In our central biobank facility  
24  
25 339 these specimens are then transferred into five 2mL tubes for 16S rRNA sequencing and shotgun  
26  
27 340 metagenomics, and two 5mL tubes which are kept as backups if a later need arises to culture  
28  
29 341 specific bacteria.

342

### 343 **E. Study outcomes**

344 Endpoints in PLUTO are recorded using a process of post-hoc adjudication, which includes a  
345  
346 chart review as well as an inventory of available diagnostic test results (i.e., chemistry,  
347  
348 microbiology, and radiology findings). All outcomes are defined according to strict criteria:

- 349 - Infectious complications are defined according to Centers for Disease Control and  
350  
351 prevention (CDC) criteria and International Sepsis Forum consensus definitions.[43,  
352  
353 44] A comprehensive list of diagnostic criteria, as well as an assessment of the  
354  
355 interobserver agreement associated with these, has previously been published by our  
356  
357 group.[45] In addition, all diagnostic criteria for infection are scored over five axes  
358  
359 (clinical signs and symptoms, radiological findings, laboratory findings and  
360  
361 microbiological findings).[46] For all events, the post hoc probability of true infection  
362  
363 will be categorized using a four-point scale (none, possible, probable, and definite  
364  
365 infection).[45] Treatment, including antibiotics and source control, is prospectively  
366  
367 registered.
- 368 - Postoperative pulmonary complications (PPC) are defined according to the European  
369  
370 Perioperative Clinical Outcome (EPCO) definitions and include respiratory infection,  
371  
372 respiratory failure, pleural effusion, atelectasis, pneumothorax, bronchospasm and/or  
373  
374 aspiration pneumonia.[16] A postoperative pulmonary complication is registered if (1)



- 1  
2  
3 361 the patient has a saturation below 90% on room air or (2) the patients oxygen  
4  
5 362 consumption is exceeding 5L/min or (3) the patient adheres to the EPCO definition of  
6  
7 363 respiratory failure.[16] In case of PPC a record is made of the duration of the episode,  
8  
9 364 its associated clinical signs and symptoms, radiology findings, instituted therapies and  
10  
11 365 the final diagnosis.
- 12 366 - Major Adverse Cardiac Events (MACE) are defined according to the Standardized  
13  
14 367 Endpoints in Perioperative medicine (StEP) criteria and include myocardial infarction,  
15  
16 368 cardiac arrest, and cardiac death.[16, 47] When this definition is met, extra items (some  
17  
18 369 part of the EPCO definition for MACE) are included in the registration, including  
19  
20 370 clinical signs and symptoms, diagnostic modalities used, radiological and laboratory  
21  
22 371 findings, instituted treatments and the presence of congestive heart failure and  
23  
24 372 arrhythmias other than atrial fibrillation. Therefore, cardiovascular complications  
25  
26 373 included in both these consensus definitions can be reconstructed from the PLUTO  
27  
28 374 database and easily be compared to other perioperative outcome studies.[16, 47]  
29  
30 375 Additionally, for every patient of 60 years and older having  $\geq 1$  risk factors as included  
31  
32 376 in the revised cardiac risk index, daily troponine-I is obtained every morning on the first  
33  
34 377 three postoperative days.
  - 35  
36 378 - Acute Kidney Injury (AKI) is defined according to the Kidney Disease Improving  
37  
38 379 Global Outcomes (KDIGO) criteria with creatinine criteria only as described by the  
39  
40 380 renal StEP criteria.[48, 49] The chart of the patients is assessed daily for  
41  
42 381 creatinine/kidney function. Use of diuretics and hemodialysis or -filtration is also  
43  
44 382 registered.
  - 45  
46 383 - Acute encephalopathy and delirium are defined as a DeltaScan score  $\geq 3$  and delirium  
47  
48 384 as either a positive CAM(-ICU) and/or  $\geq 4$  points on the 4AT.[30] Medications used to  
49  
50 385 treat delirium are extracted from the electronic health records.
  - 51  
52 386 - Acute pain is registered using daily scoring on the Numeric Rating Scale (NRS), ranging  
53  
54 387 from 0 to 10. Neuropathic characteristics are assessed by the DN4 questionnaire. Use  
55  
56 388 of pain medications is prospectively registered daily during the active surveillance  
57  
58 389 period.
  - 59  
60 390 - Long-term quality of life (one-year following surgery) is measured by the EQ-5D and  
391  
392 functional outcome measures using the WHODAS2.0-12-question version.[50]
  - 393  
- 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  $\geq 8$



- 1  
2  
3 394 on the HADS-D, and symptoms of anxiety as a score  $\geq 8$  on the HADS-A.[51]  
4  
5 395 Symptoms of PTSS are assumed to be present in case of a mean IES-R score  $\geq 1.6$ . [52]  
6  
7 396 - Cognitive dysfunction is assessed by the Cognitive Failure Questionnaire which will be  
8  
9 397 analysed as difference in median scores.[53]  
10  
11 398 - Mortality is registered as in-hospital mortality, 30-day mortality, one-year mortality and  
12 399 days alive outside of the hospital in the first 30 days following surgery.[50, 54]  
13

