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Protocol of a multicenter, prospective cohort study that evaluates cost-effectiveness of two perioperative care strategies for potential obstructive sleep apnea in morbidly obese patients undergoing bariatric surgery.

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- 3 1 **PROTOCOL OF A MULTICENTER, PROSPECTIVE COHORT STUDY THAT EVALUATES COST-**
- 4
- 5 2 **EFFECTIVENESS OF TWO PERIOPERATIVE CARE STRATEGIES FOR POTENTIAL OBSTRUCTIVE**
- 6
- 7
- 8 3 **SLEEP APNEA IN MORBIDLY OBESE PATIENTS UNDERGOING BARIATRIC SURGERY.**
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4 **ABSTRACT**

5 **Introduction**

6 Despite the high prevalence of obstructive sleep apnea (OSA) in obese patients undergoing
7 bariatric surgery, OSA is undiagnosed in the majority of patients and thus untreated. While
8 untreated OSA is associated with an increased risk of per- and postoperative complications,
9 no evidence-based guidelines on perioperative care for these patients are available. The aim
10 of the POPCORN study (*Post-Operative Pulse oximetry without OSA sCreening vs.*
11 *perioperative continuous positive airway pressure (CPAP) treatment following OSA*
12 *scReeNing by polygraphy (PG)*) is to evaluate which perioperative strategy is most cost-
13 effective for obese patients undergoing bariatric surgery without a history of OSA.

14 **Methods and analysis**

15 In this multicenter observational cohort study, data from 1380 patients who will undergo
16 bariatric surgery will be collected. Patients will either receive postoperative care with pulse
17 oximetry monitoring and supplemental oxygen during the first postoperative night, or they
18 receive care that includes preoperative PG and CPAP treatment in case of moderate or
19 severe OSA. Local protocols for perioperative care in each participating hospital will
20 determine into which cohort a patient is placed. The primary outcome is cost-effectiveness,
21 which will be calculated by comparing all health care costs to the quality-adjusted-life-years
22 (QALYs, calculated using EQ-5D questionnaires). Secondary outcomes are mortality,
23 complications within 30 days after surgery, readmissions, reoperations, length of stay,
24 weight loss, generic quality of life (QOL), OSA-specific QOL, OSA symptoms and CPAP
25 adherence. Patients will receive questionnaires before surgery and 1, 3, 6, and 12 months
26 after surgery to report QALYs and other patient reported outcomes.

27 **Ethics and dissemination**

1
2
3 28 Approval from the Medical research Ethics Committees United was granted in accordance
4
5
6 29 with the Dutch law for Medical Research Involving Human Subjects Act (WMO) (reference
7
8 30 number W17.050). Results will be submitted for publication in peer-reviewed journals and
9
10 31 presented at (inter)national conferences.

32 **Trial registration number**

33 NTR6991
34
35

36 **Article summary**

37 Strengths and limitations of this study

- 38 • This study is the first prospective study to compare and analyze cost-effective
39 methods for perioperative care of obese patients with no known OSA history. Giving
40 the growing worldwide epidemic of obesity, all aspects of bariatric surgery need to
41 be assessed for costs and efficacy in order to achieve affordable and high-quality
42 health care for patients with morbid obesity.
- 43 • Results of this study will provide insight in many aspects of pre- and perioperative
44 interventions that is currently lacking, such as the impact on postoperative
45 complications, influence on QOL, change of sleepiness symptoms, and adherence
46 rates to CPAP in patients who were asymptomatic or did not experience recognized
47 symptoms.
- 48 • This study includes a large population that will be monitored to evaluate OSA care in
49 bariatric patients. For a study that evaluates a perioperative intervention, the
50 duration of follow-up of one year is relatively long.

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2
3 51 • Despite the non-randomized design, we hypothesize that both cohorts will embody
4
5 52 the average patient that is scheduled for a primary bariatric procedure due to the
6
7
8 53 ample size and few exclusion criteria for study participants. Therefore, data gathered
9
10 54 in these cohorts will probably be applicable to the general bariatric population.
11
12
13 55

15 56 INTRODUCTION

17
18 57 Obesity is a health care issue of epidemic proportions that is rapidly increasing. Worldwide,
19
20 58 more than 650 million people are affected by obesity, defined as body mass index (BMI) ≥ 30
21
22 59 kg/m², with subsequent morbidity and mortality(1). Many conservative and life-style
23
24
25 60 interventions that are aimed at reducing weight are available but most lack effectiveness
26
27
28 61 and durable results. To date, bariatric surgery is the only effective treatment for obesity that
29
30 62 achieves sustainable, long-term weight loss(2, 3).

31
32 63 Obesity is the main risk factor for obstructive sleep apnea (OSA), a sleep-breathing
33
34
35 64 disorder with recurrent breathing cessations that occur when the pharyngeal airway
36
37
38 65 collapses completely or partially. These collapses are respectively called apneas and
39
40 66 hypopneas. The number of breathing cessations per hour of sleep, the apnea hypopnea
41
42 67 index (AHI), indicates the severity of OSA (4, 5). Intermittent hypoxemia, hypercapnia and
43
44
45 68 arousals from sleep are a result of breathing cessations, which lead to excessive daytime
46
47
48 69 sleepiness, cognitive impairment and increased risk of cardiovascular disease. The golden
49
50 70 standard for OSA diagnosis is an in-laboratory polysomnography (PSG), but in recent years
51
52 71 home-based polygraphy (PG) has also been validated as a diagnostic tool(6). Currently, the
53
54
55 72 best treatment for OSA is positive airway pressure (PAP), most commonly provided as
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57
58 73 continuous PAP (CPAP), and aims to maintain an open airway during sleep. Hereby, arousals
59
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3 74 from sleep will be reduced, which improves daytime functioning with less excessive
4
5 75 sleepiness, as well as quality of life and cognitive functioning(7).
6
7

8 76 OSA is highly prevalent in patients who are eligible for bariatric surgery, affecting
9
10 77 approximately 60-70%, compared to OSA prevalence of 3-17% in the general adult
11
12 78 population(8-10). Due to the strong correlation of OSA and obesity, weight loss should be
13
14 79 recommended to all obese patients with moderate or severe OSA(11, 12). Bariatric surgery is
15
16 80 highly effective for this disease, as 60-85% patients achieve complete remission of OSA or
17
18 81 significant reduction of their disease severity(2, 13-16).
19
20
21

22 82 Perioperative care for bariatric patients with OSA pose a clinical challenge, given that
23
24 83 the majority is asymptomatic or experiences unrecognized symptoms, and is consequently
25
26 84 untreated(17). Opioids administered during general anesthesia can induce long-lasting
27
28 85 apneas in patients with untreated OSA. As a result, (untreated) OSA is associated with a
29
30 86 higher risk of cardiopulmonary and neurovascular complications, as well as higher overall
31
32 87 mortality and morbidity in general surgery populations(18, 19). Evidence that this
33
34 88 phenomenon of increased perioperative risk also exists in bariatric patients is thin, and most
35
36 89 studies do not mention whether precautions were taken to prevent OSA-related adverse
37
38 90 events(20). More recent prospective studies and reviews demonstrate a consistently low
39
40 91 incidence of cardiopulmonary and neurovascular complications following bariatric surgery,
41
42 92 and statistical analyses fail to indicate a direct causative link to OSA(21-23).
43
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49 93 Evidence-based guidelines for perioperative care of potential OSA in bariatric
50
51 94 patients are lacking(24). Therefore, a wide variety of perioperative modalities has emerged,
52
53 95 that all aim to minimize the risk of serious adverse events related to untreated OSA. One of
54
55 96 the options is routine preoperative assessment of OSA in every bariatric patient by
56
57 97 performing PSG or PG. Newly diagnosed moderate or severe OSA patients will consequently
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3 98 be treated with CPAP. Another option relies on questionnaires to identify patients at high
4
5 99 risk of OSA who subsequently undergo PG. These questionnaires, such as the STOP-BANG or
6
7
8 100 Berlin questionnaire, are frequently used, but none of these screening tools has been able to
9
10 101 render both high sensitivity and specificity. Therefore, its applicability remains
11
12
13 102 controversial(25-27). Another alternative is routine, postoperative continuous monitoring
14
15 103 with pulse oximetry with supplemental non-invasive oxygen administration but without
16
17
18 104 preoperative OSA assessment. In this approach, all patients receive the same intervention to
19
20 105 achieve adequate saturation levels in the early post-operative phase(21).

21
22
23 106 Obesity and obesity-related disorders increasingly demand utilization of available
24
25 107 health care resources. Justification of high screening expenses for OSA is debatable given the
26
27
28 108 low incidence of OSA-related complications, despite the high prevalence of OSA. In addition,
29
30 109 CPAP adherence rates are poor even in patients with symptomatic OSA, ranging between 29-
31
32 110 83%(28). While specific data are lacking, adherence rates are putatively even lower in
33
34
35 111 asymptomatic bariatric patients, which questions the actual protective effect that is added
36
37 112 by preoperative initiation of CPAP. In contrast, adequate treatment with CPAP in
38
39
40 113 symptomatic OSA patients positively influences societal costs, as symptomatic patients
41
42 114 without treatment use more health care resources, suffer more unemployment and are
43
44
45 115 more prone to work-related or traffic accidents(29-31). However, routine screening and
46
47 116 treatment of asymptomatic patients is not likewise supported by conclusive evidence(27,
48
49
50 117 32). Deliberate consideration is needed when comparing outcomes such as safety, costs and
51
52 118 patients' satisfaction between different perioperative strategies for OSA care in bariatric
53
54 119 patients.

