Research proposal

The influence of Pain Catastrophizing, State Anxiety, Need for Information and Depression on postoperative Pain Intensity and Functional Recovery at home after surgical third molar removal under anesthesia.

A prospective observational cohort study

De invloed van pijncatastroferen, angst, informatienood en depressie op postoperatieve pijn en functioneel herstel thuis na het verwijderen van wijsheidstanden onder anesthesie.

Een prospectieve observationele cohort studie.

Short title: Psychological predictors explaining postoperative pain after third molar surgery

Acronym-ID: PPEPP version-1

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Abbreviations

VAS-P: Visual Analogue Scale – Pain

VAS-P-expected: Visual Analogue Scale expected Pain

FRI: Functional Recovery Index

BMI: Body Mass Index

SES: Socio-economic Status

ISRCTN: International Standard Registerend Clinical/social sTudy Number

PCS: Pain Catastrophizing Scale

ASA: American Society of Anesthesiologists

NSAID: Non-Steroidal Anti-Inflammatory Drugs

APAIS: Amsterdam Preoperative Anxiety and Information Scale

HADS: Hospital Anxiety and Depression Scale

MAC: Minimum Alveolar Concentration

ECG: Electrocardiogram

NNT : Nasotracheal tube

PACU: Post Anesthesia Care Unit

PRN: *Pro Re Nata* (“when needed”)

ICF: Informed Consent Form

GDPR: General Data Protection Regulation

1. Summary

Background and rationale

Third molar extraction is a frequent procedure in young healthy individuals. Although it is considered minor surgery, a lot of patients suffer from postoperative pain, disability and consequently this has an impact on functional recovery. Several psychological factors might be associated with the postoperative pain perception and functional recovery.

Design

A prospective observational cohort study up to seven days postoperatively.

Setting

ZiekenhuisNetwerkAntwerpen (ZNA) Middelheim, Lindendreef 1, 2020 Antwerpen Belgium [and ZNA Jan Palfijn, Lange Bremstraat 70, 2170 Merksem Belgium]

Aims of the study

A. To assess postoperative pain intensity and functional recovery during the first seven days after ambulatory surgery under anesthesia for third molar extraction;
B. To determine the impact and to identify possible associations between the following modifiable psychological factors: 1. catastrophizing; 2. state anxiety; 3. need for information; 4. depressive thoughts related to postoperative pain intensity scores and functional recovery up to seven days after surgery at home.

Methods

One hundred and forty-five (sample size) patients aged between 18 – 40 years undergoing third molar surgery under anesthesia in day care. All patients will receive standardized anesthesia and pain management (in hospital and at home).

Primary analysis:

1. Primary outcome parameter: pain score assessments at home using a Visual Analogue Scale – Pain (VAS-P) during 7 days postoperatively;
2. Secondary outcome parameter: functional recovery at home during 7 days postoperatively using the Functional Recovery index (FRI).
3. Pain medication adherence at home during 3 days postoperatively.

Secondary analysis:

Multivariable regression analysis or generalized linear model

Outcome variables: pain score assessments VAS-P and FRI during 7 days postoperatively at home.

Predictor variables: 1. age, 2. gender; 3. body mass index (BMI); 4. Socio-economic status (SES); 5. smoking history; 6. baseline pain (VAS-baseline-P); 7. analgesia medication use before surgery; 8. the patient's expected pain of the surgery (VAS-P-expected pain); 9. pain catastrophizing; 10. state anxiety; 11. need for information; 12. depression; 13. the use of local anaesthetic during the procedure; 14. surgical characteristics.

Trial registration

At https://www.isrctn.com = International Standard Registered Clinical/soCial sTudy Number (ISRCTN).

2. Introduction & Rationale

Third molar removal surgery is one of the most frequent carried out procedures on young healthy individuals and normally third molars are extracted before the age of 40 years with a peak between 18 and 25 years old [1-4].

Despite being considered as minor surgery, complications like postoperative pain, swelling, trismus, haemorrhage, alveolar osteitis, periodontal damage and soft-tissue infection among others, are frequently reported [5-7].

In general acute postoperative pain often remains undermanaged with up to 75% of the patients still experiencing pain in the immediate postoperative period [8-10]. Postoperative pain in itself is strongly associated with surgical complications [11] and undertreated acute pain is a risk factor for developing chronic or persistent postoperative pain [12-14]. Furthermore a strong relation exists between moderate to severe postoperative pain and patient dissatisfaction [15].

After third molar removal, patients suffer on average up to 7 days of discomfort or disability [16]. Also the patient's quality of life is significantly affected, particularly during the first three days after surgery, with acute pain as the most recorded domain (91%) impacting the quality of life. Other often recorded domains were functional limitations (76%), physical disability (75%), social disability (71%), psychological discomfort (70%) and psychological disability (69%)[17]. This definitely needs further scrutiny.

Although health-related quality of life assessments are often used as outcome parameter in clinical trials, they are not specifically designed to be used after ambulatory surgery [18]. This in contrast with a specific well validated and reliable tool such as the Functional Recovery Index (FRI)[19] with convergent validity with pain scores.

A recent meta-analysis identified that younger age, female sex, a history of depressive symptoms, a history of anxiety, sleep difficulties, higher body mass index (BMI), presence of preoperative pain and the use of preoperative analgesia were predictors of poor postoperative pain control [20].

Although a lot of progress has been made in the last decades with the emergence of procedure-specific pain-treatment recommendations to improve postoperative pain [21], not all variability in pain scores can be explained by surgical, anesthetic and pain management factors.

Indeed, the perception and severity of acute postoperative pain intensity assessments might be determined by various biological, socio-cultural and psychological factors [22,23]. In this study we are specifically interested in psychological factors like pain catastrophizing, anxiety, need for information (coping style) and depressive thoughts.

Pain catastrophizing is defined as: *'the tendency to magnify the threat value of pain stimulus and to feel helpless in the context of pain, and by a relative inability to inhibit pain-related thoughts in anticipation of, during or following a painful encounter' [24]* and as such it has been shown to be an important predictor in both chronic and acute pain contexts [25-30] and explains between 7% and 31% of variation in pain scores [24]. Furthermore it has been associated with health-related quality of life judgments [31]. Pain catastrophizing can be assessed by a well validated tool, the Pain Catastrophizing Scale (PCS), [32,33] which consists of three components: magnification, rumination and helplessness.

Furthermore it is well known that state anxiety is an important predictor of higher postoperative pain scores [25,34,35] and anxiety is further associated with depression and chronic pain conditions [36,37]. Therefore it has been hypothesized that depression is associated with higher postoperative pain scores [36,37].

Furthermore, pain catastrophizing might share together with anxiety and depression a significant amount of variance explaining postoperative pain [24]. This definitely needs further investigation.

Also a patient's coping style (active or avoidance) is related to the need for information (monitor – blunting) [38,39] and a negative coping style (avoidance) might be related with higher pain scores [40].

Obviously, early identification of patients at risk for higher postoperative pain scores is definitely also important in the context of third molar surgery. It will allow us for effective interventions that might improve postoperative management at home after day-care surgery.

The aim of this study is: 1. to assess postoperative pain and functional recovery during the first seven days after ambulatory surgery for third molar extraction; 2. to identify possible associations between modifiable psychological factors (like pain catastrophizing, state anxiety, need for information, depressive thought) and postoperative pain intensity scores and FRI up to seven day after surgery at home.

