Statistical Analysis Plan

TRIAL FULL TITLE	Do positive suggestions delivered through a sound carrier during general anesthesia reduce post-operative pain, nausea and vomiting?
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2 Abbreviations and Definitions

ASA	ASA Physical Status System
HGHSH-5	5-item version of Harvard Group Scale of Hypnotic Susceptibility
Intraop.	Intra-operative
IQR	Interquartile range
NNT	Number needed to treat
NRS	Numeric rating scale
PACU	Post-Anesthesia Care Unit
Postop.	Post-operative
RCT	Randomized controlled trial
SAP	Statistical Analysis Plan
SD	Standard deviation
STAI-S	State Trait Anxiety Inventory Scale

3 Introduction

Communication is of great importance in all areas of general health and medicine. It can assist and improve medical therapies in order to improve health outcomes. Appropriate use of language and conversations tailored to the individual can help to find the most suitable treatment plan for each patient and to get the patient fit again. Positive suggestions can reduce adverse events like pain, nausea and vomiting.

There are some clues that communication has a positive impact on narcotized patients. Apparently, direct talking to the patient but also tape recordings appear to exert this effect.

3.1 Purpose of the analyses

These analyses will assess the impact of intra-operative therapeutically communication in comparison to a control group on post-operative pain levels, nausea and vomiting of surgical patients.

4 Study Objectives and Endpoints

4.1 Study Objectives

The aim of the study is to find out to what extent intra-operative positive suggestions delivered to a patient during surgery influence post-operative pain. This will be measured through the Numerical Rating Scale (NRS) and the patient's requirement of pain medication.

4.2 Endpoints

Primary endpoint:

Requirement of pain medication (if patient experiences a pain intensity of NRS $\geq$ 3) during the first 2 and 24 hours after surgery.

For evaluation of primary endpoint post-operative pain levels need to be evaluated by NRS at 0 min (admission to PACU), 15 min, 30 min, 45 min, 60 min, 75 min, 90 min, 105 min, 2 hours and 24 hours.

Secondary endpoints:

Maximum post-operative pain levels (NRS) within 2- and 24-hours post-surgery.

Post-operative nausea and vomiting (PONV) at 2- and 24-hours post-surgery.

Requirement of antiemetic medication in presence of post-operative nausea and vomiting (PONV) during the first 2 and 24 hours after surgery.

Post-operative comfort at 2- and 24-hours post-surgery.

Post-operative anxiety at 2- and 24-hours post-surgery.

Post-operative mental orientation grade after extubation, at admission to PACU and at 2- and 24-hours post-surgery.

Anesthesia wakeup time (time from end of surgery until extubation).

5 Study Methods

5.1 General Study Design and Plan

This study is a multicenter, double-blinded, randomized, controlled trial (RCT) of intra-operative therapeutically communication (delivered through headphones of an audio player) versus a control group. Randomization is done by lottery.

	STUDY PERIOD													
	ENROLMENT	RANDOMIZATION	BASELINE	DURING SURGERY	ADMISSION TO PACU	POST-OPERATIVE								
TIME POINT	Prior inclusion	After inclusion	Baseline	Day of surgery	0	15 min	30 min	45 min	60 min	75 min	90 min	105 min	2 h	24 h
ENROLMENT:														
Eligibility screen	X													
Informed consent	X													
Randomization		X												
INTERVENTIONS:														
Audio suggestion				X										
Placebo audio suggestion				X										
ASSESSMENTS:														
Demographic & medical data			X											
Type of surgery			X											
HGHSH-5, Apfel score			X											
Duration of surgery				X										
NRS			X		X	X	X	X	X	X	X	X	X	X
Pain medication				X									X	X
PONV					X	X	X	X	X	X	X	X	X	X
Wengritzky score													X	X
Antiemetic medication				X									X	X
Comfort scale													X	X
Anxiety (STAI-S)			X										X	X
Mental Orientation				X[1]	X								X	X
Anesthesia wakeup time				X[1]										

[1] after extubation

5.2 Inclusion-Exclusion Criteria and General Study Population

Inclusion criteria:

Patients who have neurosurgery or abdominal-gynecological surgery: Duration of the surgery should be between 1 to 3 hours and the patient must obtain volatile anesthesia. Moreover, the patient has to be aged between 18 and 70 years and must have a risk of post-operative nausea and vomiting (PONV), measured via the "Apfel-Score", of ≥ 2.