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57 120

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59 121 **RATIONALE**
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3 122 The primary aim of the POPCORN study (*Post-Operative Pulse oximetry without OSA*
4
5 123 *s*creening vs. *OSA sc*reeNing) is to evaluate the most cost-effective perioperative strategy
6
7 124 for bariatric patients who have no history of OSA. We will compare postoperative
8
9 125 continuous pulse oximetry without OSA screening with routine OSA screening by PG and
10
11 126 subsequent application of CPAP. This study will provide evidence that will enable clinicians
12
13 127 to make an evidence-based decision on perioperative care of patients with no known OSA
14
15 128 undergoing bariatric surgery. This paper describes the design and protocol of the POPCORN
16
17 129 study.
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131 **METHODS AND ANALYSIS**

132 **Study design**

133 The POPCORN study is a prospective, multicenter, observational cohort study that evaluates
134 two cohorts of bariatric patients who have no history of OSA. The first cohort consists of
135 patients who are postoperatively monitored with continuous pulse oximetry (CPOX cohort)
136 who do not undergo a PG or PSG. In the second cohort, all bariatric patients undergo a
137 preoperative PG and in case of moderate or severe OSA receive consequent treatment with
138 CPAP before and after surgery (PPG cohort) (Figure 1).
139

140

140 **Recruitment procedures and consent**

141 In total, 1380 obese patients scheduled to undergo bariatric surgery will be included for
142 participation in the POPCORN study. For study participation, a subject must meet the
143 following inclusion criteria: (A) preoperative BMI ≥ 35 kg/m² combined with an obesity-
144 related comorbidity or preoperative BMI ≥ 40 kg/m²(33), (B) Age ≥ 18 years, (C) undergo a
145 primary bariatric procedure. Potential subjects will be excluded from participating in the
146

1
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3 146 following situations: (A) previous bariatric surgery, such as laparoscopic adjustable gastric
4
5 147 banding; (B) inability to speak or read the Dutch language; (C) concomitantly performed
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7
8 148 procedures during bariatric surgery that increase the risk of postoperative complications and
9
10 149 costs, such as cholecystectomy or paraoesophageal hernia repair; (D) Use of treatment
11
12
13 150 options for OSA other than PAP modalities, such as a mandibular advancement device or
14
15 151 positional therapy.

16
17
18 152 In both cohorts, 690 patients will be included. Local protocols of participating
19
20 153 hospitals will determine which strategy of perioperative care is used and this will
21
22
23 154 consequently determine the allocation of patients into one of the two cohorts. Seven
24
25 155 hospitals in the Netherlands will collaborate to recruit all study-patients. Of the participating
26
27
28 156 hospitals, the only hospital that applies CPOX without preoperative OSA screening is
29
30 157 Rijnstate Hospital, Arnhem, who will recruit patients for the CPOX arm. For the PG cohort,
31
32
33 158 patients are recruited from the other participating hospitals (St. Antonius Hospital,
34
35 159 Nieuwegein; Onze Lieve Vrouwe Hospital, Amsterdam; Dutch Obesity Clinic, the Hague;
36
37 160 Zuyderland Hospital, Heerlen; Rode Kruis Hospital, Beverwijk and Máxima Medical Center,
38
39
40 161 Veldhoven). Written or digitally signed informed consent will be obtained from all
41
42
43 162 participants enrolled in this study. Recruitment has started in April 2018 and is expected to
44
45 163 be completed in March 2020.

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48 49 165 **Continuous pulse oximetry (CPOX) - cohort**

50
51
52 166 Bariatric patients in the CPOX cohort receive no preoperative screening for OSA: no PG,
53
54 167 polysomnography or questionnaires for risk stratification are conducted. Postoperatively,
55
56
57 168 bariatric patients return to the surgical ward where continuous surveillance with pulse
58
59 169 oximetry is immediately started, with supplemental oxygen provided via a nasal cannula (2
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1
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3 170 L/min SpO₂). Pulse oximetry is performed using a Draeger Infinity Delta monitor (Draeger
4
5
6 171 Medical Systems Incorporated, USA). Clinical desaturations are defined as <92% SpO₂, lasting
7
8 172 at least 10 seconds. A desaturation sets off an alarm that alerts the attending nurse who will
9
10 173 perform a clinical evaluation.

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15 175 **Preoperative polygraphy (PPG) - cohort**

16
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18 176 The PPG cohort will consist of bariatric patients that are preoperatively screened for OSA
19
20 177 with a polygraphy or polysomnography. Patients with moderate or severe disease, defined
21
22 178 as AHI \geq 15 and AHI \geq 30 events/hour, CPAP treatment is initiated. In patients with mild
23
24 179 disease, defined as AHI 5-14 events/hour, CPAP is only advised in presence of clinically
25
26 180 significant symptoms such as excessive sleepiness and unrefreshing sleep(34). In patients
27
28 181 where an AHI of <5 events/hour is observed, OSA is excluded and no additional
29
30 182 perioperative precautions are needed. [Figure 1] In mild, moderate and severe disease,
31
32 183 automatic or bi-level continuous airway pressure (APAP and BiPAP) are considered
33
34 184 qualitatively equal, compared to CPAP. Therefore, if CPAP treatment is unsuccessful, APAP
35
36 185 and BiPAP are also defined as optimal treatment in the perioperative phase.
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44 187 **Enhanced Recovery After Bariatric Surgery Protocols**

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46
47 188 All participating hospitals will use per- and postoperative protocols during the study period
48
49 189 that are based on the principles of Enhanced Recovery After Bariatric Surgery (ERABS)(35).
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51
52 190 These principles underline aspects of care that enable quick recovery after surgery to
53
54 191 minimize per- and postoperative opioid administration and to stimulate early postoperative
55
56 192 mobilization. To prepare patients for the bariatric procedure and the associated lifestyle
57
58 193 changes, all centers have comparable pre-and postoperative programs for bariatric care. This
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3 194 enlarges a patients' knowledge and expectations on the procedure, the admission and alarm
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5 195 signs for adverse events.
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10 197 **Surgical procedures**

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13 198 Laparoscopic Roux-en-Y gastric bypass (LRYGB) is the most performed procedure in all
14
15 199 participating hospitals, followed by laparoscopic sleeve gastrectomy (LSG). No other primary
16
17 200 procedures are performed in the participating hospitals. LRYGB and LSG are both stomach-
18
19 201 reducing procedures, and thus induce significant restriction on food intake. Both procedures
20
21 202 influence metabolic and hormonal responses that additionally contribute to weight loss.
22
23 203 Furthermore, LRYGB has an additional malabsorptive element as food bypasses the
24
25 204 duodenum and a part of the ileum. Both procedures are performed in a protocolled fashion
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27 205 and will be very similar in all participating hospitals.
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35 207 **Primary outcomes**

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37 208 Cost-effectiveness of CPOX compared with standard care with PPG is the primary outcome
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39 209 and will be evaluated during the period from baseline to 12 months after surgery.
40
41 210 Effectiveness of perioperative care (e.g. CPOX and PPG) will be expressed in quality-
42
43 211 adjusted-life-years (QALYs). The QALYs will be calculated using the EuroQol 5 Dimensions – 3
44
45 212 level (EQ-5D-3L) questionnaire, which rates a person's autonomy and well-being on 5 scales;
46
47 213 mobility, self-care, usual activities, pain/discomfort and anxiety/depression(36). Additionally,
48
49 214 patients indicate their general health of that day on a Visual Analog Scale (VAS). The EQ-5D
50
51 215 score creates a so called utility between 0-1, indicating 1 as the highest form of well-being,
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53 216 and 0 as the lowest form of well-being, i.e. death.
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3 217 Direct and indirect costs during the entire study period will be assessed for each individual
4
5 218 study subject. Direct costs will be extracted from hospital files and electronic patient
6
7
8 219 records. These costs will be carefully evaluated with regard to the relationship with obesity
9
10 220 or OSA. Any unrelated costs will not be considered for the cost-effectiveness analysis.
11
12
13 221 Uncertainty regarding the involvement of OSA or obesity on certain health care costs will be
14
15 222 resolved by discussion between authors SvV, EJH and KK. In addition, we aim to collect
16
17 223 health care costs outside the hospital and so called indirect costs which refer to lost
18
19 224 resources and opportunities (for instance inability to work) resulting from OSA. These costs
20
21 225 will be evaluated using two questionnaires: the Productivity Costs Questionnaire (PCQ) and
22
23 226 the Medical Costs Questionnaire (MCQ). The PCQ is a validated questionnaire that assesses
24
25 227 the relationship of general income and productivity to physical and mental well-being (37).
26
27 228 The MCQ is used to measure extramural medical costs, e.g. visits to a general practitioner or
28
29 229 dietician, or medical care in another hospital than the bariatric center. The PCQ and MCQ
30
31 230 questionnaires are conducted at 3 and 12 months postoperatively.
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40 232 **Secondary outcomes**

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42 233 Mortality, morbidity, complications, intensive care unit (ICU) admissions, length of hospital
43
44 234 stay, OSA-related symptoms, adherence to CPAP and quality of life (QOL) are all secondary
45
46 235 outcomes.

