IMPACT

Impact of premedication on anxiety: a multi-centre, prospective observational cohort study

Registration	ClinicalTrials.gov NCT04103723
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Synopsis

Item	Description
Study Title	Impact of premedication on anxiety: a multi-centre, prospective observational cohort study
Study Short Name	IMPACT
Protocol version	Version 1.1, 17.10.2019
Registration with ClinicalTrials.gov	NCT04103723
Regulations	The implementation of this project is subject to § 15 of the medical professional code for doctors in North Rhine Westphalia (BOÄ NRW). The project will be carried out in accordance to the Declaration of Helsinki, ICH E6 Guideline for Good Clinical Practice (GCP), local rules, regulations and applicable requirements. The trial will follow the new European General Data Protection Regulation, which became applicable on 25 May 2018.
Funding	This is an investigator-initiated trial. This trial is funded by the German Society for Anaesthesia and Intensive Medicine (DGAI) and will be supported by the Department of Anaesthesiology, Medical Faculty RWTH Aachen, Germany
Risk Benefit Assessment	This is a solely observational trial, conducted during the clinical routine. The only study-related interventions are non-invasive questionnaires and one mobility task in elderly patients. We do not expect any harm related to the study. IMPACT may improve current premedication standards. It will provide evidence-based information to patients, physicians and patient advocacy groups with regard to alleviation of preoperative anxiety, improvement of functional patient outcome and the appropriate treatment of preoperative anxiety.
Key Words	Midazolam, Premedication, Preoperative anxiety, Surgery
Medical Study Rationale	Generalised premedication with benzodiazepines in all surgical patients has become questionable, regarding the risk-benefit assessment and the lack of evidence for this practice. One of the main justifications for premedication with benzodiazepines is its anxiolytic effect. Anxiety is associated with postoperative cognitive and behavioural changes, physiological reactions, increased need of anaesthetic drugs and altered perception of pain, mood swings, wound-healing problems and alteration of the immune system. However, several investigations revealed negative side-effects like dose-dependent sedation up to respiratory depression, prolonged extubation-time, impaired psychomotor function, paradox reactions, antegrade amnesia, increased pneumonia rates and postoperative

Item	Description
	delirium. In Germany midazolam is the most frequently administered premedication. A survey revealed that about one third of the German hospitals withhold a premedication in patients older than 74 years. The evidence for this practice, as well as the indiscriminate preoperative premedication for all adult patients is low.
Study Objectives	IMPACT aims to evaluate the clinical routine practice of premedication in German-speaking hospitals of the DACH countries and to estimate the influence of premedication on anxiety reduction.
Evaluation Criteria	**Primary endpoint** Change of the preoperative anxiety level, measured with the Amsterdam Preoperative Anxiety and Information Scale (APAIS), at arrival in the operating room before induction of anaesthesia. **Secondary endpoints** • Evaluation of the clinical routine practice of premedication • Perioperative haemodynamic and respiratory variables (blood pressure, heart rate and SpO2) • Frailty • Patient satisfaction on the first postoperative day • Functional and cognitive recovery • Early postoperative delirium • Perioperative change of well-being, pain and sleeping • Degree of patient cooperation immediate preoperatively • Amount of patients with rescue-midazolam application • Time to extubation • Change in the health-related quality of life assessment 30 days after surgery • Longer-term outcomes on 30th postoperative day including mortality and the new-onset of serious cardiac or pulmonary complications, acute stroke, or acute kidney injury • Subgroup analysis according to the baseline characteristics (comprising e.g. age-groups, anxiousness, comorbidity-subgroups) • Effects of baseline characteristics on the primary endpoint • Predefined perioperative complications on the surgery day • Hospital length of stay (LOS) and ICU-LOS
Study Design	International, multicentre, prospective, cohort study
Study Duration	**Duration of subject participation:** from surgery day until follow-up visit 30 days after surgery **Planned recruitment period:** The study recruitment period will be finished after enrolment of 4000 patients. The recruitment period is expected to last 12 months and to start in September 2019, followed by a follow-up period of 30 days for the last patient in. Data cleaning, processing, analysis and reporting is expected to last 5 further

Item	Description
	months.
Number of subjects	4000 patients in total
Number of sites	At least 25-30 sites from the German speaking countries (Germany, Austria and Switzerland)
Inclusion Criteria	1. Only legally competent patients 2. Written informed consent prior to study participation 3. Age ≥ 18, both genders 4. Elective surgery 5. Expected surgery duration ≥ 30 minutes 6. Planned general or combined regional and general anaesthesia 7. Planned extubation (or removal of airway device) at the end of surgery
Exclusion Criteria	1. Age < 18 years 2. Non-fluency in German language 3. Alcohol and/ or drugs abuse 4. Chronic benzodiazepine treatment 5. Intracranial surgery 6. Local or solely regional anaesthesia 7. Monitored anaesthesia care/ Sedation 8. Cardiac surgery 9. Ambulatory surgery 10. Repeated surgery, with previous participation 11. Expected continuous mandatory ventilation after surgery 12. Patients with severe neurological or psychiatric disorders 13. Refusal of study participation by the patient
Treatment and Visits	Patients, meeting all inclusion and none exclusion criteria, will be enrolled in the study, independent whether they will receive a premedication or not. **Visit 0 (Baseline Visit)** Patient information and written informed consent. Assessment of the patient demographics, vital data, medical history, laboratory values done in the clinical routine and study-specific baseline tests (anxiety, cognitive and functional assessment of independency, delirium assessment, health-related quality of life assessment, pain, sleeping and well-being, and frailty assessment). **Visit 1 (Surgery day, pre- and intraoperative)**