Our hypothesis: a major part of the patients will suffer from moderate to severe pain and will experience a significant impact on functional recovery up to seven days after surgery. Furthermore pain catastrophizing, state anxiety, need for information and depressive thoughts will be associated with postoperative pain intensity at home and with functional recovery.

3. Methods & Materials

Study design

This is a prospective observational cohort study that will be carried out at the ZiekenhuisNetwerkAntwerpen (ZNA) Middelheim, Lindendreef 1, 2020 Antwerpen Belgium [and ZNA Jan Palfijn, Lange Bremstraat 70, 2170 Merksem Belgium] and must be approved by the local ethics committee / Institutional Review Board (IRB) of the ZNA hospital (Chair: prof. Dr. P.P. De Deyn - ZNA Koningin Paola Kinderziekenhuis, P4, Route 34, Lindendreef 1, 2020 Antwerpen). Furthermore the study will be registered at https://www.isrctn.com (International Standard Registered Clinical/soCial sTudy Number -ISRCTN) and conducted in accordance with the Declaration of Helsinki and the STROBE statement for observational studies.

Enrolment and data collection

All patients will be approached regarding participation in the study at the surgeon's and / or anesthesia consultation hours and will obtain complete standardized information about the hospital admission and anesthesia procedures and at home care & pain management.

Inclusion criteria: 1. patients aged between 18 – 40 years undergoing extraction of one or more third molars under general anaesthesia in the ZNA Middelheim/Jan Palfijn hospital; 2. American Society of Anesthesiologists physical status (ASA I-II); 3. a good understanding of Dutch language; 4. written informed consent; 5. without premedication.
Exclusion criteria: 1. refusal to participate; 2. patients with a known development delay and intellectual disability; 3. intolerance for local anesthetics and non-steroidal anti-inflammatory drugs (NSAID); 4. chronic use of opioids.

All consecutive patients are eligible for inclusion in this study. Patients who initially have given their consent can at all times withdraw without any consequences.

At the day of the admission the patient will be presented the study documents with a personal identification number and a Qualtrics generated QR code which will lead the patient to the first preoperative questionnaires (see attachments).

The preoperative questionnaires (flowchart):

Demographic/medical data of patients will be collected on the day of admission (standardized interview performed by a research nurse). Demographic data include: 1. gender; 2. age / birthday; 3. length (cm) / weight (kg) (BMI); 4. level of education / (profession) as an indicator

of socioeconomic status (SES) classified into three categories: I. no education, elementary school; II. secondary school; III. higher education or university[41]. Medical data include: 1. American Society of Anesthesiologists physical status (ASA) - comorbidities: diseases such as hypertension, diabetes mellitus, renal disease and cardiovascular disease will be recorded; 2. use of medication; 3. non-smokers will be defined as having smoked no more than 100 cigarettes in their lifetime ;

Furthermore in the preoperative period patients will be additionally interviewed by using the following assessment tools: 1. baseline pain assessment using a Visual Analogue Scale – Pain scores (VAS-baseline-P); 2. patient's expected pain after the procedure using a VAS-P-expected pain; 3. Pain Catastrophizing Scale (PCS) – (additional state-PCS); 4. Amsterdam Preoperative Anxiety and Information Scale (APAIS); 5. Hospital Anxiety and Depression Scale – depression subscale (HADS);

Surgery and anesthetic plan

After filling in the preoperative questionnaires, the patient will be brought to the surgical theatre.

All patients will receive a standardized preoperative preparation and anaesthesia protocol. No premedication will be given.

Anesthetic induction will be provided using Propofol (maximum 3-4 mg/kg IV) along with the use of a strong opioid, like a low dose of Sufentanil (5-10 µg IV) and/or Remifentanil (75-100µg IV) in bolus. A short acting muscle relaxant can be added to facilitate intubation (low dose of Rocuronium .3 mg/kg IV or Atracurium .3mg/kg IV).

Maintenance of anesthesia will be carried out using Sevoflurane (VOL% 2-2.5 / 1 MAC value). Further intraoperative pain management consists of: 1. Dexamethasone (0.15 mg/kg IV); 2. Paracetamol (15mg/kg IV) and Ibuprofen (10 mg/kg IV). For prevention of postoperative nausea and vomiting a bolus of Ondansetron 4 mg IV will be additionally administered.

Standard monitoring

During anesthesia ECG, O_2-saturation, end-tidal CO_2, inhalation gas concentration, non-invasive blood pressure measurements (5 min. interval) will be monitored.

Airway management

Airway management consists of a nasotracheal tube (NNT) placed under direct laryngoscopy. Patients will be mechanically ventilated with pressure- or volume-ventilation (1. tidal volumes 6-8mL/kg ideal body weight; 2. respiratory rate of 12 breaths/minute; 3. normocapnia = end-tidal CO2 between 35 and 45 mmHg. Maintenance of a mean non-invasive arterial blood pressure ≥ 65 mmHg.

At the end of surgery the patients will be transferred to the Post Anesthesia Care Unit (PACU) and thereafter to the ward.

At the ward the patients receive their diary in which they have to note their pain intensity by using a VAS-P (3 times at the day of surgery).

The surgeon will be asked to fill in the characteristics of the third molar extraction by location (maxilla or mandibula), degree of impaction (erupted, soft tissue or bony) and number of molars removed (one to four). Whether the surgeon gives regional anaesthesia with a local anesthetic product description (10 mL of Ropivacaine 7.5% is distributed over a tuber block with spix bilateral and buccalis bilateral) will also be recorded**.**

At the end of surgery the patients will be transferred to the Post Anesthesia Care Unit (PACU) and once the discharge criteria are fulfilled, they will be transferred to the ward.

Discharge criteria: Aldrete score ≥ 6 out of 8, no postoperative nausea and vomiting and a VAS-P-PACU pain score of < 4, sinus rhythm between 50-100 beats/minute, normothermia 36-37°C, pink skin colour, no narcotic agents administered in the previous 30 minutes.

Post-surgery

Information about the standardized pain management at home will be given. This consists of conservative measures such as cold packs and a medication scheme: Paracetamol 1g 4 times/day and Ibuprofen 600mg 3 times/day during 3 days. As rescue medication: Tramadol 50mg PRN will be prescribed

After filling in the first online Qualtrics questionnaire, the patient will receive daily email starting at the day of the operation to fill in a questionnaire about: 1. pain (VAS-P), use of pain medication use; 3. FRI.

This process is automated by Qualtrics (Attachment).

Telephone calls will be made by a research nurse at day 1, at day 4 and day 7 postoperative.

Pain medication adherence

Good adherence will be defined as having at least 15 of the 24 prescribed pain medications during the first three postoperative days at home.