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49 236 Baseline morbidity will be documented and remission of OSA evaluated after 12 months in
50
51 237 the patient files, e.g. comorbidities resolution and weight loss progression during the first
52
53 238 postoperative year. Weight loss will be expressed as percentage excessive weight loss
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55 239 (%EWL), percentage total weight loss (%TWL) and change in BMI.
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3 241 Complications
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5 242 All complications that occur within 30 days of the bariatric procedure will be analyzed.
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7

8 243 Distinction will be made in each complication whether it could be caused by (untreated)
9

10 244 OSA; this will mainly entail pulmonary, cardiac, thromboembolic and neurovascular
11

12 245 complications. Uncertainty regarding these decisions will be solved by discussion between
13

14 246 authors SvV, EJH en KK. If the authors conclude that a pulmonary, cardiac, thromboembolic
15

16 247 or neurovascular complication is not a result of OSA, this will be described in the manuscript.
17

18 248 Severity of complications will be registered according to the Clavien-Dindo Classification
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20 249 (38).
21
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23 250
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26
27 251 Quality of life (QOL)
28

29 252 Generic QOL will be measured using the EQ-5D-3L, and the Rand-Short Form 36-items
30

31 253 questionnaire, which assesses general health in nine different aspects, including physical
32

33 254 activity and bodily pain(39). Sleep-related QOL will be assessed with the Functional Outcome
34

35 255 Sleep Questionnaire-10(40). This 10-item questionnaire measures the effect of tiredness and
36

37 256 sleepiness on QOL and scores are obtained through a 4-point Likert scale. The outcome
38

39 257 score ranges from 5 to 20: low scores indicate poor QOL that is greatly influenced by
40

41 258 daytime sleepiness, while high scores inversely indicate good QOL uninfluenced by daytime
42

43 259 sleepiness(41).
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49 261 OSA-related outcomes
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52 262 The main symptom of OSA, daytime sleepiness, will be assessed by the Epworth Sleepiness
53

54 263 Scale questionnaire(42). Patients report the likelihood of falling asleep during eight daytime
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3 264 activities on a Likert scale of 0-3, indicating results that range from normal daytime
4
5 265 sleepiness (score 0-5) to severe excessive daytime sleepiness (score 16-24).
6
7
8 266 Pre- and postoperative PGs (or PSGs) during the study period will be analyzed for AHI, AHI in
9
10 267 supine position, oxygen desaturation index, total sleeping time in supine position, mean
11
12 268 oxygen saturation, lowest oxygen saturation, time of saturation <90% SpO₂, number of
13
14 269 episodes of saturation <90% SpO₂ and number of episodes with >4% saturation drop below
15
16 270 mean saturation. Additional factors that could contribute to disease-load or probability are
17
18 271 also monitored; previous ENT surgery that provides a wider pharyngeal girth (i.e.
19
20 272 uvulopalatopharyngoplasty), smoking status and daily use of opioids will also be registered.
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274 CPAP adherence

275 Due to known discrepancies between patient reported adherence to treatment and
276 objective treatment adherence data, we will obtain both objective and subjective data on
277 CPAP adherence. Adherence will be expressed in days per week of CPAP treatment and
278 hours per night. To obtain objective data, we will consult online databanks for collection of
279 day-to-day adherence rates. CPAP devices automatically send adherence data and
280 corresponding AHIs to an online databank, which health care providers in the Netherlands
281 use to monitor their patients. In addition, electronic patient records will be evaluated for
282 physicians' recommendation regarding (dis)continuation of CPAP during follow-up.
283 Subjective data on CPAP adherence will be collected through patient reported outcomes
284 measurements. By using questionnaires, insight can be obtained regarding patients' motives
285 for treatment discontinuation.

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287 **Data management**

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3 288 Handling of data was prospectively addressed in a data management plan with the aim of
4
5 289 generating data in accordance with the FAIR criteria: Findable, Accessible, Intra-operable
6
7
8 290 and Reusable.
9

10 291

11 292 **Sample size calculation**

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14
15 293 A non-inferiority design was chosen to evaluate whether CPOX with no preoperative PG is
16
17 294 non-inferior to preoperative PG in bariatric patients. In patients with moderate or severe
18
19 295 OSA, CPAP treatment is part of standard care. The primary outcome is QALY difference
20
21 296 compared to costs, where QALYs are measured by the EQ-5D. Therefore, the sample size
22
23 297 calculation is based on a predefined non-inferiority margin of 0.03 on the EQ-5D score.
24
25

26
27 298 Based on an EQ-5D score of 0.68 in the usual care group, QALYs of OSA patients before and
28
29 299 after one year of CPAP treatment, and calculating with 80% power to detect the predefined
30
31 300 non-inferiority margin at a one-sided a level of 0.05, there are 621 patients needed in each
32
33 301 study group(43). Assuming a loss to follow up of 10%, the total study population will be set
34
35 302 at 1380 patients, resulting in 690 patients per arm.
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41 304 **Analysis of primary outcome measures**

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44 305 An extensive cost-effectiveness analysis (CEA) and budget impact analysis (BIA) will be
45
46 306 performed. We aim to perform a trial based economic evaluation in which we do not
47
48 307 extrapolate costs and effect outside the study period. The effect of the CEA will be expressed
49
50 308 in change of QALYs during the study period, and this outcome will be compared to the total
51
52 309 costs of each individual patient. Outcomes will be average cost per patient, differences
53
54 310 between groups and incremental costs per QALY.
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3 311 Sensitivity analysis will be carried out to correct all potential confounders, such as gender,
4
5 312 age, preoperative BMI, comorbidities, choice of bariatric center, intraoperative and
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7 313 postoperative administered opioids, smoking status, previous ENT surgery.
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11 315 **Analysis of secondary outcome measures**

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13 316 Baseline characteristics of patients will be documented with mean/standard deviation or
14
15 317 median/range, depending on normality. The number of desaturations, both
16
17 318 cardiopulmonary and general complications, interventions, total hospital stay and total costs
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19 319 between both groups will be analyzed with the independent t-test/Mann-Whitney U test.
20
21 320 Compliance of CPAP and opioids use will be evaluated with chi-square testing. Mixed model
22
23 321 analysis will be performed to evaluate the weight loss, severity of OSA symptoms and CPAP
24
25 322 adherence at different time points. Predictive values for cardiopulmonary complications will
26
27 323 be evaluated with logistic regression analysis, starting with a univariate analysis. All variables
28
29 324 with a significance level $p < 0.2$ will be included in a multivariate analysis. Within this
30
31 325 analysis, only seven independent variables may be included as ten event cases are allowed
32
33 326 per dependent predictor. Statistical significance is defined as $p < 0.05$.
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43 328 **Loss to follow-up or replacement of participants**

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45 329 Study participants will be replaced with new participants in case of A) cancellation of the
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47 330 surgery, B) uncompleted preoperative questionnaire, or C) when positive airway pressure
48
49 331 treatment is switched to a different modality such as a mandibular advancement device.
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51 332 Patients who do not complete the postoperative questionnaire at 12 months after surgery
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53 333 due to other reasons, will be considered lost-to-follow-up.
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3 335 **Patient and public involvement**
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5 336 A non-profit organization for OSA patients was consulted during the process of writing the
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8 337 protocol.
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13 339 **Ethics and dissemination**
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15 340 The Medical Ethics Committee United (MEC-U) approved this study, in accordance with the
16
17 341 Dutch law Medical Research Involving Human Subjects Act (WMO), Medical Research in
18
19 342 Humans (MEC-U, W17.050). In addition, local Medical Ethics Committees of each
20
21 343 participating hospital also reviewed and approved the study protocol.
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27 345 Findings of the POPCORN study will be disseminated to all disciplines that are involved in
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29 346 care for bariatric surgery, through articles in peer-reviewed journals, national and
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31 347 international congresses, and revising the national guidelines of the Netherlands.
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37 350 **DISCUSSION**
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40 351 The POPCORN study is a prospective observational cohort study that evaluates the cost-
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42 352 effectiveness of two strategies of perioperative care in bariatric patients without a pre-
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44 353 existent OSA diagnosis: CPOX without extensive preoperative OSA screening vs. mandatory
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46 354 PG, potentially followed by CPAP treatment. The outcomes will enable the development of
47
48 355 new, evidence-based guidelines on perioperative care for bariatric patients with no known
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50 356 OSA. The secondary outcomes, such as (cardiopulmonary) complications, OSA-related
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52 357 symptoms and quality of life, will provide an overview of the correlation between cost-
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3 358 effectiveness and clinical outcomes that are highly relevant in the decision making for
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5 359 perioperative care in bariatric patients.
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8 360 Best practice regarding perioperative care in bariatric patient has been an ongoing
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10 361 debate for many years, with high prevalence and potential detrimental effects of undetected
11
12 362 OSA on one side and substantial costs of related perioperative care and CPAP treatment on
13
14 363 the other(27, 44, 45). No comparative studies between different perioperative strategies
15
16 364 have been conducted to evaluate outcomes of postoperative complications or cost-
17
18 365 effectiveness. In a recent review, conducted by the US preventative task force, no
19
20 366 effectiveness of OSA screening in patients who are asymptomatic or who experience
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22 367 unrecognized symptoms was found(27). Despite improvements in intermediate outcomes
23
24 368 such as AHI or sleepiness symptoms, no improvement in final health outcomes have been
25
26 369 demonstrated, such as mortality or serious adverse events. The paucity in evidence
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28 370 regarding beneficial outcomes is especially relevant when cost-effectiveness is regarded. The
29
30 371 obesity epidemic and its related costs are continuously expanding, and this underlines the
31
32 372 need for optimal use of available health care resources. With no confirmative data on
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34 373 positive influence of OSA screening in bariatric patients with no known OSA, and
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36 374 approximately 700.000 bariatric procedures annually worldwide, clarification on this topic is
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38 375 needed.
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47 376 The perioperative strategies evaluated in the POPCORN study are both widely used in
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49 377 general practice and it is expected that results of this study will lead to evidence-based
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51 378 recommendations and guidelines.
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54 379 The strength of this study is that a general, bariatric population is evaluated. In both
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56 380 cohorts, large groups of bariatric patients are prospectively observed, while little exclusion
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58 381 criteria are applied. In addition, the follow-up period in this study that investigates a
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3 382 perioperative intervention is relatively long. Previous studies that describe preoperative
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5 383 assessment and treatment of OSA mainly reported prevalence of newly detected OSA and
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8 384 related adverse outcomes restricted to the direct perioperative period(46). The follow-up
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10 385 duration of one year after surgery enables us to investigate long-term clinical outcomes of a
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13 386 perioperative regime. Interesting comparisons are to be made between the preoperatively
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15 387 diagnosed OSA patients and the unscreened bariatric patients in terms of sleepiness
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18 388 symptoms, daytime productivity, general quality of life and health care resource utilization.