Item	Description
	Upon arrival into the operating room, assessment of patient's anxiety level, cooperation, pain, well-being, patient's vital data and the amount of received premedication and antihypertensive medication before anaesthesia induction. Patient's vital data shortly after induction. Anaesthesia- and surgery-related data, time to extubation. **Visit 2 (Surgery day, postoperative)** The patient will undergo further study-specific assessments in the post-anaesthesia care unit (PACU) or intensive care unit (ICU). Among others we will assess: Patients' vital data, pain, quality of well-being and predefined complications. **Visit 3 (First postoperative day)** A follow-up visit with study-specific assessments will be performed on the ward or ICU. Among others these will comprise: patient satisfaction, amnesia, cognitive assessment, delirium and predefined complications. **Visit 4 (30. postoperative day)** A follow-up visit with study-specific assessments will be performed via telephone or on ward, if the patient is still in hospital. The assessments will comprise among others: mortality, serious cardiac or pulmonary complications, acute stroke, or acute kidney injury health-related quality of life, cognitive and functional assessment and hospital/ICU length of stay data. The study participation ends after the follow-up call via telephone/ visit and the hospital database review on the 30st postoperative day.
Sample size and Statistics	The sample size is based on practical considerations and calculation examples. We assumed that a clinical relevant anxiety reduction is represented by 2 points of the APAIS score. Furthermore, from our experience, we assume that 2/3 of the cohort will receive premedication. Based on the APAIS validation study of Berth et al. we have calculated at a 5% significance level with power of 80%, using an unpaired t-test (equal variances) and with a 2:1 ratio of premedication vs. no premedication, that we need 207 patients for the overall premedication effect. We will further detect possible interaction of premedication with baseline characteristics. Applying statistical approved interaction models we need the 16-fold sample size of the overall effect. It corresponds to 3312 patients. Considering a dropout rate of 10% we would need 3680 patients. Taking these arguments into consideration, we believe that a total sample size of 4000 patients will provide reasonable and valid results for our study aims. All patients enrolled in this study will be analysed. Statistical analysis will be performed after database cleaning process and database lock. The influence of premedication on the primary endpoint *change of APAIS-score* will be analysed by a multivariable analysis of covariance considering several baseline characteristics. In case of significant interaction terms, subgroup analysis will be performed.

Abbreviations

APAIS	Amsterdam Preoperative Anxiety and Information Scale
ASA	American Society of Anesthesiologists
BMI	Body mass index
BOÄ	German medical professional code
CAM	Confusion Assessment Method
CRF	Case Report Form
DACH	Germany, Austria and Switzerland
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
GCP-V	Good Clinical Practice Act
IADL	Instrumental activities of daily living
ICH	International Declaration of Helsinki
ICU	Intensive care unit
IEC/IRB	Independent Ethics Committee/ Independent Review Board
ISF	Investigator Site File
LOS	Length of stay
NRS	Numeric rating scale
PACU	Post anaesthesia care unit
PI	Principal investigator
POD	Postoperative delirium
PP	Per protocol
RWTH	Rheinisch-Westfälische Technische Hochschule
SC	Steering Committee
SOP	Standard Operation Procedure

1 Study Rationale and Clinical Relevance

1.1 Description of evidence and medical need

At present, anxiolytic premedication with benzodiazepines is subject to controversial discussions among anaesthesiologists. On the one hand, preoperative anxiety has multi-factorial causes [1], which may lead to postoperative cognitive and behavioural changes, physiological reactions, increased need of anaesthetic drugs and altered perception of pain, mood swings, wound-healing problems and alteration of the immune system [2]. The association between state anxiety and postoperative delirium is still not fully elucidated, due to methodological hurdles [3]. On the other hand, an array of serious side effects of benzodiazepines premedication was described: Dose-dependent sedation up to respiratory depression, paradox reactions and antegrade amnesia, increased pneumonia rates and postoperative delirium (POD) [4-7]. The latter is associated with an increased mortality rate [8]. The reasons for POD are multifactorial [9, 10], but it is estimated that 30-40% of the POD cases may be avoided by preventive measures. These include the avoidance of benzodiazepines, as they potentially enhance and prolong a POD and cognitive dysfunction [8, 11]. A recently conducted randomised, placebo-controlled study in France including 1062 elective surgical patients < 70 years (mean age 50 years) showed no difference in regard to the patient satisfaction between three groups (2.5 mg lorazepam, placebo and no-premedication) [12]. Time to extubation and early postoperative recovery were significantly prolonged respectively worse in the lorazepam group than in the control- or placebo-group. Only 24 % of the patients showed an increased preoperative anxiety level and the subgroup analysis of these patients did not reveal a difference in the overall patient satisfaction [12]. A Cochrane analysis of the anxiolytic premedication effect on time to discharge in a day case surgery setting found similar discharge times between patients with premedication compared to the placebo group, though impaired psychomotor function after benzodiazepines application has been described [13]. Of note, this Cochrane analysis failed to report outcomes of efficacy of anxiolytic premedication and the included studies were of poor quality and very heterogeneous. Thus, a balanced judgement about risk and benefit of premedication was hindered. Another Cochrane review showed that there is a lack of evidence for premedication effects in elderly patients [9]. Recent guidelines for postoperative delirium suggest avoiding benzodiazepines for premedication notwithstanding the insufficient aforementioned evidence regarding this issue [14, 15]. However, in Germany midazolam is mainly used for premedication [16].