4. Research instruments

Outcome variables

A: Visual Analogue Scale – Pain (VAS-P)[42-46] (attachment 1)

The horizontal VAS-P is a single item and continuous scale of 100 mm in length and is anchored by 2 verbal descriptors, one for each symptom extreme. Verbal descriptor anchors are: 'no pain (score 0) and 'pain as bad as it could be' [or 'worst imaginable pain'] (score 100 – on a 100-mm scale). Respondents are asked to report 'current' pain intensity. Patients will receive a personal diary in which they will be asked to place a line perpendicular to the VAS-P which reflects their pain intensity. The VAS-P will be noted in a diary this three times (interval 4 hours) during the day of surgery and from day one postoperatively twice a day (morning after breakfast and in the evening from 18 PM onwards). Higher scores indicate higher pain intensity. Based on distribution analysis of VAS-P score in postsurgical patients [47], pain intensity can be described as: no pain (0 – 4 mm), mild pain (5 – 44 mm), moderate pain (45 – 74 mm) and severe pain (75 – 100). Normative data are not yet available.

Application of the VAS-P requires little training to use and scoring has been found acceptable to patients with a minimal of burden. Test-retest reliability is good but higher among literate (r=.94) compared to illiterate patients (r=.71)[48]. Validity cannot be established in absence of a gold standard in pain assessment [46]. Construct validity with a 5 point verbal descriptive scale and numeric rating scale ranges is good (correlations ranges from .71 – .78 to respectively .62 – .91) [49,50].

The VAS-P will be noted in the diary three times during the day of surgery (immediate postoperative, during the PACU-stay and at 20 PM at home) and from day one up to day seven postoperatively twice a day (at 8 AM and 8 PM) in the Qualtrics link.

B : Functional recovery Index (FRI)[19] (attachment 2)

The FRI has been developed to assess postoperative discharge functional recovery for ambulatory surgical patients and consists of 14 questions grouped under 3 factors (pain and social activity, lower limb activity, and general physical activity). Each item is scored from 0 to 10, with 0 no difficulty and 10 extreme difficulty with the activity. The 3 factors are summated for a total score. A grand score can be calculated and equals = (total of all scores) X 14/ number of answered question. If patient do not normally perform such activities, e.g., driving, the patient has to choose not applicable (NA). The same applies when patients are instructed by the surgeon not to perform the activity. The FRI has

an excellent reliability and good validity. Internal consistency for the 3 factors (pain and social activity, lower limb activity, and general physical activity) is as follows: Cronbach alpha 0.90, 0.89, and 0.86, respectively. Interrater reliability was 0.99. Convergent validity for FRI versus verbal rating scale pain score was 0.76. Discriminant validity testing showed that the type of surgery was significant and that intermediate (0.138) and major surgery (0.337) were associated with higher FRI scores than minor surgery.

The FRI will be filled from day one up to day seven postoperatively once a day through the Qualtrics link.

Predictor variables

A: Pain Catastrophizing Scale (PCS) [29,51,52] (attachment 3)

The Pain Catastrophizing Scale (PCS) is a 13-item scale to assess catastrophic thinking associated with pain. Pain catastrophizing is related to a more intense pain experience and emotional distress in more exaggerated terms compared to a an average person. These persons tend to ruminate over it more, f.i. the item 'I kept thinking this is terrible', to feelings of more helplessness about the experience, f.i. the item 'I thought it was never going to get better' and by feelings of excessive magnification, f.i. the item 'I´m afraid that something serious might happen'. Participants are asked to rate the frequency on the 13 thoughts or feelings when they are in pain. These ratings are made on a 5-point Likert scale with the following end-points: 0 = not at all and 4 = all the time. A total score is computed and 3 subscale scores assessed rumination, helplessness and magnification. The PCS is a reliable and valid measure for catastrophizing [32]. Subscales of the PCS have been shown to have adequate to high internal consistency (Cronbach alpha's ranges: total PCS = 0.87, rumination = 0.87, magnification = 0.66, and helplessness = 0.78).

The PCS scale has also been validated (not published) in Dutch by Crombez *et al* [53] and the psychometric characteristics were further investigated by Van Damme *et al* [33,54]. The Dutch questionnaire has a good reliability (ICC: R = 0.73) and a good construct / content validity. Internal consistency ranges from Cronbach alpha's between 0.70 and 0.93.

B: Amsterdam Preoperative Anxiety and Information Scale (APAIS) [55] (attachment 4)

The APAIS is a reliable and validated Dutch self-report questionnaire that consists of six questions and has been specifically developed to evaluate preoperative state anxiety and need for information requirement of / coping style in patients undergoing surgery and anesthesia.

The patients' state anxiety (APAIS-state) is assessed by 4 questions: 1. I am worried about the anesthetic; 2. the anesthetic is on my mind continually; 3. I am worried about the procedure; 4. the procedure is on my mind continually.

The patients' need for information (APAIS-information) is assessed by 2 questions: 1. I would like to know as much as possible about the anesthetic; 2. I would like to know as much as possible about the procedure. The anxiety part correlates strongly (r = 0.74) with the state part of the Spielberger State-Trait Anxiety Inventory (STAI)[56] and the correlation with the information items and the State-STAIC was low (r = 0.16).

Both the APAIS-state and APAIS-information scales – each question can be answered with response categories on a 5-point Likert scale. The APAIS-state subscale range from 4 – 20 and the APAIS-information subscale range from 2 – 10. A value ≥ 13 on the APAIS-state decreases the rate of false-positives.

APAIS-information: a score between 2 – 4 means no/little information need; 5 – 7 average information need and scores between 8 – 10 a high information need. A score ≥ 5 can be interpreted as having a positive attitude toward receiving information. The APAIS is very easily and quickly to complete.

In this study the scores will be treated as continuous variables.

C: Hospital Anxiety and Depression Scale (HADS)[57,58] (attachment 5)

The HADS was developed in 1983 to identify possible anxiety disorders and depression among patients in nonpsychiatric hospital clinics. Evidence exists for a two-factor solution in accordance with the HADS subscales for anxiety (HADS-A) and depression (HADS-D) – correlations varied from .40 to .74 - mean .56. Cronbach's alpha for the HADS-A varied from .068 to .93 (mean .83) and for the HADS-D from .67 to .90 (mean .82). An optimal balance between sensitivity and specificity (for both 0.80) has been achieved at a score of ≥ 8 on the HADS-A and HADS-D. The total HADS scale showed a good balance between sensitivity and positive predictive value (PPV) in identifying a psychiatric disorder. Homogeneity and test-retest reliability of the total scale and the subscales are good. The dimensional structure and reliability of the HADS is stable

across medical settings and age groups. The HADS consists of 2 (7-items) subscales measuring anxiety (HADS-A) and depression (HADS-D) in patients in hospital setting. Each item can be answered in a Likert from 0 to 3 form. Subscales range from 0 – 21. Higher scores implicate higher levels of anxiety and depression.

D: VAS-P-baseline pain scale before surgery[30,34](attachment 6)

The VAS-P-baseline assesses preoperative pain. It is the same horizontal VAS-P (as described above) which is a single item and continuous scale of 100 mm in length and is anchored by 2 verbal descriptors, one for each symptom extreme. Verbal descriptor anchors are: 'no pain (score 0) and 'pain as bad as it could be' [or 'worst imaginable pain'] (score 100 – on a 100-mm scale).

E: VAS-P-expected pain[30,59](attachment 6)

The VAS-P-expected assesses the patients expected pain after surgery. It is the same horizontal as the VAS-P (as described above) which is a single item and continuous scale of 100 mm in length and is anchored by 2 verbal descriptors, one for each symptom extreme. Verbal descriptor anchors are: 'no pain (score 0) and 'pain as bad as it could be' [or 'worst imaginable pain'] (score 100 – on a 100-mm scale).