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20 389 Ideally, a randomized controlled trial would have been conducted, in which all
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23 390 patients would undergo a preoperative PG. Consecutive randomization would have
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25 391 determined the type of perioperative care: CPOX monitoring or treatment based on the PG
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28 392 outcome. However, this was considered unethical, as randomization into the CPOX cohort
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30 393 would result in withholding appropriate treatment from patients with confirmed OSA
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33 394 diagnosis, which is associated with many health care hazards (30, 31, 47). Despite the non-
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35 395 randomized design of the POPCORN trial, the large sample size will provide sufficient data to
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37 396 render a balanced statement that will be representable for the general bariatric population
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40 397 in the Netherlands. Furthermore, it is expected that implementation of these perioperative
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42 398 strategies is also feasible in countries other than the Netherlands.

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47 400 In conclusion, the POPCORN study will conclude which perioperative strategy is most
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49 401 cost-effective for obese patients scheduled for bariatric surgery and who have an unknown
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52 402 OSA status. These data will contribute to evidence-based guidelines which are urgently
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54 403 needed in this particular field of bariatric care.

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59 405 **Author contributions**

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3 406 EJH conceived and designed the study, with support of CALDR and KK. SVV wrote and
4
5 407 developed the protocol together with EJH, CALDR, KK, GJWF and LR. EJH is the principal
6
7 408 investigator and SVV is the main investigator. All authors critically reviewed the content and
8
9 409 approved the final manuscript.
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25
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27
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29
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31
32 420 Department of Surgery, Máxima Medical Center, Veldhoven, the Netherlands.
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48 424
49 425 **Competing interests**

50 426 Not applicable for any of the authors
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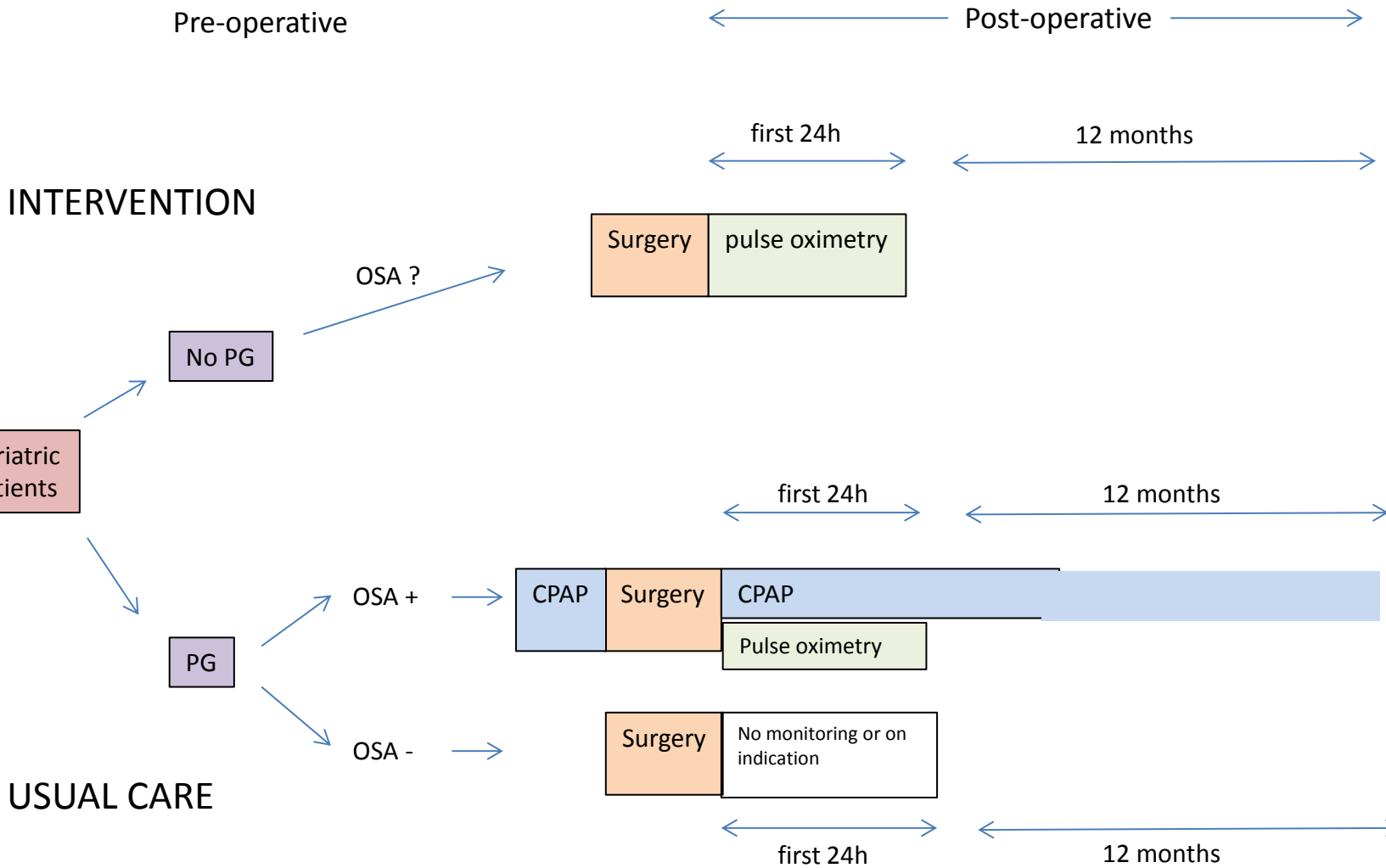


Figure 1. Flowchart of POPCORN study

PG polygraphy, OSA obstructive sleep apnea, CPAP continuous positive airway pressure

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

1	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and
2			sensitivity analyses
3			
4	Discussion		
5	Key results	18	Summarise key results with reference to study objectives
6	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or
7			imprecision. Discuss both direction and magnitude of any potential bias
8			
9	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations,
10			multiplicity of analyses, results from similar studies, and other relevant evidence
11	Generalisability	21	Discuss the generalisability (external validity) of the study results
12			
13	Other information		
14	Funding	22	Give the source of funding and the role of the funders for the present study and, if
15			applicable, for the original study on which the present article is based
16			

17
18 *Give information separately for exposed and unexposed groups.

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21 **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and
22 published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely
23 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
24 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
25 available at <http://www.strobe-statement.org>.

BMJ Open

Protocol of a multicentre, prospective cohort study that evaluates cost-effectiveness of two perioperative care strategies for potential obstructive sleep apnea in morbidly obese patients undergoing bariatric surgery.

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Respiratory medicine
Keywords:	Sleep medicine < ANAESTHETICS, SLEEP MEDICINE, Adult surgery < SURGERY, RESPIRATORY MEDICINE (see Thoracic Medicine)

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3 **1 Protocol of a multicentre, prospective cohort study that evaluates cost-effectiveness of**
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5 **2 two perioperative care strategies for potential obstructive sleep apnea in morbidly obese**
6
7 **3 patients undergoing bariatric surgery.**
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38 **ABSTRACT**

39 **Introduction**

40 Despite the high prevalence of obstructive sleep apnea (OSA) in obese patients undergoing
41 bariatric surgery, OSA is undiagnosed in the majority of patients and thus untreated. While
42 untreated OSA is associated with an increased risk of per- and postoperative complications,
43 no evidence-based guidelines on perioperative care for these patients are available. The aim
44 of the POPCORN study (*Post-Operative Pulse oximetry without OSA sCreening vs.*
45 *perioperative continuous positive airway pressure (CPAP) treatment following OSA*
46 *scReeNing by polygraphy (PG)*) is to evaluate which perioperative strategy is most cost-
47 effective for obese patients undergoing bariatric surgery without a history of OSA.