1.2 Rationale and Clinical Evidence

There is an urge for a large pragmatic prospective trial to clarify the evidence for or against the preoperative benzodiazepine application in clinical routine independent of age. Saller et al. have performed an online survey to evaluate premedication practice in Germany. The authors have contacted 922 in-hospital anaesthesia departments and 726 out-of hospital anaesthetists/anaesthesia departments in 2016. In total 290 of 310 received responses, were fully completed and analysed in this survey. The questionnaires revealed a mean and standard deviation (SD) age threshold of 74.3 (6.4) years in which 31.7% anaesthesia departments withhold premedication with benzodiazepines [16]. The evidence for this practice as well as the indiscriminate preoperative premedication is low.

2 Objectives

IMPACT aims to evaluate the clinical routine practice of premedication and to estimate the influence of premedication on anxiety reduction.

2.1 Primary endpoint

The primary endpoint is to evaluate, whether preoperative premedication with midazolam has an impact on alleviation of the patient's anxiety level at arrival in the operating room before anaesthesia induction.

2.2 Secondary endpoints

Evaluation of the clinical routine practice of premedication.

Evaluation of the differences between the patients receiving premedication or without premedication regarding:

- Haemodynamic and respiratory variables (blood pressure, heart rate and SpO2) before anaesthesia induction and at admission to the recovery room
- Frailty among the patients
- Patient satisfaction on the 1st postoperative day
- Functional and cognitive recovery on the 30th and 1st postoperative day, respectively
- Early postoperative delirium until the 1st postoperative day

- Perioperative change of well-being, pain and sleeping
- Patient cooperation directly preoperatively
- Amount of patients with rescue-midazolam application before anaesthesia induction
- Time to extubation
- Change in the health-related quality of life assessment 30 days after surgery
- Longer-term outcomes on the 30th postoperative day including mortality and the new-onset of serious cardiac or pulmonary complications, acute stroke, or acute kidney injury Subgroup analysis depending on the baseline characteristics (comprising e.g. age-groups, anxiousness, comorbidity-subgroups)
- Effects of baseline characteristics such as age, centre, sex, American Society of Anesthesiology (ASA) score, Charlson Comorbidity Index, and anxiety at baseline on the influence of the premedication on the primary endpoint
- Predefined complications on the surgery day according to the medical charts
- Hospital length of stay (LOS) and intensive care unit (ICU)-LOS

3 Investigational Plan

3.1 Study Design and Duration

3.1.1 Study Design

This is an international, multicentre, cohort study.

3.1.2 Study Duration

Duration of subject participation:
From surgery day until follow-up visit 30 days after surgery
Entire study duration:
The study recruitment period is expected to start in September 2019. It will be finished after enrolment of 4000 patients. The recruitment period is expected to last 12 months, followed by a follow-up period of 30 days for the last patient in. The study period may be extended to reach the calculated sample size of 4000 patients.
Data cleaning, processing, analysis and the draft of the manuscript are expected to last 5 further months.

3.1.3 Early termination of the trial

IMPACT is an observational cohort study. It is not expected that the trial has to be terminated prematurely due to any ethical or safety reasons.

3.1.4 Trial Sites

The study will be conducted in at least 25-30 European German-speaking sites. The sites will be recruited by advertisement on national and international congresses and meetings and via German Society for Anaesthesia and Intensive Medicine (DGAI). A list of the participating sites will be provided in the study registry and upon request at the corresponding author.

3.2 Study Population

3.2.1 Number of Patients

We will enrol 4000 patients in total, including the assumption of 10% drop-outs.