F: Demographic/medical data (attachment 6)

Demographic/medical data of patients as collected on the day of admission including: 1. gender; 2. age / birthday; 3. length (cm) / weight (kg) (BMI); 4. level of education / (profession) as an indicator of socioeconomic status (SES) classified into three categories: I. no education, elementary school; II. secondary school; III. higher education or university university. Medical data include: 1. use of pain medication; 2. non-smokers will be defined as having smoked no more than 100 cigarettes in their lifetime

G: Pain medication adherence (attachment 7)

H: Use of local anaesthetic during the procedure (attachment 8)

I: Surgical characteristics (attachment 8): the Pederson's index[60] classification will be used as an assessment tool to quantify the surgical characteristic's – to be filled in by the surgeons after the intervention.

5. Statistical analysis

Power analysis

An a priori sample size calculation for multiple regression by G*Power 3.9.1.7 based on a fixed model (model parameters are fixed or non-random quantities) is performed [61]. Based on effect size obtained from literature, we assume that the final model will explain 20% of variability (effect size .025 with VAS-P as outcome) [6,7]. This analysis revealed that 108 patients are needed to detect a medium effect size (Cohen's $f^2 = 0,25$) with a probability of 0,05 and a power of 0,80, and using 15 predictors. Allowing for a 35% loss to follow up, a sample size of 145 is considered large enough.

Statistics

Baseline/summary demographic and psychological data of the patients will be presented: 1. for continuous data as means ± standard deviation or as median with interquartile range; 2. for categorical items as frequencies and proportions. Normal distribution will be indicated by characteristics (skewness and kurtosis) and will be further checked by Shapiro-Wilk and Kolmogorov-Smirnov tests as well as with Q-Q plots. Numerical variables may have high skewed and non-normal distribution (Gaussian Distribution) caused by outliers, highly exponential distributions, etc.[62,63] These distributions can be converted to normal by data transformation e.g. the log transformation, the square root transformation, the Box-Cox transformation.

Further analyses:

A. **a univariate regression** will be conducted to identify variables who are individually associated with increased pain intensity scores (mean VAS-P values) and functional recovery (FRI) as outcome parameters. Based on previous literature relevant predictors will be considered: age, gender, BMI, SES, smoking history, baseline VAS-P-baseline, pain medication use before surgery, patient's expected pain of the surgery VAS-P-expected, need for information, anxiety, depression, pain catastrophizing, pain medication adherence, the use of local anaesthetic during the procedure and surgical characteristics. To avoid issues with multicollinearity, independent variables which correlate highly with other independent variables will be excluded for further analyses.

   Several grouping variables (levels) sorting data into categories or groups can be defined.

Grouping variables can be: gender (i.e. male/female), level of education (grade I, grade II, grade III), use of local anesthesia by the surgeon (1/0), different sites within ZNA (Middelheim or Jan Palfijn)

Principal Component Analysis (PCA)[64]

Furthermore we will use PCA to examine the internal structure of this complicated dataset and explore interrelations among variables.

B. separate **multiple regression models (MLR)[65]** and a **Generalized Linear Mixed-Effects Model (GLMM)[66]** will be constructed to assess if pain catastrophizing, state anxiety, need for information and depression might explain VAS-P scores at home and functional recovery index after third molar surgery (after adjusting for baseline pain).

'Longitudinal data have traditionally been analyzed using techniques like the paired t test or repeated measures analysis of variance (RM-ANOVA). In recent years, linear mixed-effects models—also referred to as multilevel models or hierarchical models—are becoming increasingly popular because they are much more flexible and overcome many of the limitations of more traditional methods.'[66,67]

Frequentist (traditional) analysis

The results will be reported as adjusted R^2 and standardized β.

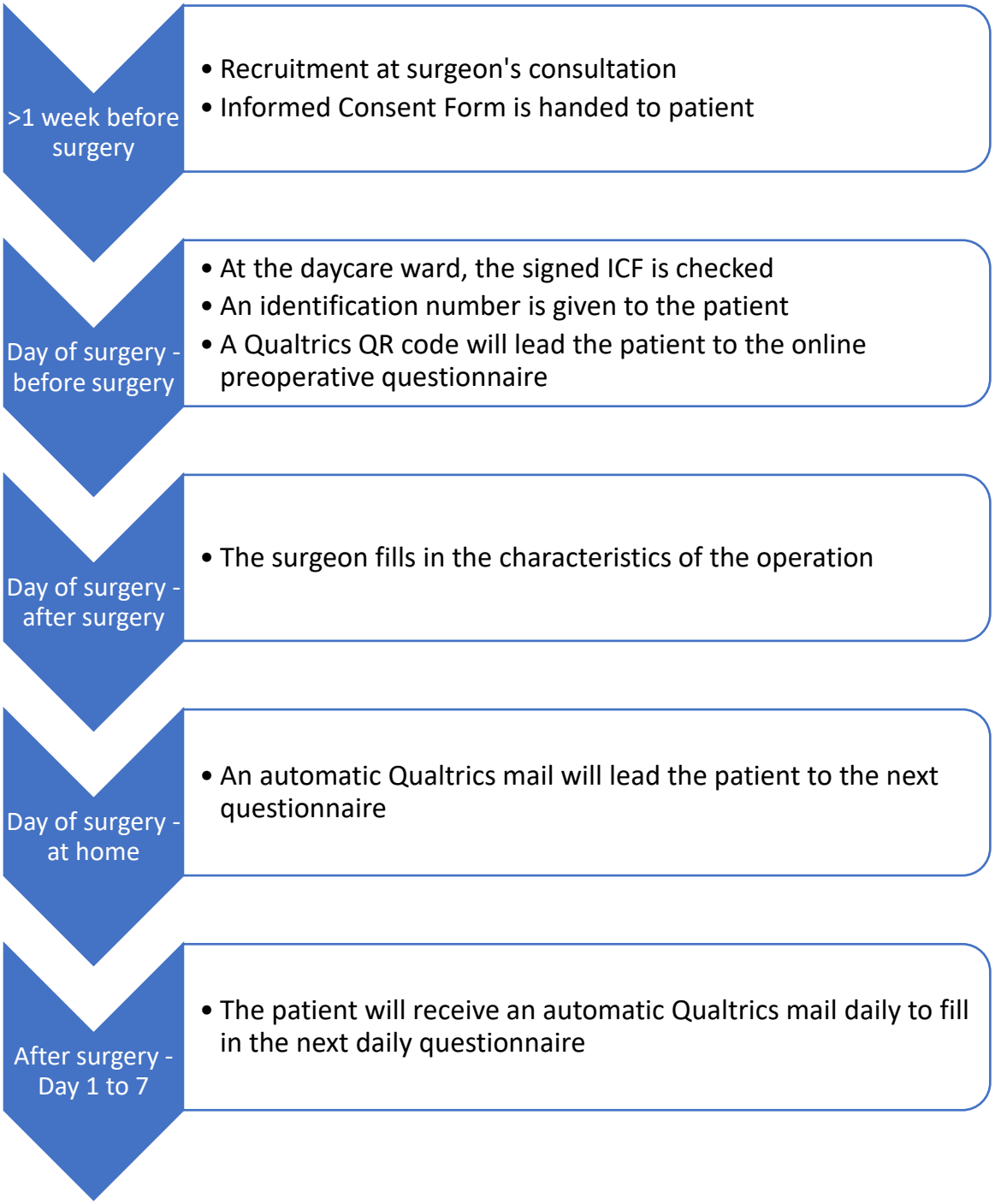
All analyses will be performed with IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM. Corp.

