# Analysis Plan

## Study title:

Intraoperative fresh gas flow and ventilation settings in Germany (NO-HARM)

## Version:

0.6

## Protocol version:

V1.2 09.03.2023

## Software

R version 4.1.0 (2021-05-18) -- "Camp Pontanezen" or later

Platform: x86_64-w64-mingw32/x64 (64-bit)

Packages used: ggplot2 version 3.3.6. or higher

### Database

Microsoft Excel 2016

## Study design

Pre- and postinterventional cross-sectional multi-center observational study. (See Protocol section 3.1.1.)

## Study objectives

NO-HARM aims to evaluate the intraoperative fresh gas flow and ventilation settings used by anesthesiologists in Germany. (See Protocol section 2.0)

### Primary endpoint

The primary outcome measure will include the fresh gas flow rate (FGF) during balanced anesthesia and in steady state measured as indicated by FGF reading (L/min) by the anesthesiologist.

The second measure of interest is tidal volume per ideal body weight (kg) (Vt) in ventilated patients. It will be measured as indicated by the anesthesiologist. (For calculation see section Data transformations).

### Secondary endpoints

The following are secondary outcomes of interest

- Proportion of use of desflurane, sevoflurane, isoflurane, nitrous oxide and propofol
- Proportion of patients ventilated with Vt ≥10 ml/kg ideal body weight
- Average PEEP level
- Average Driving pressure
- Average Peak inspiratory pressure
- Average End-tidal carbon dioxide ($etCO_2$)
- Average of Fraction of inspired oxygen ($FiO_2$)
- Respiratory rate

- Average FGF in induction phase
- Proportion of use of neuromuscular monitoring
- Proportion of use of temperature monitoring

All endpoints will be measured as indicated by the anesthesiologist.

## Study Flow

See Protocol section 3.5

## Study Population

The full analysis set includes all cases whose data has been recorded within at least one of the two assessments in the study. Descriptive analyses of all outcome data, patient characteristics, anesthesiologist characteristics and hospital/department characteristics will be performed on this set.

The balanced anesthesia set includes data of a subset of subjects for whom balanced anesthesia is recorded and are in steady state. Patients treated with heart-lung machine will be excluded from the set. The balanced anesthesia set will be used for the primary analysis of FGF.

The ventilated set includes data of a subset of subjects for whom ventilation mode volume-controlled, pressure-controlled or pressure-supported is recorded. Patients treated with heart-lung machine and one-lung ventilation will be excluded from the set. The ventilated set will be used for the primary analysis of Vt.

Additional analysis sets may be defined for additional exploratory analyses.

## Target variables

Data type and unit of recorded variables are tabulated in table 1.

| Variable | Description | Data type | Unit | Response set |
|---|---|---|---|---|
| cs_id | Cross-section identification | nominal | | I-Assessment 1; II-Assessment 2 |
| id | identifier | nominal | | positive integer |
| sex_a | sex anesthesiologist | nominal | | male;female;divers;not specified |
| experience | Anesthesiologist´s work experience | ratio | years | positive real |
| age_y | Patient´s age | ratio | years | positive real |
| age_m | Patient´s age | ratio | months | positive real |
| height | height patient | ratio | cm | positive integer |
| weight | weight patient | ratio | kg | positive real |
| sex_p | sex patient | nominal | | male;female |
| ASA | ASA | ordinal | | I,II,III,IV,V |
| type_surgery | type of surgery | nominal | | general; gynecology/urology; orthopedics/trauma; cardiac/thoracic; vascular; plastic surgery; head&neck; neurosurgery; other |
| CPB | heart-lung machine | nominal | | yes; no |

| | | | | |
|---|---|---|---|---|
| grade_surgery | procedure severity | ordinal | | minor; intermediate; major |
| type_anesth | Kind of anesthesia | nominal | | TIVA; balanced; regional; sedation; TIVA-regional; balanced-regional; sedation-regional |
| phase | OP phase | nominal | | induction; maintenance; extubation; not applicable |
| vent_mode | Ventilation mode | nominal | | volume-controlled; pressure-controlled; pressure-supported; O2-insufflation; none |
| airway_device | Type of airway device | nominal | | endotracheal tube; laryngeal mask; laryngeal tube; tracheostoma; O2-mask; none |
| hypnotic | Kind of hypnotic agent | nominal | | Propofol; sevoflurane; desflurane; isoflurane; nitrous oxide; other; combination; none |
| hypnotic_other | Kind of hypnotic agent if other | free text | | free text |
| position | Positioning for surgery | nominal | | Supine; prone; lateral; head up; head down |
| laparoscop | Laparoscopy | nominal | | yes; no |
| FGF | fresh gas flow | ratio | L/min | non-negative real |
| tidal_volume | tidal volume | ratio | ml | non-negative real |
| one_lung_vent | one-lung ventilation | nominal | | yes/no |
| resp_rate | respiratory rate | ratio | $min^{-1}$ | Non-negative integer |
| PEEP | positive end-expiratory pressure | ratio | mbar | Non-negative integer |
| Pmax | max ventilation pressure | ratio | mbar | Non-negative integer |
| Pplateau | plateau pressure | ratio | mbar | Non-negative integer |
| etCO2 | end-tidal $CO_2$ | ratio | mmHg | Non-negative integer |
| iFiO2 | inspiratory oxygen fraction | ratio | | Non-negative real |
| relaxation | current relaxation | nominal | | yes/no |
| relaxometry | use of relaxometry | nominal | | yes/no |
| temperature | use of temperature monitoring | nominal | | yes/no |
| FGFind | FGF in first 5 minutes | ratio | L/min | non-negative real |
| closed_system | Using a closed system | nominal | | yes; otherwise |
| hospital_id | hospital identifier | nominal | | positive integer |
| no_bed | number of beds in hospital | ordinal | | <300;301-600;601-900;>900 |