3.2.2 Inclusion Criteria

Subjects, fulfilling the following inclusion criteria are suitable for participation in the study:

1. Only legally competent patients
2. Written informed consent prior to study participation
3. Age ≥18 years, both genders
4. Elective surgery
5. Expected surgery duration ≥ 30 minutes
6. Planned general or combined regional and general anaesthesia
7. Planned extubation (or removal of airway device) at the end of surgery

3.2.3 Exclusion Criteria

Subjects, fulfilling one or more of the following exclusion criteria will not be included in the study:

1. Age <18 years
2. Non-fluency in German language
3. Alcohol and/ or drug abuse

4. Chronic benzodiazepine treatment
5. Intracranial surgery
6. Local or solely regional anaesthesia
7. Monitored anaesthesia care/ Sedation
8. Cardiac surgery
9. Ambulatory surgery
10. Repeated surgery with previous participation in the trial
11. Expected continuous mandatory ventilation after surgery
12. Patients with severe neurological or psychiatric disorders
13. Refusal of study participation by the patient

3.3 Subjects of Reproductive Potential

This trial will also include pregnant patients, as it is a solely observational trial. Pregnancy will be evaluated according to the clinical routine in the respective centre before each surgery.

3.4 Risk-Benefit Assessment

Risks: This is a solely observational trial, with detailed non-invasive assessment being the only study-related interventions. It will be conducted during the clinical routine of the participating centres. We do not expect any harm related to the trial. The premedication policy in the respective centres will only be recorded for each patient. Therefore, the risks are limited to data protection. Please see also section 6 below.

Benefits: We do not expect any significant individual benefit for the participants in this trial. However, the preoperative questionnaires might provide additional information for the attending personnel.

Furthermore, during the follow-up visits, the patients will get the additional possibility to give feedback or ask questions to the study personnel. This applies also for the 30 days follow-up, which is performed even after their hospital discharge.

For future patients, IMPACT may improve current premedication standards with regard to the anxiety, the functional patient outcome and appropriate treatment of preoperative anxiety. IMPACT will support regulatory guidance and policy makers and will provide evidence-based information to patients, physicians and patient advocacy groups.

4 Study Procedures

4.1 Recruitment

The patients will be screened and recruited after or before the preoperative anaesthesia consultation in the clinical routine by the study investigators. Of note, the patient recruitment will occur independent of the preoperative anaesthesia consultation in the routine, where the attending anaesthetists decide whether the patient will receive a premedication or not. Each participating centre will recruit as many patients as possible. Each screened patient will receive a consecutive screening number, beginning with the number 1. A screening/ enrolment log will be completed for each centre. This has to include all screened patients (including the screening failures and enrolled patients). The investigators will have to decide when they have the capacity to screen the patients for the study. On the screening days they will have to make every effort to include all eligible patients in order to reduce non-response bias. Therefore, we will provide the opportunity to reduce the amount of potential eligible patients for centres. Each centre will be asked to provide an estimate number of potentially eligible patients per day. Depending on their estimate of patient enrolment capacity per screening day, they will receive a number of 1-3 randomly allocated months of birth as an inclusion criterion for their study population from the project management team. This means that the centre will have to recruit the patients with *at least* these selected months of birth. This will reduce the potentially eligible patient number.

4.2 Overview Study Flow

All visits are presented in figure 1 according to the SPIRIT Statement.

The study will consist of 4 visits.

Visit 0 (Preoperative Screening and Baseline Visit)

This visit may be conducted within 30 days prior to surgery.

A written informed consent will be sought from the patient after comprehensive information about the study. The patient will receive the next consecutive patient identification number. This number will consist of 6 digits in the following format XXX-YYY. The first three digits will indicate the assigned centre number and the last three digits will indicate the patient in the respective centre and start with 001.

Thereafter, the investigators will perform the study-specific testing. This will comprise *baseline questionnaires* regarding the patient demographics, and medical history, anxiety, delirium, cognitive and functional assessment, health-related quality of life assessment, pain, sleeping, well-being and frailty assessment. The frailty assessment will also contain a *mobility task* (Timed Up and Go test) [17] and the most recent preoperative routine laboratory values (only if done in the clinical routine). In addition, the patient's vital data (blood pressure, oxygen saturation, heart rate) at rest will be assessed for all patients.

Visit 1 (Surgery day, pre- and intraoperative)

Upon arrival into the operating room, the investigator will assess the patient's anxiety level, cooperation, pain, and well-being. Furthermore, he will assess the patient's vital data and the amount of received premedication and antihypertensive medication before anaesthesia induction.

The attending anaesthetists and surgeons will perform the anaesthesia and surgery according to the clinical routine in the respective centre. The investigator will record the intraoperative surgery- and anaesthesia-related data. The attending anaesthetist will measure the time until extubation after cessation of the anaesthetic agent (inhalative or intravenous). The removal of a laryngeal mask will be equated to an extubation.

Visit 2 (Surgery day, postoperative)

The patient will undergo further study-specific assessments in the post-anaesthesia care unit (PACU) or ICU.

Visit 3 (First postoperative day)

A follow-up visit with study-specific assessments including the postoperative patient satisfaction and amnesia will be performed on the ward or ICU.

Visit 4 (30. postoperative day)

A follow-up visit with study-specific assessments will be performed via telephone or visit on ward, if the patient is still in hospital. The hospital LOS and ICU-LOS data will be collected from the hospital database.