Bayesian approaches

Bayesian approaches to GLMM inference offer several advantages over frequentist (traditional) and information-theoretic Methods[68].

Bayesian modeling can be done in Winbugs[69].

6. Flowchart


>1 week before surgery
• Recruitment at surgeon's consultation
• Informed Consent Form is handed to patient
Day of surgery - before surgery
• At the daycare ward, the signed ICF is checked
• An identification number is given to the patient
• A Qualtrics QR code will lead the patient to the online preoperative questionnaire
Day of surgery - after surgery
• The surgeon fills in the characteristics of the operation
Day of surgery - at home
• An automatic Qualtrics mail will lead the patient to the next questionnaire
After surgery - Day 1 to 7
• The patient will receive an automatic Qualtrics mail daily to fill in the next daily questionnaire

7. Ethical Considerations

This study will be conducted according to the principles of the Declaration of Helsinki (version of 2008, updated 23/11/2017). Prior to patient enrolment, the protocol must be approved by the ZiekenhuisNetwerkAntwerpen (ZNA) Institutional Review Board (IRB) (Chair: prof. Dr. P.P. De Deyn - ZNA Koningin Paola Kinderziekenhuis, P4, Route 34, Lindendreef 1, 2020 Antwerpen).

8. Administrative aspects, monitoring and publication

Most of the data will be collected with Qualtrics, an online tool which allows user to set up surveys and gather data. Qualtrics is GDPR (General Data Protection Regulation) compliant. See also: https://www.qualtrics.com/support/survey-platform/getting-started/qualtrics-gdpr-compliance/ .

All the data gathered through Qualtrics, will only be accessible directly by the primary researcher, Dr. Sander Kempenaers and by the project leader Dr. Johan Berghmans.

The only paper documents left are the Informed Consent Form which needs to be signed by the patient and the paper with the characteristics of the surgery. The latter one can be connected to the other data by a personal identification number that the patient receives at the day of the surgery. This identification number is also needed to fill in the Qualtrics surveys. Thus data will be pseudonymised.

As per legal requirement, all data will be held for 15 years after which it will be permanently deleted.

After collecting all data and the necessary statistical analysis, an manuscript will be written. This manuscript will be presented for publication in a peer-reviewed medical journal.

9. Attachments

Attachment 1 – VAS-P

Hoe zou u uw pijn scoren vandaag omstreeks 8uur 's ochtends?

Plaats de bol daar op de horizontale lijn waar die het best de ernst van uw pijn weergeeft.

Geen enkele pijn — Meest voorstelbare pijn

0 — 100

Hoe hevig is uw pijn vandaag om 8u 's ochtends?

Hoe zou u uw pijn scoren vandaag omstreeks 20uur 's avonds?

Plaats de bol daar op de horizontale lijn waar die het best de ernst van uw pijn weergeeft.

Geen enkele pijn — Meest voorstelbare pijn

0 — 100

Hoe hevig is uw pijn vandaag om 20u 's avonds?

Attachment 2 – FRI

De volgende vragen peilen naar uw functioneel herstel na de operatie.

Heeft u sinds uw operatie moeilijkheden ervaren met een van de volgende:

Helemaal geen moeilijkheden — Extreme moeilijkheden

0 1 2 3 4 5 6 7 8 9 10

het werk/de studie opvatten ☐ Niet van toepassing

familie en vrienden bezoeken ☐ Niet van toepassing

voor familieleden zorgen ☐ Niet van toepassing

met de auto rijden ☐ Niet van toepassing

bescheiden fysieke activiteiten uitvoeren, zoals een tafel verzetten of stofzuigen ☐ Niet van toepassing

boodschappen opheffen of dragen ☐ Niet van toepassing

Sinds uw operatie, heeft u last van pijn? ☐ Niet van toepassing

Heeft u sinds uw operatie moeilijkheden ervaren met een van de volgende:

Helemaal geen moeilijkheden — Extreme moeilijkheden

0 1 2 3 4 5 6 7 8 9 10

binnenshuis en rond het huis wandelen ☐ Niet van toepassing

in een stoel gaan zitten en opstaan uit een stoel ☐ Niet van toepassing

de trap opgaan ☐ Niet van toepassing

buigen, door de knieën gaan, hurken ☐ Niet van toepassing

Heeft u sinds uw operatie moeilijkheden ervaren met een van de volgende:

Helemaal geen moeilijkheden — Extreme moeilijkheden

0 1 2 3 4 5 6 7 8 9 10

een bad of douche nemen / zichzelf wassen ☐ Niet van toepassing

zichzelf aankleden ☐ Niet van toepassing

neerliggen ☐ Niet van toepassing

Attachment 3 – PCS

Denk aan een moment waar u reeds pijn voelde en geef aan in welke mate een aantal gedachten of gevoelens bij u opkomt. Duid het bolletje aan dat hierop van toepassing is.

Als ik pijn heb...

	0 (Helemaal niet)	1	2	3	4 (Altijd)
Vraag ik mij voortdurend af of de pijn wel zal ophouden.	○	○	○	○	○
Voel ik dat ik zo niet verder kan.	○	○	○	○	○
Is dat verschrikkelijk en denk ik dat het nooit beter zal worden.	○	○	○	○	○
Is dat afschuwelijk en voel ik dat de pijn mij overweldigt.	○	○	○	○	○
Voel ik dat ik het niet meer uithoud.	○	○	○	○	○
Word ik bang dat de pijn erger zal worden.	○	○	○	○	○
Blijf ik denken aan andere pijnlijke gebeurtenissen.	○	○	○	○	○
Verlang ik hevig dat de pijn weggaat.	○	○	○	○	○
Kan ik de pijn niet uit mijn gedachten zetten.	○	○	○	○	○
Blijf ik eraan denken hoeveel pijn het wel doet.	○	○	○	○	○
Blijf ik denken hoe graag ik zou willen dat de pijn ophoudt	○	○	○	○	○
Is er niets dat ik kan om de intensiteit van de pijn te verminderen.	○	○	○	○	○
Vraag ik mij af of er iets ernstigs kan gebeuren.	○	○	○	○	○

Attachment 4 – APAIS

Wilt u voor alle uitspraken aangeven in hoeverre die op u van toepassing zijn. Kruis het juiste antwoord aan.

	Helemaal niet	Niet erg	Enigszins	Nogal	Zeer
Ik zie erg op tegen de anesthesie.	○	○	○	○	○
Ik moet voortdurende denken aan de anesthesie.	○	○	○	○	○
Ik zou zoveel mogelijk willen weten over de anesthesie.	○	○	○	○	○
Ik zie erg op tegen de ingreep.	○	○	○	○	○
Ik moet voortdurende denken aan de ingreep.	○	○	○	○	○
Ik zou zoveel mogelijk willen weten over de ingreep.	○	○	○	○	○

Attachment 5 – HADS-D

Wij willen graag weten hoe u zich de laatste tijd heeft gevoeld. Wilt u bij elke vraag het bolletje aankruisen voor het antwoord dat het meest op u van toepassing is? Denk erom, het gaat bij deze vragen om hoe u zich de laatste tijd (in het bijzonder de afgelopen 4 weken) voelde, dus niet om hoe u zich in het verleden heeft gevoeld.