48 **Methods and analysis**

49 In this multicentre observational cohort study, data from 1380 patients who will undergo
50 bariatric surgery will be collected. Patients will either receive postoperative care with pulse
51 oximetry monitoring and supplemental oxygen during the first postoperative night, or they
52 receive care that includes preoperative PG and CPAP treatment in case of moderate or
53 severe OSA. Local protocols for perioperative care in each participating hospital will
54 determine into which cohort a patient is placed. The primary outcome is cost-effectiveness,
55 which will be calculated by comparing all health care costs to the quality-adjusted-life-years
56 (QALYs, calculated using EQ-5D questionnaires). Secondary outcomes are mortality,
57 complications within 30 days after surgery, readmissions, reoperations, length of stay,
58 weight loss, generic quality of life (QOL), OSA-specific QOL, OSA symptoms and CPAP
59 adherence. Patients will receive questionnaires before surgery and 1, 3, 6, and 12 months
60 after surgery to report QALYs and other patient reported outcomes.

61 **Ethics and dissemination**

62 Approval from the Medical research Ethics Committees United was granted in accordance
63 with the Dutch law for Medical Research Involving Human Subjects Act (WMO) (reference
64 number W17.050). Results will be submitted for publication in peer-reviewed journals and
65 presented at (inter)national conferences.

66 **Trial registration number**

67 NTR6991, registered at the Netherlands Trial register, <https://www.trialregister.nl>.

70 **Article summary**

71 Strengths and limitations of this study

72 - This is the first prospective study to compare continuous postoperative pulse
73 oximetry without preoperative OSA screening to routine OSA screening with consequent
74 CPAP treatment as perioperative care for bariatric patients with potential OSA.

76 - The main outcome of this study is cost-effectiveness of these two perioperative care
77 strategies in obese patients with no known OSA history.

79 - Results of this study will provide new insights in unknown aspects of perioperative
80 interventions for undetected OSA, such as the impact on postoperative complications and
81 general quality of life.

83 - Despite the non-randomized design, we hypothesize that the results are
84 generalizable to most bariatric centres due to the large sample size and limited exclusion
85 criteria.

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4
5 87 - Our follow-up duration of one year enables analysis of long-term outcomes of
6
7
8 88 perioperative interventions for OSA, such as influence on weight loss, sleepiness symptoms,
9
10 89 quality of life with sleepiness and adherence to CPAP.
11

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13 90

15 91 INTRODUCTION

16
17 92 Obesity is a health care issue of epidemic proportions that is rapidly increasing. Worldwide,
18
19 93 more than 650 million people are affected by obesity, defined as body mass index (BMI) ≥ 30
20
21 94 kg/m², with subsequent morbidity and mortality(1). Many conservative and life-style
22
23 95 interventions that are aimed at reducing weight are available but most lack effectiveness
24
25 96 and durable results. To date, bariatric surgery is the only effective treatment for obesity that
26
27 97 achieves sustainable, long-term weight loss(2, 3).
28
29

30
31 98 Obesity is the main risk factor for obstructive sleep apnea (OSA), a sleep-breathing
32
33 99 disorder with recurrent breathing cessations that occur when the pharyngeal airway
34
35 100 collapses completely or partially. These collapses are respectively called apneas and
36
37 101 hypopneas. The number of breathing cessations per hour of sleep, the apnea hypopnea
38
39 102 index (AHI), indicates the severity of OSA (4, 5). Intermittent hypoxemia, hypercapnia and
40
41 103 arousals from sleep are a result of breathing cessations, which lead to excessive daytime
42
43 104 sleepiness, cognitive impairment and increased risk of cardiovascular disease. The golden
44
45 105 standard for OSA diagnosis is an in-laboratory polysomnography (PSG), but in recent years
46
47 106 home-based polygraphy (PG) has also been validated as a diagnostic tool(6). Currently, the
48
49 107 best treatment for OSA is positive airway pressure (PAP), most commonly provided as
50
51 108 continuous PAP (CPAP), and aims to maintain an open airway during sleep. Hereby, arousals
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3 109 from sleep will be reduced, which improves daytime functioning with less excessive
4
5 110 sleepiness, as well as quality of life and cognitive functioning(7).

6
7
8 111 OSA is highly prevalent in patients who are eligible for bariatric surgery, affecting
9
10 112 approximately 60-70%, compared to OSA prevalence of 3-17% in the general adult
11
12 113 population(8-10). Due to the strong correlation of OSA and obesity, weight loss should be
13
14 114 recommended to all obese patients with moderate or severe OSA(11, 12). Bariatric surgery is
15
16 115 highly effective for this disease, as 60-85% patients achieve complete remission of OSA or
17
18 116 significant reduction of their disease severity(2, 13-16).

19
20
21
22 117 Perioperative care for bariatric patients with OSA pose a clinical challenge, given that
23
24 118 the majority is asymptomatic or experiences unrecognized symptoms, and is consequently
25
26 119 untreated(17). Opioids administered during general anesthesia can induce long-lasting
27
28 120 apneas in patients with untreated OSA. As a result, (untreated) OSA is associated with a
29
30 121 higher risk of cardiopulmonary and neurovascular complications, as well as higher overall
31
32 122 mortality and morbidity in general surgery populations(18, 19). Evidence that this
33
34 123 phenomenon of increased perioperative risk also exists in bariatric patients is thin, and most
35
36 124 studies do not mention whether precautions were taken to prevent OSA-related adverse
37
38 125 events(20). More recent prospective studies and reviews demonstrate a consistently low
39
40 126 incidence of cardiopulmonary and neurovascular complications following bariatric surgery,
41
42 127 and statistical analyses fail to indicate a direct causative link to OSA(21-23).

43
44
45 128 Evidence-based guidelines for perioperative care of potential OSA in bariatric
46
47 129 patients are lacking(24). Therefore, a wide variety of perioperative modalities has emerged,
48
49 130 that all aim to minimize the risk of serious adverse events related to untreated OSA. One of
50
51 131 the options is routine preoperative assessment of OSA in every bariatric patient by
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53 132 performing PSG or PG. Newly diagnosed moderate or severe OSA patients will consequently
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1
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3 133 be treated with CPAP. Another option relies on questionnaires to identify patients at high
4
5 134 risk of OSA who subsequently undergo PG. These questionnaires, such as the STOP-BANG or
6
7
8 135 Berlin questionnaire, are frequently used, but none of these screening tools has been able to
9
10 136 render both high sensitivity and specificity. Therefore, its applicability remains
11
12
13 137 controversial(25-27). Another alternative is routine, postoperative continuous monitoring
14
15 138 with pulse oximetry with supplemental non-invasive oxygen administration but without
16
17
18 139 preoperative OSA assessment. In this approach, all patients receive the same intervention to
19
20 140 achieve adequate saturation levels in the early post-operative phase(21).

21
22
23 141 Obesity and obesity-related disorders increasingly demand utilization of available
24
25 142 health care resources. Justification of high screening expenses for OSA is debatable given the
26
27
28 143 low incidence of OSA-related complications, despite the high prevalence of OSA. In addition,
29
30 144 CPAP adherence rates are poor even in patients with symptomatic OSA, ranging between 29-
31
32 145 83%(28). While specific data are lacking, adherence rates are putatively even lower in
33
34
35 146 asymptomatic bariatric patients, which questions the actual protective effect that is added
36
37 147 by preoperative initiation of CPAP. In contrast, adequate treatment with CPAP in
38
39
40 148 symptomatic OSA patients positively influences societal costs, as symptomatic patients
41
42 149 without treatment use more health care resources, suffer more unemployment and are
43
44
45 150 more prone to work-related or traffic accidents(29-31). However, routine screening and
46
47 151 treatment of asymptomatic patients is not likewise supported by conclusive evidence(27,
48
49
50 152 32). Deliberate consideration is needed when comparing outcomes such as safety, costs and
51
52 153 patients' satisfaction between different perioperative strategies for OSA care in bariatric
53
54 154 patients.

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58
59 156 **RATIONALE**

1
2
3 157 The primary aim of the POPCORN study (*Post-Operative Pulse oximetry without OSA*
4
5
6 158 *s*creening vs. *OSA sc*reeNing) is to evaluate the most cost-effective perioperative strategy
7
8 159 for bariatric patients who have no history of OSA. We will compare postoperative
9
10 160 continuous pulse oximetry without OSA screening with routine OSA screening by PG and
11
12
13 161 subsequent application of CPAP. This study will provide evidence that will enable clinicians
14
15 162 to make an evidence-based decision on perioperative care of patients with no known OSA
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17
18 163 undergoing bariatric surgery. This paper describes the design and protocol of the POPCORN
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20 164 study.
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25 166 **METHODS AND ANALYSIS**

27 167 **Study design**

29
30 168 The POPCORN study is a prospective, multicentre, observational cohort study that evaluates
31
32 169 two cohorts of bariatric patients who have no history of OSA. The first cohort consists of
33
34
35 170 patients who are postoperatively monitored with continuous pulse oximetry (CPOX cohort)
36
37 171 who do not undergo a PG or PSG. In the second cohort, all bariatric patients undergo a
38
39
40 172 preoperative PG and in case of moderate or severe OSA receive consequent treatment with
41
42 173 CPAP before and after surgery (PPG cohort) (Figure 1).
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45 174

47 175 **Recruitment procedures and consent**

48
49 176 In total, 1380 obese patients scheduled to undergo bariatric surgery will be included for
50
51
52 177 participation in the POPCORN study. For study participation, a subject must meet the
53
54 178 following inclusion criteria: (A) preoperative BMI ≥ 35 kg/m² combined with an obesity-
55
56
57 179 related comorbidity or preoperative BMI ≥ 40 kg/m²(33), (B) Age ≥ 18 years, (C) undergo a
58
59 180 primary bariatric procedure. Potential subjects will be excluded from participating in the
60

1
2
3 181 following situations: (A) previous bariatric surgery, such as laparoscopic adjustable gastric
4
5 182 banding; (B) inability to speak or read the Dutch language; (C) concomitantly performed
6
7
8 183 procedures during bariatric surgery that increase the risk of postoperative complications and
9
10 184 costs, such as cholecystectomy or paraesophageal hernia repair; (D) Use of treatment
11
12
13 185 options for OSA other than PAP modalities, such as a mandibular advancement device or
14
15 186 positional therapy.