5 Outcome measures

5.1 Variables

The primary aim of this study is to evaluate the clinical practice of premedication and estimate the influence of premedication on anxiety reduction. And secondary, to evaluate whether there is a difference in regard to the perioperative outcomes between the study groups with premedication and without.

5.1.1 Primary outcome measure:

The primary outcome variable of IMPACT is preoperative anxiety measured with the Amsterdam Preoperative Anxiety and Information Scale (APAIS) [18] at arrival in the operating room before induction of anaesthesia (1-2 minutes).

5.1.2 Baseline data and secondary outcome measures:

Visit 0 (within 30 days preceding surgery)

- Patient demographics (age, gender, weight, height, body mass index (BMI), smoking status, alcohol status, American Society of Anaesthesiologists (ASA) physical status).
- Patient's vital data at rest, if done in the clinical routine
- Patient's functional status of independency assessed by interview of the patient according to the National Surgical Quality Improvement Program (NSQIP) [19] (Independent, partially dependent, totally dependent).
- Pre-existing diseases and medical/ surgical history (including Charlson Comorbidity Index [20])
- Most recent preoperative routine laboratory values (only if done in the clinical routine): haemoglobin and haematocrit level; serum creatinine and serum albumin
- Study-specific testing: baseline assessment prior to surgery:
    1. Amsterdam Preoperative Anxiety and Information Scale (APAIS) (1-2 minutes) [18]
    2. Numeric rating scale (NRS) pain, sleeping quality and quality of well-being (1 minute).
    3. Confusion Assessment Method (CAM) (1-3 minutes) [21]
    4. Health-related quality of life assessment EQ-5D-5L (EuroQuol Group) (2-5 minutes) [22]

5. Patient's cognitive status assessed with the Mini-Cog [23] (1-3 minutes)
6. Frailty assessment according to Oresanya et al. [24] This includes beside the Mini-Cog, the medical history and laboratory values, history of falls, the timed "Up & Go" test [17].

Visit 1 (surgery day, operating room)

- Anxiety before anaesthesia induction in the operating room with APAIS (1-2 minutes) [18]
- Patient cooperation rated by the attending anaesthetist (via NRS)
- Numeric rating scale (NRS) pain, sleeping quality and quality of well-being (1 minute)
- Assessment of preoperatively administered sleeping medication the evening before surgery, premedication and antihypertensive medication on the surgery day
- Anaesthesia and surgery-related data (9-18 minutes)
    1. Drugs and kind of general anaesthesia
    2. Kind of regional anaesthesia
    3. Durations (anaesthesia/ surgery/ time to extubation)
    4. Kind of surgery
    5. Severity of surgery
    6. Rescue benzodiazepine application
    7. Patients vital data comprising peripheral oxygen saturation (SpO_2), systolic blood pressure (BP_{sys}), diastolic blood pressure (BP_{dia}), Heart rate
        - Upon arrival in the operating room

Once before leaving the operating room after extubation:

- NRS pain and quality of well-being directly after end of anaesthesia (1-2 minutes)
- Predefined intraoperative (first anaesthesia measure and last skin stich) complications according to the medical charts (2-5 minutes)

Visit 2

Study-specific testing within 0.5-1.5 hours after surgery in PACU and ICU:

a. Patients vital data (SpO_2, BP_{sys}, BP_{dia}, Heart rate) at arrival
b. SpO_2 < 95% with air at any time until 1.5 hours after surgery
c. NRS pain and quality of well-being 0.5-1.5 hours later (1-2 minutes)
d. Predefined complications according to the medical charts (1-2 minutes)

Visit 3

Study-specific testing on the first postoperative day:

a. Bauer satisfaction questionnaire (2 minutes) [25]
b. Amnesia (1 minute)

c. Mini Cog [23] (1-3 minutes)

d. CAM [21] or CAM-ICU [26] for patients on the intensive care unit (ICU), (1-3 minutes) and chart review for delirium

e. NRS pain, sleeping quality and quality of well-being, (1-2 minutes)

Visit 4

Study-specific follow-up on the 30th postoperative day (via telephone interview (if discharged)/ visit (if still in hospital) and hospital database review)

After hospital discharge, events will only be defined as present if they led to hospital re-admission or death.

1. Mortality within 30 postoperative days
2. EQ-5D-5L (2-5 minutes) [22]
3. Patient's functional status of independency [19]
4. Hospital LOS and ICU-LOS data collection from the hospital database.

- Analysis of the new-onset of serious cardiac or pulmonary complications, acute stroke, or acute kidney injury within 30 postoperative days (according to the following definitions:)

  Please note: after hospital discharge, events will only be defined as present if they led to hospital re-admission, death or occurred during the first hospital stay.