Exclusion criteria:

- Massive impairment measured with ASA-Score > 3
- Post-operative requirement of ventilation or requirement of intensive care treatment
- Patients with an epidural catheter
- Patient refuses to participate

5.3 Randomization and Blinding

Patients are assigned in a 1:1 ratio to intervention or control group by simple randomization technique (drawing lots), for each study center.

This is a double-blinded trial. Assignment to treatment group and conduct of study procedure is performed by independent study personnel, which is not involved in conduct of general anesthesia or post-operative treatment of pain. Medical personnel which is involved in treatment of the patient has no information about group allocation. Headphones of the audio player for therapeutically communication are placed on the ears of patients in control group as well (whereas no audio file will be played).

5.4 Study Variables

	Baseline	End of surgery (post extubation)	Post-surgery every 15 min (from admission on PACU until 1 h, 45 mins)	Post-surgery at 2 h after admission on PACU	Post-surgery at 24 h after admission on PACU
History[1]	x				
Age, Sex	x				
NRS[2]	x		x	x	x
HGSHS-5[3]	x				
STAI-S[4]	x			x	x
Apfel[5]	x				
Duration of surgery		x			x
Intra-operative analgesic drugs[6]		x			
Intra-operative analgesic co-medication[7]		x			x
Post-operative analgesic drugs[8]				x	x
Post-operative analgesic co-medication[9]				x	x
PONV[10]			x	x	
Wengritzky[11]				x	x
Intra-operative antiemetic medication[12]		x			
Post-operative antiemetic				x	x

	Baseline	End of surgery (post extubation)	Post-surgery every 15 min (from admission on PACU until 1 h, 45 mins)	Post-surgery at 2 h after admission on PACU	Post-surgery at 24 h after admission on PACU
medication[13]					
Comfort[14]				x	x
Mental Orientation[15]		x	At admission to PACU	x	x
Anesthesia wakeup time[16]		x			
Adverse Events[17]		x	x	x	x

(1) **History** – Medical condition (diseases, medication). Type of surgery.

(2) **NRS** (Numeric rating scale) – Items are measured ranging from 0 to 10 for which 0 = no pain and 10 = worst pain imaginable.[1]

(3) **HGSHS-5** – 5-item version of Harvard Group Scale of Hypnotic Susceptibility (ranging from 0 to 5).[2]

(4) **STAI-S** – State Trait Anxiety Inventory Scale (ranging from 20 to 80).[3]

[1] Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken) 2011;63 Suppl 11(S11):S240-52.

[2] Bongartz W. German Norms for the Harvard Group Scale of Hypnotic Susceptibility, Form a. Int J Clin Exp Hypn 1985;33(2):131-9.

[3] Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). Br J Clin Psychol 1992;31 (Pt 3):301-6.

(5) **Apfel** – Apfel score of risk for postoperative nausea and vomiting (ranging from 0 to 5).[4]

(6) **Intraop. analgesic drugs** – Sum of sufentanil dose, sum of fentanyl dose, sum of piritramide dose, sum of metamizole dose, sum of paracetamol dose, sum of COX2-inhibitor (cyclooxygenase 2) dose. Cumulative dosage of non-opioids as percentage of maximum daily dose (maximum daily doses for conversion: metamizole=4000mg, paracetamol=4000mg, ibuprofen=2400mg, diclofenac=150mg).

(7) **Intraop. analgesic Co-medication** – Sum of clonidine dose.