| | | | | |
|---|---|---|---|---|
| no_op_room | Number of operating rooms | ratio | | non-negative integer |
| no_doctors | number of physicians in department | ratio | | non-negative integer |
| no_specialists | number of specialists in department | ratio | | non-negative integer |
| sustainability | sustainability project | nominal | | yes/no |
| sustain_sp | Specify sustainability project | free text | | free text |
| teaching | teaching hospital | nominal | | yes/no |

Table 1: Data types of recorded data

# Data handling

Data will be merged into a one-row per patient table for both cross-sections.

## Data validation

All patient records will be double-checked for data entry errors.

## Data transformations

The following derived variables will be calculated

age_y = 0 if age_y is missing and age_m is non-missing

age_m = 0 if age_m is missing and age_y is non-missing

Patient_age (year) = age_y + age_m/12

BMI (kg/$m^2$) = weight/(height/100)^2

ideal_body_weight for men = 50 + 2.3*(height*0.393701 - 60) [Bender SP et al. Anesth Analg 2015;121:1231-9.; https://www.ardsnet.org/tools.shtml]

ideal_body_weight for women = 45.5 + 2.3*(height*0.393701 - 60)

Vt = tidal_volume / ideal_body_weight

Vt_ge10 = 1 if Vt >=10 else Vt_ge10 = 0

ASA_cat12_35 = 1 if ASA == ´I´ OR ASA ==´II´ else ASA_cat12_35 = 2

logFGF = log(FGF, base = exp(1))

log10FGF = log(FGF, base = 10)

Pdriving = Pplateau-PEEP

# Descriptive Statistics

Descriptive statistics of continuous characteristics will be tabulated using number of observations, mean, standard deviation, minimum, maximum and quartiles. Categorical variables will be described using number of observations and frequencies. Variables will be tabulated by cross-sectional assessment occasions. Continuous variables will be graphically presented using boxplots. Other visualization methods will also be considered.

Number and frequency of responding institutions will be tabulated. If available, data on all German hospitals will be considered in the analysis.

## FGF during balanced anesthesia

Descriptive statistics of the primary endpoint FGF will be performed by age, BMI, experience, FiO2 and FGFind using scatter plots or similar graphical techniques. Descriptive statistics of FGF will be tabulated by categories of CPB, phase, vent_mode, airway_device, position, laparoscop, hypnotic agent, one_lung_vent, ASA, ASA_cat12_35, closed_system, sustainability, teaching hospital, no_bed, no_op_room, no_doctors and no_specialists.

## Vt in ventilated patients

Descriptive statistics of the primary endpoint Vt will be performed by BMI, experience, resp_rate, PEEP, Pdriving, Pplateau and etCO2 using scatter plots or similar graphical techniques. Descriptive statistics of Vt will be tabulated by categories of ASA, ASA_cat12_35, CPB, phase, vent_mode, laparoscop, one_lung_vent and teaching hospital.

## Secondary outcome variables

### Use of desflurane, sevoflurane, isoflurane, nitrous oxide and propofol

Numbers and frequencies of the variable hypnotic agent will be tabulated by occasion and by sustainability project (yes/no), teaching hospital (yes/no), weight categories, type of airway device, type of surgery and anesthesiologist´s experience.

### Patients ventilated with Vt ≥10 ml/kg ideal body weight

Numbers and frequencies of Vt_ge10 will be tabulated by sex_p. Descriptive statistics of age, height, weight, BMI, PEEP, Pdriving, Plateau and etCO2 will tabulated by Vt_ge10.

### PEEP level

Descriptive statistics of PEEP will be performed by occasion, type_anesth, phase and by teaching, airway_device, type of surgery, vent_mode, one_lung_vent, position and laparoscop. Graphical presentation will be done to explore the relationship with BMI, etCO2 and Pdriving. A secondary analysis described elsewhere will explore PEEP levels in more detail.