14 400 Severity of all outcomes that occur in hospital (i.e., infectious complications, PPC, MACE, AKI  
15 401 and delirium) is registered according to the Clavien-Dindo classification.[55] For all in-hospital  
16 402 complications the diagnostic modalities used are recorded.  
17  
18 403

19 403

#### 20 404 **F. Data management**

21 405 All bedside observations are entered into an electronic data capture system (Castor®, Ciwit  
22 406 B.V., Amsterdam, the Netherlands) and periodically paired with batchwise data extractions  
23 407 from the electronic hospital information system (HiX, Chipsoft, Amsterdam, the Netherlands).  
24 408 Additionally, pulmonary flow-volume curves and raw EEG data are saved to separate databases  
25 409 for post-hoc quality control. All patient-level information is pseudonymized before storage,  
26 410 with the key being accessible only to authorized personnel. The PLUTO cohort has no set end-  
27 411 date and data will be stored for a minimum of 15 years after termination.  
28  
29 412

30 412

#### 31 413 **G. Public and patient involvement**

32 414 During the design of this study we did not involve patient organisations.  
33 415

34 415

#### 35 416 **Findings to date**

36 417 During a project pilot phase which extended from February 2020 to February 2022, 431 eligible  
37 418 subjects were approached for study participation, of whom 297 (69%) provided written  
38 419 informed consent and were successfully enrolled despite several restrictions being in place due  
39 420 to the COVID-19 pandemic. Observed event rate was 42% overall, with the most frequent  
40 421 complication being infectious complications. Based on the observed inclusion rate during the  
41 422 pilot phase and the number of surgical procedures known to be eligible in our hospital each  
42 423 year, we anticipate enrolling 400-450 patients into PLUTO annually.  
43 424

44 424

45 425

46 426

### 427 **Strengths and limitations**

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

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

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

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

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

1  
2  
3 461 strength and pulmonary function, or perform more elaborate diagnostic tests, for instance  
4  
5 462 focused on the prevalence of late neuropathic pain. However, we plan to implement in-person  
6  
7 463 follow-up visits for specific subgroups in the future.  
8  
9 464

### 10 465 **Collaboration**

11 466 All data and biomaterials collected in PLUTO will – in principle – be made available for future  
12  
13 467 studies that fit within the scope of the project’s scientific aims and informed consent provided  
14  
15 468 by participants. When interested in exploring the PLUTO biorepository, the study team can be  
16  
17 469 contacted via [PLUTO@umcutrecht.nl](mailto:PLUTO@umcutrecht.nl). The latest version of the biobank protocol and a detailed  
18  
19 470 data dictionary is also available upon request. Please note that we may seek methodological,  
20  
21 471 statistical, ethical, or legal advice when evaluating your study proposal. Also, approval from  
22  
23 472 the UMCU Biobank Research Ethics Committee will need to be obtained. In case data and  
24  
25 473 specimens are shared with external parties, adequate pseudonymisation of subjects will be  
26  
27 474 enforced and Data and/or Material Transfer Agreements with UMCU may apply.  
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### 29 476 **Conclusion**

30 477 In conclusion, the PLUTO cohort entails patients undergoing elective intermediate- to high-  
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32 478 risk surgery in whom both comprehensive data/sample collection and rigorous outcome  
33  
34 479 adjudication takes place throughout the perioperative period. The resulting biorepository thus  
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36 480 supports the development of prediction models aimed at perioperative risk stratification and  
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38 481 early diagnosis of postoperative complications, as well as etiological models based on robust  
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40 482 methodologies for causal inference. Furthermore, PLUTO will create a local infrastructure for  
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42 483 intervention research. Experiences in our center during the two-year initiation phase of this  
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44 484 project indicate that PLUTO will be feasible and sustainable for the foreseeable future.  
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3 487 **Contributorship statement**

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5 488 OLC, MJMB, AJCS and WJMS conceived the idea for the PLUTO biobank, NM and OLC  
6  
7 489 drafted the study protocol, which was critically reviewed by all authors. The manuscript was  
8  
9 490 drafted by NM and critically revised and approved by DV, JPR, WMUG, JH, GJB, MRV, RB,  
10  
11 491 RPZ, HCV, JLGHM, LMV, JBR, MRZ, JT,, JAJK, IEH, PN, TR, MM, AMGAS, LPGD,  
12  
13 492 JARW, MR, WJMS, MJMB, AJCS and OLC before submission.

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14 493

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18  
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20  
21 497

22 498 **Competing interests**

23  
24 499 None declared.