(8) **Postop. analgesic drugs** – Sum of opioid dose represented as morphine equivalents (factors for conversion: piritramide=0.7, tilidine=0.2, tramadol=0.1, oxycodone=2.0). Sum of metamizole dose, sum of paracetamol dose, sum of ibuprofen dose, sum of diclofenac dose, sum of COX2-inhibitor (cyclooxygenase 2) dose. Cumulative dosage of non-opioids as percentage of maximum daily dose (maximum daily doses for conversion: metamizole=4000mg, paracetamol=4000mg, ibuprofen=2400mg, diclofenac=150mg).

(9) **Postop. analgesic Co-medication** – Sum of clonidine dose.

(10) **PONV** (post-operative nausea and vomiting) – Items are 'true' or 'false', depending on patient reporting nausea or vomiting within the specified time interval.

(11) **Wengritzky** – PONV impact scale score (ranging from 0-6), a score of $\geq$ 5 defines clinically important PONV.[5]

(12) **Intraop. antiemetic medication** – Sum of granisetron dose, sum of ondansetron dose, sum of dexamethasone dose, sum of droperidol dose.

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[4] Apfel CC, Heidrich FM, Jukar-Rao S, et al. Evidence-based analysis of risk factors for postoperative nausea and vomiting †. Br J Anaesth 2012;109(5):742-53.

[5] Myles PS, Wengritzky R. Simplified postoperative nausea and vomiting impact scale for audit and post-discharge review. Br J Anaesth. 2012 Mar;108(3):423-9.

(13) **Postop. antiemetic medication** – Antiemetics Milligram Equivalents (ondansetron = 4, dexamethasone = 4, droperidol = 1.25, metoclopramide = 20, dimenhydrinate = 50).[6]

(14) **Comfort** – Scale items are measured ranging from 0 to 10 for which 0 = no comfort and 10 = highest comfort.

(15) **Orientation grade** – Items are 'full', 'mostly', 'partly' and 'not'. Patients will be asked for their name, location and day of week (3 correct answers = full, 2 correct answers = mostly, 1 correct answer = partly, no correct answer = not).

(16) **Anesthesia wakeup time** – Time from end of surgery until extubation.

(17) **Adverse events** – all adverse events during study visits will be documented.

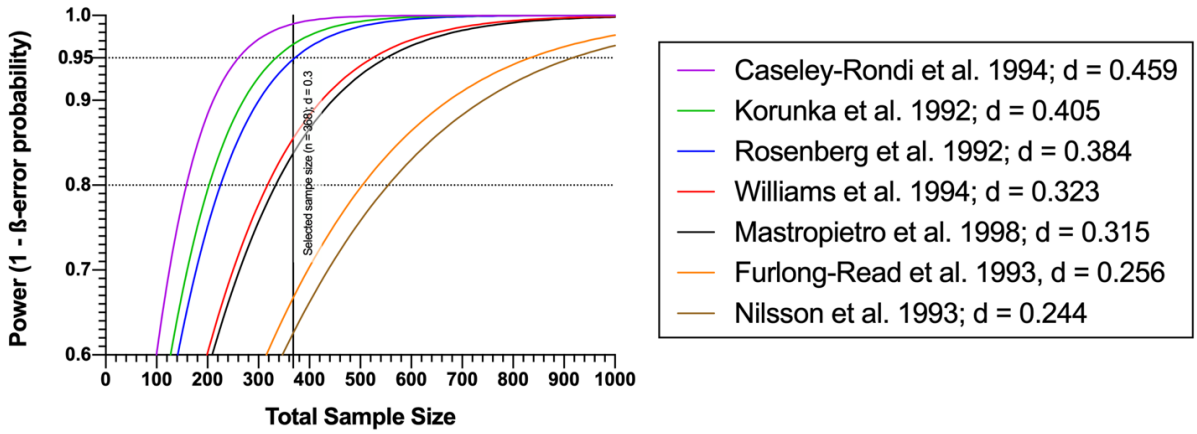
6 Sample Size

On basis of a 1:1 randomization ratio, we calculated that a planned sample of 368 patients would provide the trial with approximately 80% power to detect a difference in postoperative pain therapy on the basis of an effect size of 0.3 at a two-sided alpha level of 0.05. With 5 participating study centers, approximately 70-80 patients need to be included per center.