  1. ***Serious cardiac complication*** (Cardiac arrest: The absence of cardiac rhythm or presence of a chaotic cardiac rhythm requiring the initiation of CPR, which includes chest compressions. Myocardial infarction: Electrocardiography (ECG) changes, new elevation in troponin, or physician diagnosis. Signs of myocardial infarction in the autopsy.)
  2. ***Serious pulmonary complication*** (Pneumonia: Clinical or radiological diagnosis. Pulmonary embolism: Radiological diagnosis. Signs of pneumonia or pulmonary embolism in the autopsy)
  3. ***Acute Stroke*** (Defined as a new focal or generalised neurological deficit of >24h duration in motor, sensory, or coordination functions with compatible brain imaging and confirmed by a neurologist. Transient ischemic attack is not considered as acute stroke. Signs of stroke in the autopsy.)
  4. ***Acute kidney injury*** (Defined according to the AKIN classification [27] as AKI stage ≥2. This means increase of creatinine >2-3x from baseline within the hospital stay. Or urine output less than 0.5 ml kg^{-1} per hour for more than 12 hours. Or signs of acute kidney injury in the autopsy.)

6 Safety Data Collection, Recording and Reporting

All patients will receive routine care; no research related interventions will be introduced. The only study-related procedures in the IMPACT trial are the completion of questionnaires and the timed up and go test for frailty assessment. As such, the potential for adverse events or serious adverse events appears too remote to require their definition, assessment, documentation or reporting. There will only be an assessment of predefined not-study related complications in Visit 1,2 and 4.

Routine safety assessments will consist of the regular monitoring of intraoperative and postoperative vital data by the attending anaesthetist and the attending physicians or nurses on ward/ICU.

7 Study Termination

The study will be prematurely terminated for an individual subject in case of:

- Request of the patient or withdrawal of informed consent
- Patient did not meet the inclusion and/or exclusion criteria

IMPACT is an observational cohort study. Therefore, premature termination of the study resulting from ethical or safety concerns is most unlikely. In case of insufficient participant recruitment, the study period may be extended to reach the calculated sample size of 4000 patients.

8 Sample size and Statistics

8.1 Sample size

According to the aim of our multicentre observational cohort study, a sample size or power calculation is explorative rather than rigorous. The sample size based on practical considerations and calculation examples. Main objective of the study is to evaluate clinical practice of premedication and estimate the influence of premedication on anxiety reduction. We believe a clinical relevant anxiety reduction is 2 points of APAIS score. It means that one APAIS-item e.g. “I am worried about the anaesthetic” is changed from “extremely” (5 points) to “moderately” (3 points). Furthermore, from our experience, we assume that 2/3 of the cohort will receive premedication and 1/3 not [16]. Based on the validation study of Berth et al. [18] we assume a standard deviation of 4.79 (calculated pooled standard deviation). At a

5% significance level with power of 80%, using an unpaired t-test (equal variances) and with a 1:2 ratio of premedication vs. no premedication, we need 207 patients for the overall premedication effect. We will further detect possible interaction of premedication with a baseline characteristic e.g. sex. Relevant interaction is assumed one point of APAIS score that corresponds to a half of the overall effect of premedication. It means e. g. women would have an anxiety reduction of 2 points of APAIS score, but men only of 1 point. Therefore, applying statistical approved interaction models [28] we need the 16-fold sample size of the overall effect. It corresponds to 3312 patients. Considering a dropout rate of 10% we would need 3680 patients. Taking these arguments into consideration, we believe that a total sample size of 4000 patients will provide reasonable and valid results for our study aims.

8.2 Statistics

All patients enrolled in this study will be analysed. Statistical analysis will be performed after database cleaning process and database lock. The influence of premedication on the primary endpoint “change of APAIS-score” will be analysed by a multivariable analysis of covariance considering baseline characteristics such as age, centre, sex, ASA score, Charlson Comorbidity Index, APAIS score at baseline as well as significant interaction terms of premedication and baseline characteristics. In case of significant interaction terms, subgroup analysis will be performed. The importance of the independent factors will be investigated based on the parameter estimates and corresponding 95% confidence intervals. Similar methods will be used to evaluate secondary endpoints. Binary outcomes will be analysed by multivariable logistic regression model. Everything possible will be done to avoid missing data. In case of missing data multiple imputation will be used as well as different sensitivity analyses to secure the robustness of the results. We will use SAS 9.4 or a follow-up version for statistical analysis.

9 Ethical and Legal Aspects

The proposed study is an observational study. Therefore, no ethical concerns exist.

9.1 Independent Ethics Committees

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the Good clinical practice (GCP)-guideline and the German § 15 medical professional code (BOÄ, Berufsordnung für Ärzte) or the respective national regulations for other countries than Germany, respectively.

The study will be presented to the respective Independent Ethics Committee/ Independent Review Board (IEC/IRB) for each centre and an approval of the IMPACT study will be obtained prior to inclusion of any subject.

Any change in the study protocol and/or informed consent form will be presented to the respective IEC/IRB. They have to be approved by the IEC/IRB before implementation (except for changes in logistics and administration or when necessary to eliminate immediate hazards).

9.2 Informed Consent

A written informed consent will be obtained from the patients prior study-participation. The patients will voluntarily confirm their willingness to participate in the study, after comprehensive written and verbally information by an investigator. Patients will be informed about the requirements, concerning data protection and have to agree to the direct access to their individual data. Patients will get ample time and the opportunity to ask questions about the study, before signature. The patients will sign an informed consent form for study participation as well as disclosure of individual data. The patients will receive a copy of the consent from.