Ik geniet nog steeds van de dingen waar ik vroeger van genoot.

- ○ Zeker zo veel
- ○ Wat minder
- ○ Duidelijk Minder
- ○ Nauwelijks nog

Ik kan lachen en de dingen van de vrolijke kant zien.

- ○ Net zoveel als vroeger
- ○ Nu wat minder
- ○ Nu duidelijk minder
- ○ Helemaal niet meer

Ik voel me de laatste tijd opgewekt.

- ○ Helemaal niet
- ○ Niet vaak
- ○ Soms
- ○ Meestal

Ik voel me de laatste tijd alsof alles moeizamer gaat.

- ○ Bijna altijd
- ○ Heel vaak
- ○ Soms
- ○ Helemaal niet

Ik heb de laatste tijd geen interesse meer in mijn uiterlijk.

- ○ Zeker
- ○ Niet meer zoveel als ik zou moeten
- ○ Mogelijk wat minder
- ○ Evenveel interesse als voorheen

Ik verheug me van tevoren al op dingen.

- ○ Net zoveel als vroeger
- ○ Een beetje minder dan vroeger
- ○ Zeker minder dan vroeger
- ○ Bijna nooit

Ik kan van een goed boek genieten of een radio- of televisieprogramma.

- ○ Vaak
- ○ Soms
- ○ Niet vaak
- ○ Heel zelden

Attachment 6 – Biometric, SES, smoking history, preoperative pain medication, VAS-P-Baseline, VAS-P-expected

De volgende vragen gaan specifiek over uw biometrische gegevens, socio-demografische achtergrond, rookstatus en huidige pijnniveau en medicatiegebruik.

Biometrische data

Leeftijd (jaren)
Gewicht (kilogram)
Lengte (meter)

Wat is uw (biologisch) geslacht?

- ○ Man
- ○ Vrouw

Hoogst behaalde diploma of huidig onderwijsniveau

- ○ Geen diploma / diploma lagere school
- ○ Diploma secundair onderwijs
- ○ Diploma hoger onderwijs / universiteit

Hebt u in uw leven meer dan 100 sigaretten gerookt tot nu toe?

- ○ Ja
- ○ Nee

Plaats de bol daar op de horizontale lijn waar die het best de ernst van uw pijn weergeeft op dit moment vóór de operatie.

Geen enkele pijn — Meest voorstelbare pijn

0 — 100

Hoeveel pijn hebt u momenteel?

Neemt u momenteel pijnmedicatie in vóór de operatie?

Ja — Nee

Indien u momenteel pijnmedicatie inneemt vóór de operatie, gelieve deze hieronder te beschrijven.
Bijvoorbeeld: Tradonal Odis 50mg, 1 tablet 3x per dag

Hoeveel pijn verwacht u globaal te voelen in de dagen na de operatie? Plaats de bol daar op de horizontale lijn waar die het best de ernst van de de pijn weergeeft die u verwacht.

Geen enkele pijn — Meest voorstelbare pijn

0 — 100

Hoeveel pijn verwacht u te voelen?

Attachment 7 Pain medication adherence

Hoeveel pijnmedicatie hebt u vandaag tegen 20 uur 's avonds zelf ingenomen?

Hoe vaak hebt paracematol 1000mg / 1g ingenomen. (Merknaam: Dafalgan, algostase, ...)

0 1 2 3 4

Inname van paracetamol 1g in de afgelopen 24 uur

Hoe vaak hebt ibuprofen 600mg of 400mg ingenomen. (Merknaam: Brufen)

0 1 2 3

Inname van ibuprofen 600 of 400mg in de afgelopen 24 uur

Hebt u andere medicatie tegen de pijn ingenomen?

Ja Nee

Welke andere medicatie hebt u ingenomen en hoeveel.
Bijvoorbeeld:
Tradonal Odis 50mg 3 pilletjes
Of
Contramal Retard 100mg 1 pil

Attachment 8 - Surgery Characteristics

Karakteristieken van de operatie

Gelieve de juiste vakjes te omcirkelen.

	Verhouding in te ruimte 1: Mesioangulair 2: Horizontaal 3: Verticaal 4: Distoangulair				**Diepte** 1: Hoge occlusie 2: Medium occlusie 3: Lage occlusie			**Relatie van de ramus** 1: Voldoende ruimte 2: Verminderde ruimte 3: geen ruimte			**Moeilijkheidsgraad** Zeer moeilijk: 7-10 Moeilijk: 5-6 Moeizaam: 3-4	
Wijsheidstand 1	1	2	3	4	1	2	3	1	2	3	SOM =	
Wijsheidstand 2	1	2	3	4	1	2	3	1	2	3	SOM =	
Wijsheidstand 3	1	2	3	4	1	2	3	1	2	3	SOM =	
Wijsheidstand 4	1	2	3	4	1	2	3	1	2	3	SOM =	
Hebt U lokale anesthesie gebruikt?											Ja	Nee

Attachment 9 – Permanent link preview of Qualtrics surveys

Identification questionnaire:

https://kuleuven.eu.qualtrics.com/jfe/preview/SV_8vx76H8BRvX8GBE?Q_CHL=preview&Q_SurveyVersionID=current

Preoperative questionnaire:

https://kuleuven.eu.qualtrics.com/jfe/preview/SV_a5z6gLYCuHAyBpA?Q_CHL=preview&Q_SurveyVersionID=current

Day of operation:

https://kuleuven.eu.qualtrics.com/jfe/preview/SV_9KrL0JXFfefV8Cq?Q_CHL=preview&Q_SurveyVersionID=current

Postoperative day 1:

https://kuleuven.eu.qualtrics.com/jfe/preview/SV_3aa7HVr6gP9BmYK?Q_CHL=preview&Q_SurveyVersionID=current

Postoperative day 2:

https://kuleuven.eu.qualtrics.com/jfe/preview/SV_3lwZifZ2D7V2KNw?Q_CHL=preview&Q_SurveyVersionID=current

Postoperative day 3:

https://kuleuven.eu.qualtrics.com/jfe/preview/SV_cMZwVsBBEct54uq?Q_CHL=preview&Q_SurveyVersionID=current

Postoperative day 4:

https://kuleuven.eu.qualtrics.com/jfe/preview/SV_9FAJ8oZZUEnv6gC?Q_CHL=preview&Q_SurveyVersionID=current

Postoperative day 5:

https://kuleuven.eu.qualtrics.com/jfe/preview/SV_9XrwVPi90ZEKJPo?Q_CHL=preview&Q_SurveyVersionID=current