### Peak inspiratory pressure

Descriptive statistics of Pmax will be performed by occasion, type_anesth, phase and by teaching, airway_device, type_surgery, vent_mode, one_lung vent, PEEP, Pdriving, position and laparoscop. Graphical presentation will be done to explore the relationship with BMI and tidal_volume.

### Driving pressure

Descriptive statistics of Pdriving will be performed by occasion, type_anesth, phase and by teaching, airway_device, type_surgery, vent_mode, one_lung_vent, PEEP, Pdriving, position and laparoscop. Graphical presentation will be done to explore the relationship with BMI and tidal_volume.

### End expiratory $CO_2$

Descriptive statistics of etCO2 will be performed by occasion and by teaching, airway_device, type_surgery, position and laparoscop. Graphical presentation will be done to explore the relationship with BMI, PEEP, Pmax, tidal_volume and resp_rate.

# Models

## FGF during balanced anesthesia

A multilevel linear regression model will be used to model FGF during balanced anesthesia. The log transformed FGF shall be modelled and the model will include intercepts for state and hospital, and predictors for teaching hospital, sustainability projects, airway device, measurement occasion, age, sex, BMI, and one-lung ventilation. However, predictors occurring less than 1% in the dataset will not be used in the model. We will include interactions between measurement occasion and teaching hospital, as well as measurement occasion and sustainability project.

$Y = \alpha_0 + \alpha_{state\ i} + \alpha_{hospital\ i} + \beta_{teaching} \cdot teaching + \beta_{sustainability} \cdot sustainability + \beta_{endo\ tube} \cdot endotracheal\ tube + \beta_{lmask} \cdot laryngeal\ mask + \beta_{ltube} \cdot laryngeal\ tube + \beta_{tstoma} \cdot tracheostoma + \beta_{Des} \cdot hypnoticDes + \beta_{Iso} \cdot hypnoticIso + \beta_{comb} \cdot hypnoticComb + \beta_{occ} \cdot cs\_id + \beta_{age} \cdot age + \beta_{sex} \cdot sex\_p + \beta_{bmi} \cdot BMI + \beta_{onelv} \cdot one\_lung\_vent + \beta_{occ\text{-}teaching} \cdot cs\_id \cdot teaching + \beta_{occ\text{-}sustainability} \cdot cs\_id \cdot sustainability + \varepsilon_i$

Y is log transformed FGF

$\alpha_{state} \sim normal(0, \sigma_{state}^2)$

$\alpha_{hospital} \sim normal(0, \sigma_{hospital}^2)$

β’s are fixed parameters

$\varepsilon_i \sim normal(0, \sigma^2)$

The subject indicator i is omitted after variable names for simplicity.

The model assumption of linear relationship with age and BMI will be graphically checked.

## Vt in ventilated patients

A multilevel linear regression model will be used to model Vt in ventilated patients. The model will include intercepts for state and hospital, and predictors for measurement occasion, teaching hospital, age, sex, BMI, ventilation mode, OP phase, laparoscopy, respiratory rate, PEEP, Pdriving and $etCO_2$. Predictors with insufficient variability, occurring less than 1% in the dataset, will, however, not be used in the model.

$Y = \alpha_0 + \alpha_{state\ i} + \alpha_{hospital\ i} + \beta_{occ} \cdot cs\_id + \beta_{teaching} \cdot teaching + \beta_{age} \cdot age + \beta_{sex} \cdot sex\_p + \beta_{bmi} \cdot BMI + \beta_{pres\text{-}contr} \cdot pressure\text{-}controlled + \beta_{pres\text{-}sup} \cdot pressure\text{-}supported + \beta_{ind} \cdot induction + \beta_{ext} \cdot extubation + \beta_{laparoscop} \cdot laparoscop + \beta_{resp} \cdot resp\_rate + \beta_{PEEP} \cdot PEEP + \beta_{Pdriving} \cdot Pdriving + \beta_{etCO2} \cdot etCO2 + \varepsilon_i$

Y is Vt

$\alpha_{state} \sim normal(0, \sigma_{state}^2)$

$\alpha_{hospital} \sim normal(0, \sigma_{hospital}^2)$

β’s are fixed parameters

$\varepsilon_i \sim normal(0, \sigma^2)$

The subject indicator i is omitted after variable names for simplicity.

The model assumption of linear relationship with BMI, respiratory rate, PEEP, Pmax, Pplateau and $etCO_2$ will be graphically checked.

### Missing data

For missing data on categorical variables a separate category will be used in the models. Missing data on continuous variables will be imputed using multiple imputations by chained equations using predictive mean matching. Rubin´s rule will be used to pool parameter estimates.

## Future analyses

Additional analyses of the collected data may be planned in the future. All analyses planned and carried out after finalizing data collection will be distinguished from the pre-planned analyses.