9.3 Post-study treatment

No specific post-study treatment will be performed after this study. All subjects will return to their standard medical care after the study, as needed. This also applies to subjects who withdraw their consent during the course of the study.

9.4 Subject privacy

Patients will be informed about data protection. All patient data will be pseudonymised and handed to third party anonymised. Access to encoded data or source documents will only be given to authorised bodies or persons (authorised staff, auditors, IEC/IRB) for validation of data. Also in case of publication confidentiality of collected data will be warranted.

9.5 Duties of the Investigator

The Principal Investigator (PI) will be responsible for the entire study conduction in his/her centre. The investigator will ensure that all sub-investigators and the assisting study personnel will be adequately qualified and informed about the study protocol, any amendments, and their study related responsibilities and functions. The investigator will maintain a study staff authorisation log, where the responsibilities of each person are listed.

9.6 Data Protection

The trial will follow the new European General Data Protection Regulation, which became applicable on 25 May 2018.

All subjects will be identified by a unique 6-digits patient identification number (see 4.2 Overview study flow – Visit 0). Each PI will safely keep a list, which will allow the identification of the pseudonymised patients.

The patient's informed consent, with their printed name and signature will be filed separately in the Investigator Site File (ISF).

Monitors, authorised representatives of the coordinating PI, or the respective IEC/IRB may require direct access to parts of the medical records relevant to the study, including participants' medical history, for data verification purposes. They are not allowed to make any copy of the data.

10 Data Quality Assurance

10.1 Quality control

Standardisation procedures will be implemented to ensure accurate, consistent, complete, and reliable data, including methods to ensure standardisation among sites (e.g., training, newsletters, investigator meetings, monitoring, centralised evaluations, and validation methods).

To prepare the investigators and to standardise performance, training will be held during an investigators' meeting before study start.

This study will be monitored by the team of the study management centre "Partnerinstitut des Klinischen Studienzentrums der DGAI" according to GCP guidelines and the respective standard operating procedures (SOPs).

10.2 Source documentation requirements

All collected patient data during the course of this clinical study should be entered and/ or filed in the respective patient file (CRF- Case Report Forms). The patient's participation in this study must be appropriately documented in the subject file with study number, subject number, date of subject information, and date of informed consent, date of each visit, and date of the telephone contact. Source data should be filed according to the GCP guidelines.

10.3 Data management

Investigators will enter the information required by the protocol into a web-based electronic data collection system (eCRF). The eCRF will be developed by the data manager for the study. Detailed information on the eCRF completion will be provided within an eCRF completion manual. In general, all persons who will enter data into the eCRF will be trained by an e-learning tool and telephone contacts with the study management centre. The access to the e-learning tool and to the eCRF is password controlled. Plausibility checks will be performed according to a data validation plan. Inconsistencies in the data will be queried to the investigators via the electronic data collection system; answers to queries or changes of the data will directly be documented in the system. Plausibility checks will be performed to ensure correctness and completeness of these data. The database will be closed, after all data are entered and all queries are solved.

10.4 Monitoring

On-site monitoring visits by the study management centre are not planned. The local PI will be responsible for careful data entries into the eCRF by his/her team. The PI will ensure that the data are entered carefully into the eCRF and verified regularly by his team. It will be the responsibility of the local PI to conduct periodic and random checks to ensure data quality in her/his centre. The study management centre will perform an online data monitoring continuously according to the SOPs of the study management centre. The participating sites will be urged to answer the queries, raised by the data monitoring team, in a timely manner.

11 Data Handling and Record Keeping

11.1 Conclusion of Documentation

By marking the eCRF as complete, the investigator confirms that all investigations have been completed and conducted in compliance with the clinical study protocol, and that reliable and complete data have been entered into the eCRF.

11.2 Corrections to data

If corrections in the paper-based CRF are necessary, the study staff should be instructed to make a correction by drawing only a single line through the error, leaving the incorrect entry legible. The subject should date the correction and initial it. The investigators should not make any changes to these documents.

11.3 Record keeping and archiving of documents

The local PI will keep the subject's files and original data as long as possible and according to the local methods and facilities. The local PI should maintain the trial documents as specified in the ICH-GCP-Guideline for at least 10 years. The local PI should take measures to prevent accidental or premature destruction of these documents.

Essential documents at the investigational site include (among other documents):

- Subject files including the paper-based CRF.
- Subject identification code list, which identifies the subject by number, name, and date of birth.
- A signed copy of the final clinical study protocol and any amendment.
- Signed informed consent forms.
- Copies of site investigators' and co-workers' curricula vitae.
- Copies of all direct correspondence with the respective IEC/IRB.

12 Publication Policy

The study will be registered and study results will be disclosed by the coordinating PI in one or more public clinical study registry(ies), according to national/international use. The registration will include a list of the investigational sites. The study results will be presented at national and international congresses or conferences and published in appropriate international peer-reviewed scientific journals.