17
18 187 In both cohorts, 690 patients will be included. Local protocols of participating
19
20 188 hospitals will determine which strategy of perioperative care is used and this will
21
22
23 189 consequently determine the allocation of patients into one of the two cohorts. Seven
24
25 190 hospitals in the Netherlands will collaborate to recruit all study-patients. Of the participating
26
27 191 hospitals, the only hospital that applies CPOX without preoperative OSA screening is
28
29 192 Rijnstate Hospital, Arnhem, who will recruit patients for the CPOX arm. For the PG cohort,
30
31 193 patients are recruited from the other participating hospitals (St. Antonius Hospital,
32
33 194 Nieuwegein; Onze Lieve Vrouwe Hospital, Amsterdam; Dutch Obesity Clinic, the Hague;
34
35 195 Zuyderland Hospital, Heerlen; Rode Kruis Hospital, Beverwijk and Máxima Medical Centre,
36
37 196 Veldhoven). Written or digitally signed informed consent will be obtained from all
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39
40 197 participants enrolled in this study. Recruitment has started in April 2018 and is expected to
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42
43 198 be completed in March 2020.

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47 199

200 **Continuous pulse oximetry (CPOX) - cohort**

51
52 201 Bariatric patients in the CPOX cohort receive no preoperative screening for OSA: no PG,
53
54 202 polysomnography or questionnaires for risk stratification are conducted. Postoperatively,
55
56 203 bariatric patients return to the surgical ward where continuous surveillance with pulse
57
58 204 oximetry is immediately started, with supplemental oxygen provided via a nasal cannula (2
59
60

1
2
3 205 L/min SpO₂). Pulse oximetry is performed using a Draeger Infinity Delta monitor (Draeger
4
5
6 206 Medical Systems Incorporated, USA). Clinical desaturations are defined as <92% SpO₂, lasting
7
8 207 at least 10 seconds. A desaturation sets off an alarm that alerts the attending nurse who will
9
10 208 perform a clinical evaluation. Long-lasting apneas can either be terminated by awaking the
11
12
13 209 respective patient, or by providing additional supplemental oxygen via the non-invasive
14
15 210 nasal cannula. In case of a serious desaturation that cannot be managed appropriately by
16
17 211 these minor interventions, patients can be admitted to the intensive care unit for potential
18
19
20 212 reintubation at discretion of the treating physician.
21
22

213

214 **Preoperative polygraphy (PPG) - cohort**

215 The PPG cohort will consist of bariatric patients that are preoperatively screened for OSA
216 with a polygraphy or polysomnography. Patients with moderate or severe disease, defined
217 as AHI \geq 15 and AHI \geq 30 events/hour, CPAP treatment is initiated. In patients with mild
218 disease, defined as AHI 5-14 events/hour, CPAP is only advised in presence of clinically
219 significant symptoms such as excessive sleepiness and unrefreshing sleep(34). In patients
220 where an AHI of <5 events/hour is observed, OSA is excluded and no additional
221 perioperative precautions are needed. [Figure 1] In mild, moderate and severe disease,
222 automatic or bi-level continuous airway pressure (APAP and BiPAP) are considered
223 qualitatively equal, compared to CPAP. Therefore, if CPAP treatment is unsuccessful, APAP
224 and BiPAP are also defined as optimal treatment in the perioperative phase.

225

226 **Enhanced Recovery After Bariatric Surgery Protocols**

227 All participating hospitals will use per- and postoperative protocols during the study period
228 that are based on the principles of Enhanced Recovery After Bariatric Surgery (ERABS)(35).

1
2
3 229 These principles underline aspects of care that enable quick recovery after surgery to
4
5 230 minimize per- and postoperative opioid administration and to stimulate early postoperative
6
7
8 231 mobilization. To prepare patients for the bariatric procedure and the associated lifestyle
9
10 232 changes, all centres have comparable pre-and postoperative programs for bariatric care. This
11
12
13 233 enlarges a patients' knowledge and expectations on the procedure, the admission and alarm
14
15 234 signs for adverse events.
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236 **Surgical procedures**

237 Laparoscopic Roux-en-Y gastric bypass (LRYGB) is the most performed procedure in all
238 participating hospitals, followed by laparoscopic sleeve gastrectomy (LSG). LRYGB and LSG
239 are both stomach-reducing procedures, and thus induce significant restriction on food
240 intake. Both procedures influence metabolic and hormonal responses that additionally
241 contribute to weight loss. Furthermore, LRYGB has an additional malabsorptive element as
242 food bypasses the duodenum and a part of the ileum. Both procedures are performed in a
243 protocolled fashion and will be very similar in all participating hospitals.
244

245

245 **Primary outcomes**

246 Cost-effectiveness of CPOX compared with standard care with PPG is the primary outcome
247 and will be evaluated during the period from baseline to 12 months after surgery from a
248 societal perspective. Effectiveness of perioperative care (e.g. CPOX and PPG) will be
249 expressed in quality-adjusted-life-years (QALYs). The QALYs will be calculated using the
250 EuroQol 5 Dimensions – 3 level (EQ-5D-3L) questionnaire, which rates a person's autonomy
251 and well-being on 5 scales; mobility, self-care, usual activities, pain/discomfort and
252 anxiety/depression(36). All scores will be calculated using the subset that was validated for

1
2
3 253 the Dutch population of the EQ-5d-3L(37) . Additionally, patients indicate their general
4
5
6 254 health of that day on a Visual Analog Scale (VAS). The EQ-5D score creates a so called utility
7
8 255 between 0-1, indicating 1 as the highest form of well-being, and 0 as the lowest form of well-
9
10 256 being, i.e. death.

11
12
13 257 Direct and indirect costs during the entire study period will be assessed for each individual
14
15 258 study subject. Direct costs will be extracted from hospital files and electronic patient
16
17 259 records. These costs will be carefully evaluated with regard to the relationship with obesity
18
19 260 or OSA. Any unrelated costs will not be considered for the cost-effectiveness analysis.
20
21
22 261 Uncertainty regarding the involvement of OSA or obesity on certain health care costs will be
23
24
25 262 resolved by discussion between authors SvV, EJH and KK.
26
27

28 263
29
30 264 In addition, we aim to collect health care costs outside the hospital and so called indirect
31
32 265 costs which refer to lost resources and opportunities (for instance inability to work) resulting
33
34 266 from OSA. These costs will be evaluated using two questionnaires: the Productivity Costs
35
36 267 Questionnaire (PCQ) and the Medical Costs Questionnaire (MCQ). The PCQ is a validated
37
38 268 questionnaire that assesses the relationship of general income and productivity to physical
39
40 269 and mental well-being (38). The MCQ is used to measure extramural medical costs, e.g. visits
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42 270 to a general practitioner or dietician, or medical care in another hospital than the bariatric
43
44 271 centre. The PCQ and MCQ questionnaires are conducted at 3 and 12 months
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46 272 postoperatively.
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54 274 **Secondary outcomes**
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3 275 Mortality, morbidity, complications, intensive care unit (ICU) admissions, length of hospital
4
5 276 stay, OSA-related symptoms, adherence to CPAP and quality of life (QOL) are all secondary
6
7
8 277 outcomes.

9
10 278 Baseline morbidity will be documented and remission of OSA evaluated after 12 months in
11
12
13 279 the patient files, e.g. comorbidities resolution and weight loss progression during the first
14
15 280 postoperative year. Weight loss will be expressed as percentage excessive weight loss
16
17 281 (%EWL), percentage total weight loss (%TWL) and change in BMI.

18
19
20 282

21 22 283 Complications

23
24
25 284 All complications that occur within 30 days of the bariatric procedure will be analysed.

26
27 285 Distinction will be made in each complication whether it could be caused by (untreated)

28
29 286 OSA; this will mainly entail pulmonary, cardiac, thromboembolic and neurovascular

30
31 287 complications. Uncertainty regarding these decisions will be solved by discussion between

32
33 288 authors SvV, EJJ en KK. If the authors conclude that a pulmonary, cardiac, thromboembolic

34
35 289 or neurovascular complication is not a result of OSA, this will be described in the manuscript.

36
37 290 Severity of complications will be registered according to the Clavien-Dindo Classification

38
39 291 (39).

40
41
42 292

43 44 293 Quality of life (QOL)

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46
47 294 Generic QOL will be measured using the EQ-5D-3L, and the Rand-Short Form 36-items

48
49 295 questionnaire, which assesses general health in nine different aspects, including physical

50
51 296 activity and bodily pain(40). Sleep-related QOL will be assessed with the Functional Outcome

52
53 297 Sleep Questionnaire-10(41). This 10-item questionnaire measures the effect of tiredness and

54
55 298 sleepiness on QOL and scores are obtained through a 4-point Likert scale. The outcome

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1
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3 299 score ranges from 5 to 20: low scores indicate poor QOL that is greatly influenced by
4
5 300 daytime sleepiness, while high scores inversely indicate good QOL uninfluenced by daytime
6
7
8 301 sleepiness(42).
9

10 302

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12
13 303 OSA-related outcomes

14
15 304 The main symptom of OSA, daytime sleepiness, will be assessed by the Epworth Sleepiness
16
17 305 Scale questionnaire(43). Patients report the likelihood of falling asleep during eight daytime
18
19
20 306 activities on a Likert scale of 0-3, indicating results that range from normal daytime
21
22
23 307 sleepiness (score 0-5) to severe excessive daytime sleepiness (score 16-24).