The sample size calculation is based on a previously published meta-analysis by Rosendahl et al.[7] Sample size calculation for a power of 80% was done using G*Power software (University Dusseldorf, Dusseldorf, Germany, http://www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower.html).

[6] Apfel CC, Korttila K, Abdalla M, et al. A Factorial Trial of Six Interventions for the Prevention of Postoperative Nausea and Vomiting. N Engl J Med 2004; 350(24): 2441-51.

[7] Rosendahl J, Koranyi S, Jacob D, Zech N, Hansen E. Efficacy of therapeutic suggestions under general anesthesia: A systematic review and meta-analysis of randomized controlled trials. BMC Anesthesiol 2016;16(1).



7 General Considerations

7.1 Timing of Analyses

The final analysis will be performed after participation of 400 patients in this study.

7.2 Analysis Populations

Analysis will be performed 'per protocol'. All subjects who did not substantially deviate from the protocol as to be determined on a per-subject basis at the trial steering committee immediately before data base lock, will be included in the final analysis.

7.3 Covariates and Subgroups

If applicable, covariates for analyses (e.g. multivariate regression analysis) will be chosen whether they are expected to have an important influence on endpoints of this study according to literature recherche. Selection of these variables for the final model will be performed by a forward stepwise selection process.

Analyses of subgroups in accordance with covariates which may have an important influence on endpoints may be performed. Covariates will be selected by literature recherche.

7.4 Missing Data

Missing data will be excluded from each specific statistical analysis and reported.

7.5 Interim Analyses and Data Monitoring

Interim analyses are not planned.

7.6 Multi-center Studies

Patients from all 5 participating study centers will be combined for final analysis. This will be performed by the coordinating study center, University Knappschaftskrankenhaus Bochum. Therefore, data of each study center will be transferred to Bochum. Before transfer, data will be pseudonymized. An excel sheet for documentation of study variables will be provided for each study center.

8 Summary of Study Data

All continuous, normally distributed variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation (SD). All continuous, not-normally distributed variables will be summarized using the following descriptive statistics: n (non-missing sample size), median, interquartile range (IQR). The frequency and percentages (based on the non-missing sample size) of observed levels will be reported for all categorical measures of baseline characteristics. Moreover, for dichotomous outcomes point estimates and 95% CI and absolute differences as difference of percentage points and 95% CI will be calculated. In general, all data will be listed, sorted by site, treatment and subject, and when appropriate by visit number within subject. All summary tables will be structured with a column for each treatment in the order (Control, Intervention) and will be annotated with the total population size relevant to that table/treatment, including any missing observations.

8.1 Protocol Deviations

Major deviations are defined as follows:

- Deviation from main study procedure (audio suggestion) like discontinuation during surgery of more than 10 minutes, wrong treatment in contrast to randomization.
- Violation of inclusion and exclusion criteria.
- Missing informed consent.
- Malfunction of the audio player.
- Unexpected transfer to ICU.

Patients with major deviations will be excluded in the 'per protocol' analysis (see section 7.2).

8.2 Demographic and Baseline Variables

The following variables are considered to be demographic and baseline:

- Medical condition (diseases, medication). Type of surgery.
- Age, sex.
- Pre-operative NRS, HGSHS-5, STAI-S, and Apfel score.
- Duration of surgery.
- Intra-operative analgesic drug dose (opioids and non-opioids).
- Intra-operative analgesic co-medication.
- Intra-operative antiemetic medication.

Demographic and baseline values will be grouped by treatment groups. If applicable, subgroups may be used in accordance with section 7.3. Differences between groups will be investigated as follows: Student's t-test for normally distributed continuous variables, Mann-Whitney U test for not-normally distributed continuous variables, and Pearson's chi-squared test for categorical variables. Tests will be performed two-sided. A p-value of less than 0.05 will be considered to be statistically significant. Demographic and baseline values with p-value will be presented as a table.