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27 501 **Data sharing statement**

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29 502 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<sup>1,2</sup>) 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  $\geq 5$  days.<sup>2</sup> 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  $\geq 5$  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.
- Transhiatal 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)

- Hemicolecotomy, right-sided (open)
- Subtotal colectomy (open)
- Entero-enterostomy (open)
- Duodenal ulcer perforation repair
- Appendectomy (open)
- Rectosigmoid resection (open)
- Choledocho-duodenostomy (open)
- Choledocho-jejunostomie (Roux-Y)
- Cholecystectomy (open)
- Correction cicatricial 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 radical neck dissection

### Orthopedic surgery

- Spondylodesis  $\geq 4$  segments (thoracic)

### Vascular surgery

- Abdominal aortic repair (open)
- Nephrectomy

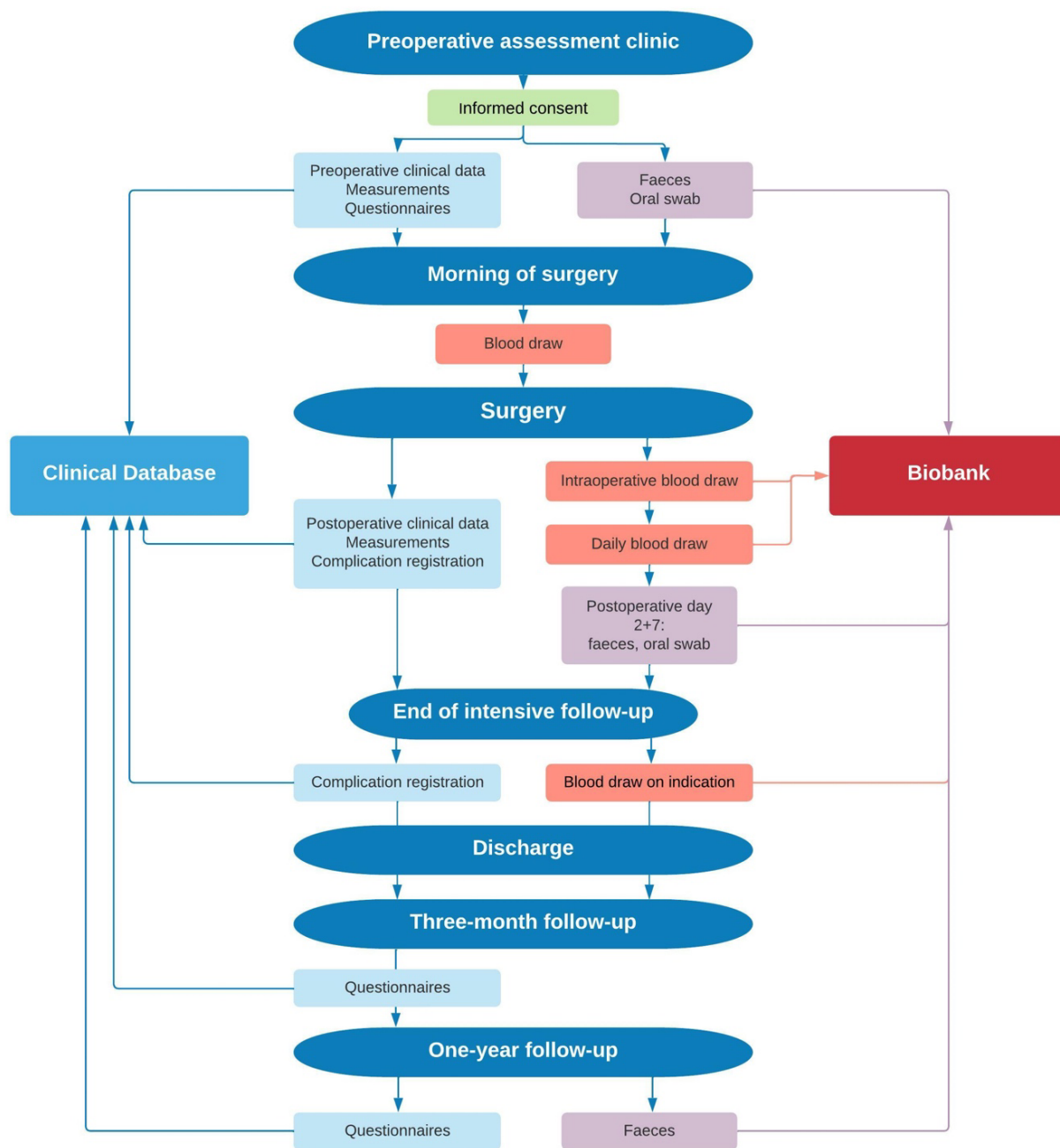
## Pulmonary surgery

- 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, except 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 <sub>2</sub> 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 arthritis and polymyositis, vasculitis such as M. Wegener for example, diagnosed by internal specialist or rheumatologist.
Dyspepsia and/or ulcer 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-arhythmics
- 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)