24
25 308 Pre- and postoperative PGs (or PSGs) during the study period will be analysed for AHI, AHI in
26
27 309 supine position, oxygen desaturation index, total sleeping time in supine position, mean
28
29
30 310 oxygen saturation, lowest oxygen saturation, time of saturation <90% SpO₂, number of
31
32 311 episodes of saturation <90% SpO₂ and number of episodes with >4% saturation drop below
33
34
35 312 mean saturation. Additional factors that could contribute to disease-load or probability are
36
37 313 also monitored; previous ENT surgery that provides a wider pharyngeal girth (i.e.
38
39
40 314 uvulopalatopharyngoplasty), smoking status, alcohol consumption and daily use of opioids
41
42 315 and benzodiazepines will also be registered.
43

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45
46
47 317 CPAP adherence

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49 318 Due to known discrepancies between patient reported adherence to treatment and
50
51
52 319 objective treatment adherence data, we will obtain both objective and subjective data on
53
54
55 320 CPAP adherence. Adherence will be expressed in days per week of CPAP treatment and
56
57 321 hours per night. To obtain objective data, we will consult online databanks for collection of
58
59 322 day-to-day adherence rates. CPAP devices automatically send adherence data and
60

1
2
3 323 corresponding AHIs to an online databank, which health care providers in the Netherlands
4
5 324 use to monitor their patients. In addition, electronic patient records will be evaluated for
6
7
8 325 physicians' recommendation regarding (dis)continuation of CPAP during follow-up.
9
10 326 Subjective data on CPAP adherence will be collected through patient reported outcomes
11
12
13 327 measurements. By using questionnaires, insight can be obtained regarding patients' motives
14
15 328 for treatment discontinuation.
16

17 329

20 330 **Data management**

21
22 331 Handling of data was prospectively addressed in a data management plan with the aim of
23
24 332 generating data in accordance with the FAIR criteria: Findable, Accessible, Intra-operable
25
26 333 and Reusable.
27
28
29

30 334

32 335 **Sample size calculation**

33
34 336 A non-inferiority design was chosen to evaluate whether CPOX with no preoperative PG is
35
36 337 non-inferior to preoperative PG in bariatric patients. In patients with moderate or severe
37
38 338 OSA, CPAP treatment is part of standard care. The primary outcome is QALY difference
39
40 339 compared to costs, where QALYs are measured by the EQ-5D. Therefore, the sample size
41
42 340 calculation is based on a predefined non-inferiority margin of 0.03 on the EQ-5D score.
43
44 341 Based on an EQ-5D score of 0.68 in the usual care group, QALYs of OSA patients before and
45
46 342 after one year of CPAP treatment, and calculating with 80% power to detect the predefined
47
48 343 non-inferiority margin at a one-sided a level of 0.05, there are 621 patients needed in each
49
50 344 study group(44). Assuming a loss to follow up of 10%, the total study population will be set
51
52 345 at 1380 patients, resulting in 690 patients per arm.
53
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347 **Analysis of primary outcome measures**

348 An extensive cost-effectiveness analysis (CEA) and budget impact analysis (BIA) will be
349 performed. The cost-effectiveness analysis adheres to the Dutch guideline (45) and reporting
350 will adhere to the CHEERS checklist(46). The BIA will adhere to current Dutch guidelines and
351 also guidelines as published by Sullivan et al. (47). We aim to perform a trial based economic
352 evaluation in which we do not extrapolate costs and effect outside the study period. The
353 effect of the CEA will be expressed in change of QALYs during the study period, and this
354 outcome will be compared to the total costs of each individual patient. Outcomes will be
355 average cost per patient, differences between groups and incremental costs per QALY. An
356 incremental cost-effectiveness ratio analysis will be performed to compare the outcomes (in
357 QALY) rendered by the CPOX and the PPG strategy to the costs related to each perioperative
358 strategy.

359 Sensitivity analysis will be carried out to correct all potential confounders, such as gender,
360 age, preoperative BMI, comorbidities, choice of bariatric centre, intraoperative and
361 postoperative administered opioids, smoking status, previous ENT surgery. One-way
362 sensitivity analyses will be illustrated graphically using tornado diagrams; probabilistic
363 sensitivity analyses (PSA) will be illustrated in cost-effectiveness planes and so called cost-
364 effectiveness acceptability curves. Bootstrapping will be used if deemed necessary.

365

366 Cost assessment

367 This analysis will be performed using a societal perspective.

368

- 369 • Identification: we aim to identify all health care utilization for every included patient
370 within the study period. All consumption potentially related to obesity, bariatric

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3 371 surgery, and obstructive sleep apnea will be identified in this total set of health care
4
5 372 consumption. The latter comprised a vast amount of health care resources that are
6
7
8 373 potentially related to OSA: costs resources related to sleep medicine, cardiovascular
9
10 374 disease, pulmonary disease, ear-, nose and throat disease, and work- or traffic
11
12
13 375 related accidents.

14
15 376 • Measurement: utilization of health care resources within the hospital were gathered
16
17 377 by using each hospital billing system (detailed health care consumption data send to
18
19 378 insurance companies). Additional medical costs that were made in a different
20
21 379 hospital or outside of hospitals (i.e. visits to the general practitioner, dietician,
22
23 380 physical therapist) were scored based on patients' answers in the Medical Cost
24
25 381 Questionnaire. The outcomes were scored in a numerical manner, for example 0, 1, 2
26
27 382 visits to the GP, etc. These results were analysed and valued based on a fixed
28
29 383 national cost as documented in the Dutch Health Care Institute guideline.
30
31 384 • Evaluation of costs: Unit costs used are derived from the guidelines commissioned by
32
33 385 the Dutch Health Care Institute (Zorginstituut Nederland). Moreover, additional unit
34
35 386 costs are gathered from the Dutch Health Care Authority (Nederlandse Zorg
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37 387 Autoriteit; <https://www.nza.nl/>)
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389 **Analysis of secondary outcome measures**

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49 390 Baseline characteristics of patients will be documented with mean/standard deviation or
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51 391 median/range, depending on normality. The number of desaturations, both
52
53 392 cardiopulmonary and general complications, interventions, total hospital stay and total costs
54
55 393 between both groups will be analysed with the independent t-test/Mann-Whitney U test.
56
57 394 Compliance of CPAP and opioids use will be evaluated with chi-square testing. Mixed model
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3 395 analysis will be performed to evaluate the weight loss, severity of OSA symptoms and CPAP
4
5 396 adherence at different time points. Predictive values for cardiopulmonary complications will
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7
8 397 be evaluated with logistic regression analysis, starting with a univariate analysis. All variables
9
10 398 with a significance level $p < 0.2$ will be included in a multivariate analysis. Within this
11
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13 399 analysis, only seven independent variables may be included as ten event cases are allowed
14
15 400 per dependent predictor. Statistical significance is defined as $p < 0.05$.

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18 401 To correct for potential confounder between these (non-randomized) cohorts, all outcomes
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20 402 will be analysed by propensity score matching or multivariate analysis, depending on the
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22
23 403 secondary outcome of interest (48).

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26 27 405 **Loss to follow-up or replacement of participants**

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30 406 Study participants will be replaced with new participants in case of A) cancellation of the
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32 407 surgery, B) uncompleted preoperative questionnaire, or C) when positive airway pressure
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34 408 treatment is switched to a different modality such as a mandibular advancement device.

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37 409 Patients who do not complete the postoperative questionnaire at 12 months after surgery
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39 410 due to other reasons, will be considered lost-to-follow-up.

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43 44 412 **Patient and public involvement**

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46
47 413 Patients and the public were not involved in the design, or conduct, of our research.