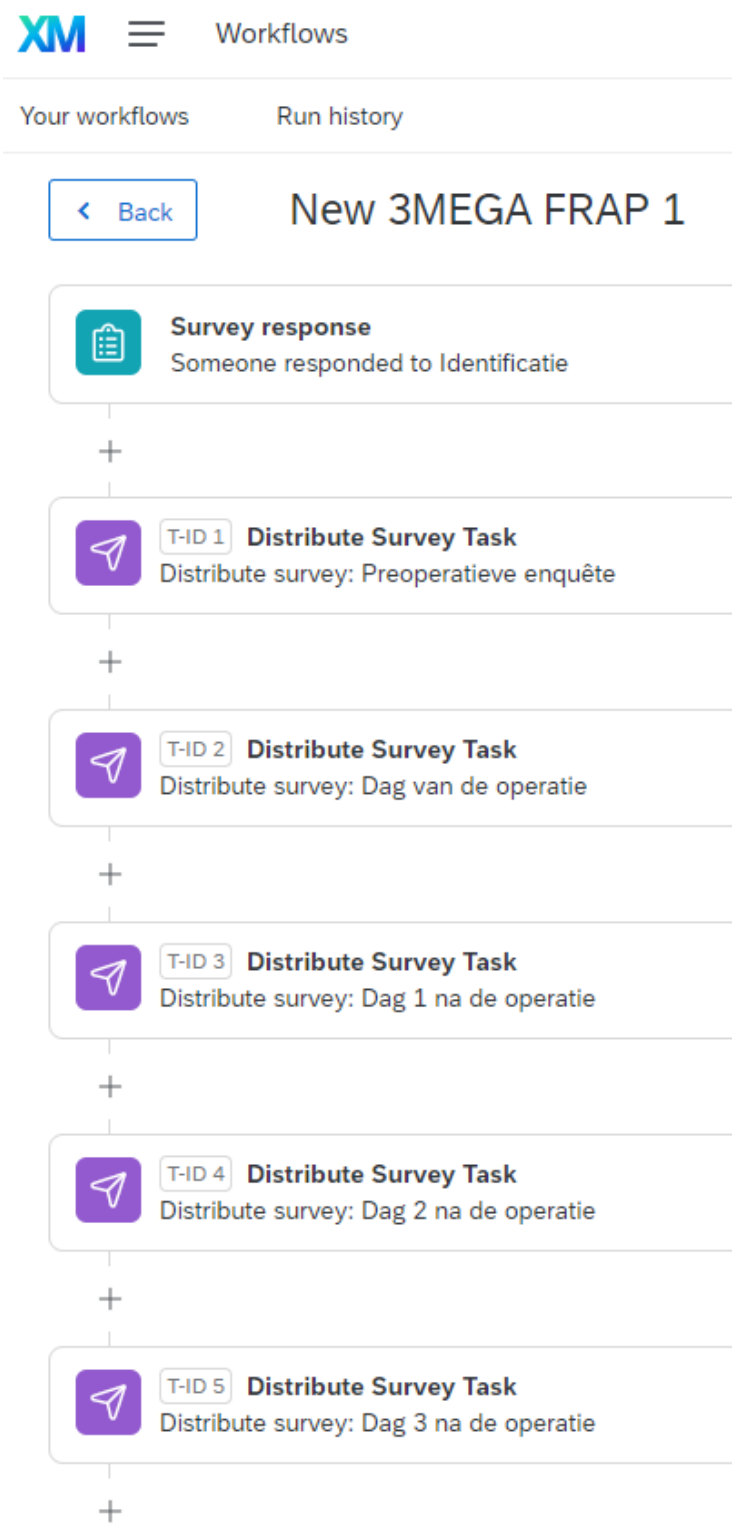
Postoperative day 6:

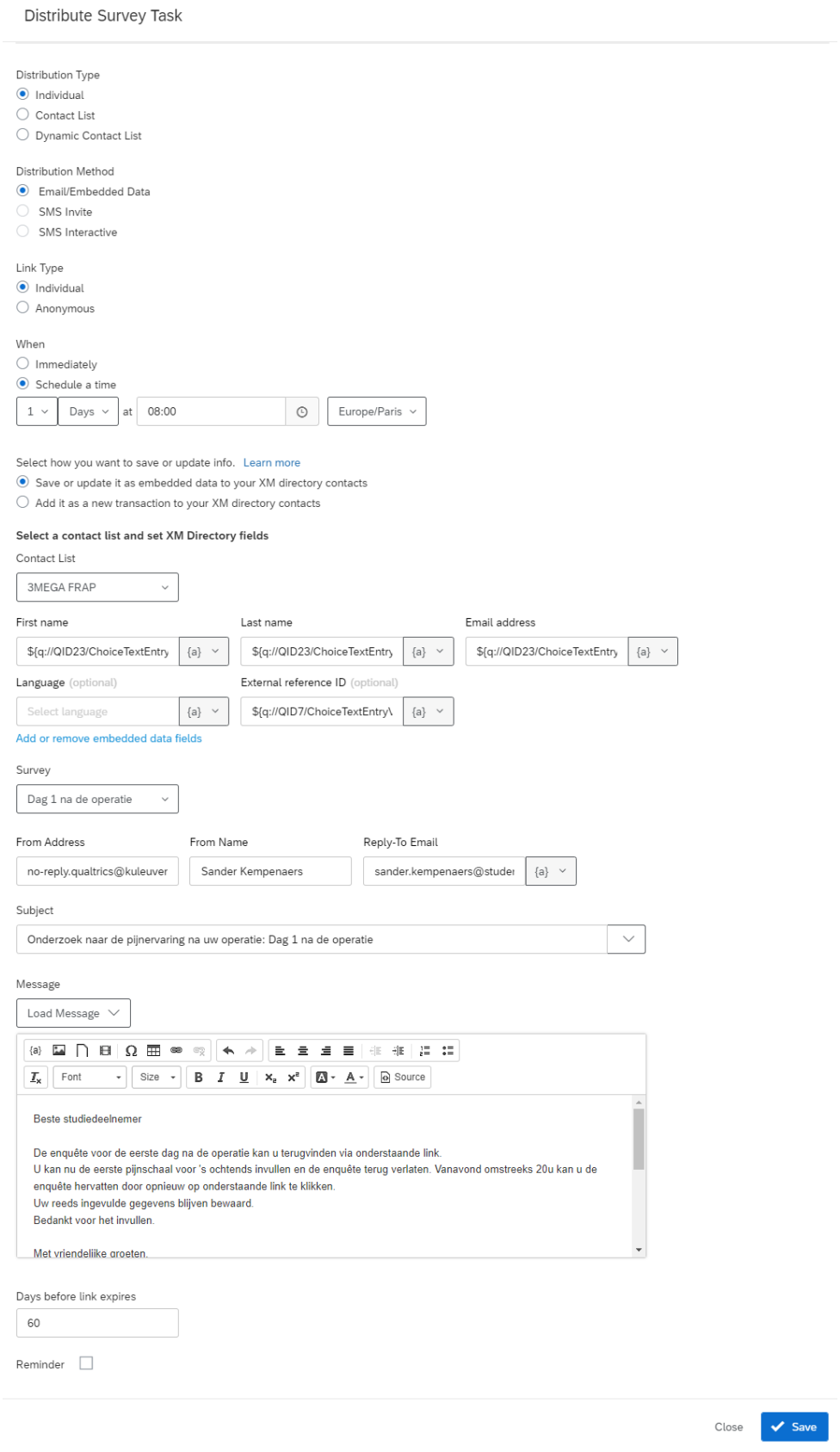
https://kuleuven.eu.qualtrics.com/jfe/preview/SV_51oOhRACJr7BvPo?Q_CHL=preview&Q_SurveyVersionID=current