9 Efficacy Analyses

For statistical analyses of outcome variables, values will be grouped by treatment groups. If applicable, subgroups may be used in accordance with section 7.3. All continuous, normally distributed variables will be summarized using the following descriptive statistics: n (non-missing sample size), mean, standard deviation (SD). All continuous, not-normally distributed variables will be summarized using the following descriptive statistics: n (non-missing sample size), median, interquartile range (IQR). The point estimates and 95% CI (based on the non-missing sample size) of observed levels and absolute difference of percentage points with 95% CU as well will be reported for categorical measures.

Differences between groups will be investigated as follows: Student's t-test for normally distributed continuous variables, Mann-Whitney U test for not-normally distributed continuous variables, and Pearson's chi-squared test for categorical variables. Tests will be performed two-sided. A p-value of less than 0.05 will be considered to be statistically significant.

Effect sizes for outcome variables will be described by Cohen's d with 95% confidence interval. For dichotomous outcome variables, differences between groups will be expressed as number needed to treat (NNT).

If applicable, all assumptions for regression models will be assessed by viewing plots of the residual values. Analyses of categorical efficacy measures will be performed using logistic regression. Multivariate regression models will be built by a forward stepwise selection process of possible covariates in accordance to literature research.

Results of efficacy analyses will be presented as tables or in text in the final publication(s), including p-values, effect size and NNT.

9.1 Primary Efficacy Analysis

Analysis of primary endpoint (post-operative pain medication at 2- and 24-hours post-surgery) will be performed in accordance with section 9.

9.2 Secondary Efficacy Analyses

Analyses of secondary endpoints will be performed in accordance with section 9.

9.3 Exploratory Efficacy Analyses

Further analysis of exploratory analyses will be performed in accordance with section 9.

10 Safety Analyses

All adverse events which are directly connected to study procedures will be documented and reported by appropriate statistical methods in accordance with section 9.

Due to the non-invasiveness of the study procedure, no severe adverse events are expected to occur.

11 Figures

The following figures will be considered for presentation in final publication(s):

- Post-operative pain levels (NRS) at 2- and 24-hours post-surgery.
- Post-operative pain levels (NRS) over course of time: pre-operative, at 0 min (at admission to PACU), 15 min, 30 min, 45 min, 60 min, 75 min, 90 min, 105 min, 2 hours and 24 hours.
- Usage of pain medication (opioids as morphine equivalents, non-opioids as percentage of maximum daily dose) at 2 and 24 hours after admission to PACU.
- Post-operative nausea and vomiting (PONV) at 2- and 24-hours post-surgery.
- Requirement/Dosage of antiemetic medication in presence of post-operative nausea and vomiting (PONV) during the first 2 and 24 hours after surgery.
- Post-operative comfort at 2- and 24-hours post-surgery.
- Post-operative orientation grade after extubation, and at 2- and 24- hours post-surgery.

Figure types will be chosen by the trial steering committee and statistician. Measures of central tendency will be presented as mean (normally distributed continuous variables) and median (not-normally distributed continuous variables). Error bars will be presented as SD for normally distributed continuous variables and as IQR for not-normally distributed continuous variables. Bootstrapping technique with resampling may be considered for presentation of non-parametric values with mean and 95% confidence interval, where applicable.

12 Reporting Conventions

P-values $\geq$0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as '<0.001'. The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data. Estimated parameters,

not on the same scale as raw observations (e.g. regression coefficients) will be reported to 3 significant figures.

13 Technical Details

Statistical analyses will be performed using the following computer software. The used version number at the time of writing will be reported.

- The R Project for Statistical Computing (The R Foundation for Statistical Computing, Vienna, Austria).
- SPSS Statistics (IBM Corp., Armonk, New York, NY, USA).
- GraphPad Prism (GraphPad Software Inc., San Diego, CA, USA).

Any outputs will have

- The date and time included
- The name of the code file that produced the analysis
- The author
- A log capturing the version of the software and any external add-on code used.

At the start of any code file there will be a set of comments that give

- the author
- the date and time of writing
- references to inputs and outputs
- reference to any parent code file that runs the child code file