As recommended by the International Committee of Medical Journal Editors (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html; accessed May 15, 2019), authorship will be considered based on contributions to

- conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Members of the Steering committee (SC) and the investigators, who fulfil those criteria and the below mentioned number of recruited and included patients (at least 75 per investigator) will be part of the Writing Group. The members of the Writing group and the "IMPACT Study

group" will be authors of the publications derived from the IMPACT study. Each participating centre with at least 25 included and completely documented patients will be able to designate one collaborator. For each further 25 included and completely documented patients one more collaborator can be designated. These collaborators will be mentioned in the IMPACT Study group and will be trackable via PubMed. Each participating centre will be able to nominate one co-author for the writing group for each 75 included and documented patients. In line with the principles of data preservation and sharing, the steering committee will, after publication of the overall dataset, consider all reasonable requests to make the dataset available in whole or part for secondary analyses and scientific publication. The SC will consider proposals for secondary analyses on the basis of the scientific quality of the proposal. Proposals will need to be revised and approved by the SC prior to submission.

13 Finance and Insurance

13.1 Financing

This trial is funded by the DGAI and will be supported by the Department of Anaesthesiology, Medical Faculty RWTH Aachen, Germany.

13.2 Insurance

Not applicable for this observational trial without any study-specific treatment.

14 Statement of compliance

Investigational Site(s)

I have thoroughly read and reviewed the clinical study protocol. Having understood the requirements and conditions of the clinical study protocol, I agree to perform the clinical study according to the clinical study protocol, the case report form, ICH-GCP principles (EU Directive 2001/20/EG), the Declaration of Helsinki, and the respective IEC/IRB requirements.

I also agree to

- sign this clinical study protocol before the study formally starts.
- wait until I have received approval from the appropriate IEC/IRB before enrolling any patient in this study.
- obtain informed consent for all patients prior to any study-related action performed.
- permit study-related monitoring, audits, or IEC/IRB review.
- ensure a timely response to any queries raised by the monitoring team

Furthermore, I understand that

- changes to the study protocol must be made in the form of an amendment that has the prior written approval of RWTH University and – as applicable – of the appropriate IEC/IRB.
- the content of the study protocol is confidential and proprietary to Medical Faculty, RWTH Aachen
- with my signature below, I also acknowledge receipt of the study protocol.

15 Signatures

The study protocol is accepted by

The Coordinating Investigator

Dr. med. Ana Kowark **Department of Anaesthesiology** **Medical Faculty, RWTH Aachen**	Aachen, 17.10.2019

The Biostatistician

Dr. med. (HU) Andras Keszei **Translational & Clinical Research Aachen (CTC-A)** **Medical Faculty, RWTH Aachen**	Aachen,

Local Principal Investigator

Name, Department	City, Date

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17 Figure 1

Figure 1 according to the SPIRIT Statement

	Enrolment	**Intraoperative**	**Postoperative**		
Visit**	***0***	***1***	***2***	***3***	***4***
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
ASSESSMENTS:					
Patients` demographics and medical history *(*age, gender, weight, height, BMI, smoking status, alcohol, ASA)	X				
Cognitive testing (Mini Cog (V1+3)	X			X	
Delirium testing (CAM)	X			X	
Anxiety (APAIS)	X	X			
Quality of Life (EQ-5D-5L)	X				X
Functional status of independency	X				X
Pain (NRS)	X	X	X	X	
Sleeping quality (NRS)	X				
Well-being (NRS)	X	X	X	X	
Patient cooperation (NRS)		X			
Frailty (Timed up & go test, history of falls, weight loss)	X				
Nausea and vomiting			X		
Amnesia				X	

	Enrolment	**Intraoperative**	**Postoperative**		
Visit**	***0***	***1***	***2***	***3***	***4***
Laboratory values, only if routinely done (Haematocrit, haemoglobin, creatinine, albumin)	(X)***				
Predefined complications		X	X		X
Anaesthesia related data (Drugs, type, duration, extubation-time)		X			
Surgery related data (Duration, kind and severity)		X			
Rescue midazolam application		X			
Patients vital data (SpO_2, RR_{sys}, HR)	(X)***	X	X		
Bauer satisfaction questionnaire				X	
Mortality					X
Postoperative serious cardiac or pulmonary complications, acute stroke, or acute kidney injury					X
Hospital length of stay					X
ICU length of stay					X

APAIS, Amsterdam Preoperative Anxiety and Information Scale; ASA, American Society of Anaesthesiologists physical status; BMI, body mass index; CAM, Confusion Assessment Method; EQ-5D-5L, health-related quality of life assessment; ICU, intensive care unit; NRS, numeric rating scale; RR_{sys}, systolic blood pressure; SpO_2, peripheral oxygen saturation.

**Visit 0: Preoperative screening and baseline visit, Visit 1: Surgery day: pre-and intraoperative, Visit 2: Surgery day: postoperative, Visit 3: first postoperative day; Visit 4: 30^{th} postoperative day

*** if done in clinical routine