Postoperative day 7:

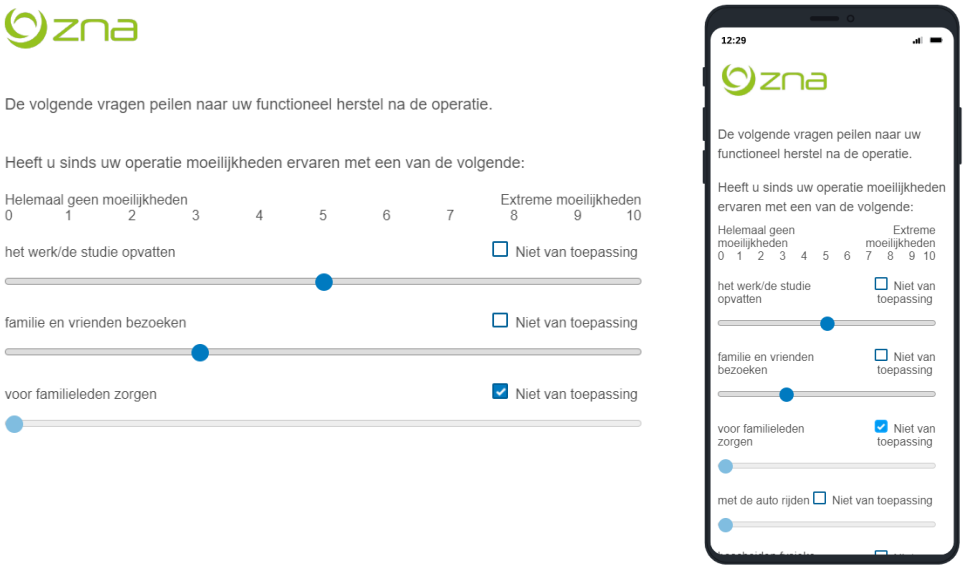
https://kuleuven.eu.qualtrics.com/jfe/preview/SV_0SNk3FS04uuECHQ?Q_CHL=preview&Q_SurveyVersionID=current

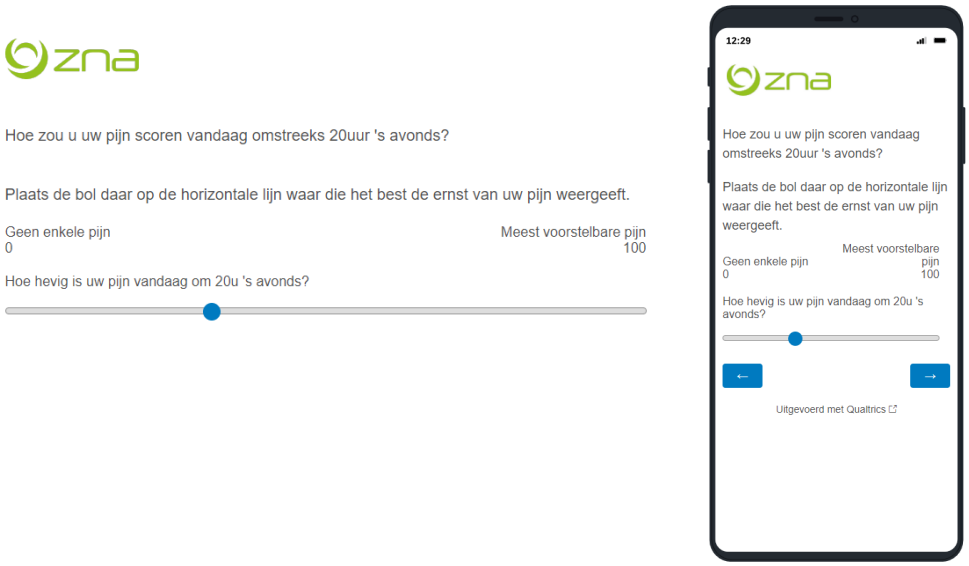
Attachment 11 – Qualtrics workflow for automatic distribution of surveys through email

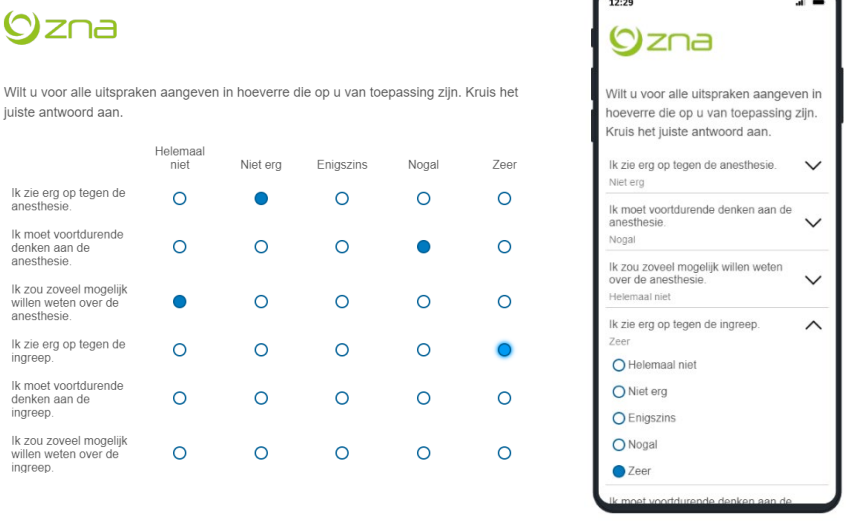



Distribute Survey Task
Distribution Type
Individual
Contact List
Dynamic Contact List
Distribution Method
Email/Embedded Data
SMS Invite
SMS Interactive
Link Type
Individual
Anonymous
When
Immediately
Schedule a time
1
Days
at
08:00
Europe/Paris
Select how you want to save or update info. Learn more
Save or update it as embedded data to your XM directory contacts
Add it as a new transaction to your XM directory contacts
Select a contact list and set XM Directory fields
Contact List
3MEGA FRAP
First name
${q://QID23/ChoiceTextEntry
Last name
${q://QID23/ChoiceTextEntry
Email address
${q://QID23/ChoiceTextEntry
Language (optional)
Select language
External reference ID (optional)
${q://QID7/ChoiceTextEntry\
Add or remove embedded data fields
Survey
Dag 1 na de operatie
From Address
no-reply.qualtrics@kuleuver
From Name
Sander Kempenaers
Reply-To Email
sander.kempenaers@studer
Subject
Onderzoek naar de pijnervaring na uw operatie: Dag 1 na de operatie
Message
Load Message
Font
Size
Source
Beste studiedeelnemer
De enquête voor de eerste dag na de operatie kan u terugvinden via onderstaande link.
U kan nu de eerste pijnschaal voor 's ochtends invullen en de enquête terug verlaten. Vanavond omstreeks 20u kan u de enquête hervatten door opnieuw op onderstaande link te klikken.
Uw reeds ingevulde gegevens blijven bewaard.
Bedankt voor het invullen.
Met vriendelijke groeten.
Days before link expires
60
Reminder
Close
Save

Attachment 12 – Comparison of Qualtrics Web View vs Mobile View







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