48
49 414 However, a non-profit organization for OSA patients was consulted in the final phase of
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51
52 415 designing this study. The organization underlined the need for this research and requested
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54 416 no significant changes to the protocol. In addition, OSA patients who previously underwent
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56 417 bariatric surgery in the hospital that initiated this study were invited to share their opinion
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58
59 418 on the questionnaires and OSA outcomes.
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56 420 **Ethics and dissemination**

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8 421 The Medical Ethics Committee United (MEC-U) approved this study, in accordance with the
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10 422 Dutch law Medical Research Involving Human Subjects Act (WMO), Medical Research in
11
12 423 Humans (MEC-U, W17.050). In addition, local Medical Ethics Committees of each
13
14
15 424 participating hospital also reviewed and approved the study protocol.
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17

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19
20 426 Findings of the POPCORN study will be disseminated to all disciplines that are involved in
21
22 427 care for bariatric surgery, through articles in peer-reviewed journals, national and
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24 428 international congresses, and revising the national guidelines of the Netherlands.
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30 430 **DISCUSSION**

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32 431 The POPCORN study is a prospective observational cohort study that evaluates the cost-
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34 432 effectiveness of two strategies of perioperative care in bariatric patients without a pre-
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36 433 existent OSA diagnosis: CPOX without extensive preoperative OSA screening vs. mandatory
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38 434 PG, potentially followed by CPAP treatment. The outcomes will enable the development of
39
40 435 new, evidence-based guidelines on perioperative care for bariatric patients with no known
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42 436 OSA. The secondary outcomes, such as (cardiopulmonary) complications, OSA-related
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44 437 symptoms and quality of life, will provide an overview of the correlation between cost-
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46 438 effectiveness and clinical outcomes that are highly relevant in the decision making for
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48 439 perioperative care in bariatric patients.
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53 440 Best practice regarding perioperative care in bariatric patient has been an ongoing
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55 441 debate for many years, with high prevalence and potential detrimental effects of undetected
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57 442 OSA on one side and substantial costs of related perioperative care and CPAP treatment on
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3 443 the other(27, 49, 50). No comparative studies between different perioperative strategies
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6 444 have been conducted to evaluate outcomes of postoperative complications or cost-
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8 445 effectiveness. In a recent review, conducted by the US preventative task force, no
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10 446 effectiveness of OSA screening in patients who are asymptomatic or who experience
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13 447 unrecognized symptoms was found(27). Despite improvements in intermediate outcomes
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15 448 such as AHI or sleepiness symptoms, no improvement in final health outcomes have been
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17 449 demonstrated, such as mortality or serious adverse events. The paucity in evidence
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20 450 regarding beneficial outcomes is especially relevant when cost-effectiveness is regarded. The
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23 451 obesity epidemic and its related costs are continuously expanding, and this underlines the
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25 452 need for optimal use of available health care resources. With no confirmative data on
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27 453 positive influence of OSA screening in bariatric patients with no known OSA, and
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30 454 approximately 700.000 bariatric procedures annually worldwide, clarification on this topic is
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32 455 needed.

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35 456 The perioperative strategies evaluated in the POPCORN study are both widely used in
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37 457 general practice and it is expected that results of this study will lead to evidence-based
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40 458 recommendations and guidelines.

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42 459 The strength of this study is that a general, bariatric population is evaluated. In both
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44 460 cohorts, large groups of bariatric patients are prospectively observed, while little exclusion
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47 461 criteria are applied. In addition, the follow-up period in this study that investigates a
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50 462 perioperative intervention is relatively long. Previous studies that describe preoperative
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52 463 assessment and treatment of OSA mainly reported prevalence of newly detected OSA and
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54 464 related adverse outcomes restricted to the direct perioperative period (51). The follow-up
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57 465 duration of one year after surgery enables us to investigate long-term clinical outcomes of a
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59 466 perioperative regime. Interesting comparisons are to be made between the preoperatively
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3 467 diagnosed OSA patients and the unscreened bariatric patients in terms of sleepiness
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5 468 symptoms, daytime productivity, general quality of life and health care resource utilization.
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8 469 Ideally, a randomized controlled trial would have been conducted, in which all
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10 470 patients would undergo a preoperative PG. Consecutive randomization would have
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12 471 determined the type of perioperative care: CPOX monitoring or treatment based on the PG
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14 472 outcome. However, this was considered unethical, as randomization into the CPOX cohort
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16 473 would result in withholding appropriate treatment from patients with confirmed OSA
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18 474 diagnosis, which is associated with many health care hazards (30, 31, 52). Despite the non-
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20 475 randomized design of the POPCORN trial, the large sample size will provide sufficient data to
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22 476 render a balanced statement that will be representable for the general bariatric population
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24 477 in the Netherlands. Furthermore, it is expected that implementation of these perioperative
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26 478 strategies is also feasible in countries other than the Netherlands.
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32 479 In addition to the non-randomized design of the POPCORN study, another limitation
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34 480 is that preoperative weight loss programs can result in changes in comorbidities. This can be
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36 481 particularly true for OSA, a comorbidity that is greatly influenced by weight loss. Each
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38 482 participating hospital applied local protocols which advocates weight loss before surgery,
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40 483 but in absence of a strict program we do not expect major changes in weight between
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42 484 preoperative (OSA) assessment and the surgical procedure. In conclusion, the POPCORN
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44 485 study will conclude which perioperative strategy is most cost-effective for obese patients
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46 486 scheduled for bariatric surgery and who have an unknown OSA status. These data will
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48 487 contribute to evidence-based guidelines which are urgently needed in this particular field of
49
50 488 bariatric care.
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59 490 **Contributors**
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3 491 EJH conceived and designed the study, with support of RJW, SMMDC, RNVV, DJS, AD, EGB,
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5
6 492 JWMG and FMHVD, who all contributed significantly to the study design. CALDR, KK and
7
8 493 GWJF reviewed and refined the research questions and search strategy. SVV wrote the first
9
10 494 draft of this manuscript. EJH is the principal investigator and SVV is the main investigator. All
11
12
13 495 authors critically reviewed the content and approved the final manuscript.
14

15 496

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19
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22

23 499

25 500 **Competing interests**

27 501 Not applicable for any of the authors
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30 502

32 503 **Data sharing statement**

34 504 After completion of the project, the research data will be stored and shared via EASY, a
35
36 505 certified sustainable data archive of Data Archiving and Networked Services (DANS). In EASY
37
38 506 each dataset will receive a Digital Object Identifier (DOI). The preferred formats of DANS
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40 507 (e.g. PDF/A, Unicode text, DB tables, SPSS Portable) and the Dublin Core Metadata standard
41
42 508 will be used.
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For peer review only

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3 663 **Legends**

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8 665 **Figure 1 – Flowchart of the POPCORN study**

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10 666 *PG* Polygraphy, *OSA* obstructive sleep apnea, *CPAP* continuous positive airway pressure
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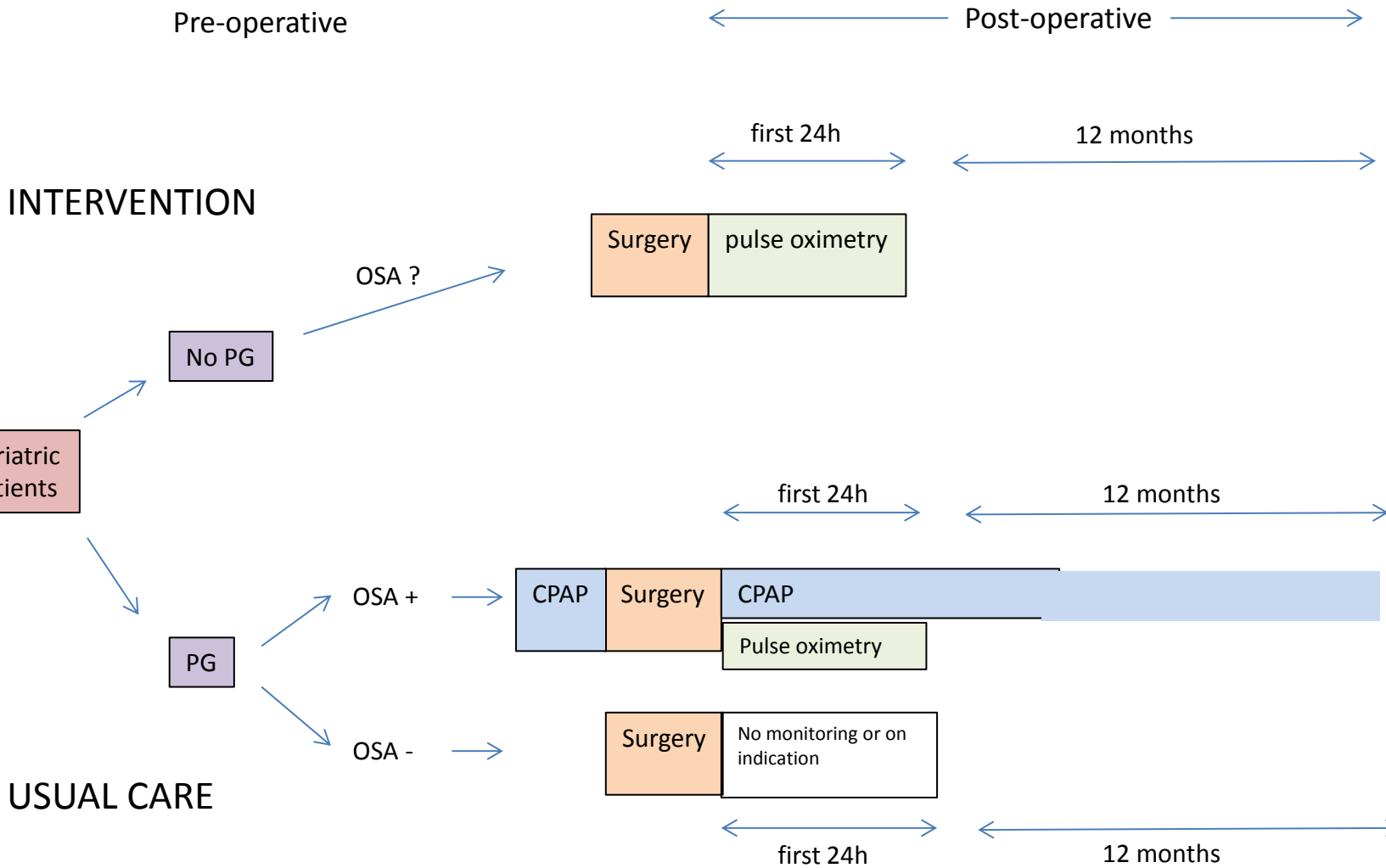


Figure 1. Flowchart of POPCORN study

PG polygraphy, OSA obstructive sleep apnea, CPAP continuous positive airway pressure