Research Proposal

Title: Quantitative Analysis of Postoperative Analgesia Following Abdominal Surgery Using Repeated Time-to-Event Modeling of Rescue Analgesic Administration

ClinicalTrials.gov Identifier: Pending

1. Background and Rationale

Effective postoperative pain control following abdominal surgery is essential for patient comfort, facilitates early mobilisation, and reduces the risk of chronic postsurgical pain (CPSP). CPSP develops in an estimated 10–50% of patients after abdominal procedures and represents a major source of long-term patient morbidity.[1, 2] Despite widespread adoption of multimodal analgesic protocols, studies consistently demonstrate that 40–70% of surgical patients continue to experience moderate-to-severe pain during the early postoperative period. [3] Current titration-based analgesic regimens are inherently reactive: rescue analgesia is administered only after pain becomes unacceptable rather than being prevented through anticipatory, model-informed dosing.

Quantifying analgesic pharmacodynamics (PD) is a prerequisite for rational, model-informed dosing. The choice of analgesic endpoint significantly influences both the interpretability and the statistical power of clinical studies. Analgesic consumption has conventionally been reported as total dose administered or as the time to the first rescue analgesic event. Both approaches carry well-recognised limitations: total opioid consumption follows a non-normal distribution that violates the assumptions of standard parametric tests [4]; and time-to-first event (TTE) analysis discards all subsequent events through informative censoring, leading to a substantial loss of clinical information and statistical power.[4, 5]

Repeated time-to-event (RTTE) modelling overcomes both limitations by analysing the timing of each consecutive rescue analgesic event rather than only the first. Juul *et al.* applied this approach to postoperative pain, demonstrating in 63 patients after hip fracture surgery that a Gompertz-distributed hazard model accurately described the declining risk of rescue analgesic events over 96 hours, with a significant night-time elevation in hazard.[4] Besides, RTTE modelling revealed that each preceding analgesic event independently increased the hazard of subsequent events, an effect which could not be detected by total-consumption or first-event analyses.[4] Using simulation, Juul *et al.* subsequently demonstrated that RTTE modeling requires as few as 50 patients to detect a 37% opioid-sparing effect with 80% power in a 24-hour trial, compared with 200 patients for the Mann–Whitney test and 180 for the t-test, establishing RTTE as a statistically efficient endpoint for analgesic trials.[5]

Goulooze *et al.* extended RTTE to a full pharmacokinetic–pharmacodynamic (PKPD) framework in 118 patients after cardiac surgery, demonstrating that morphine plasma concentration, time after surgery, and a circadian cycle jointly determined the hazard for rescue analgesic administration, with 50% hazard reduction at a morphine concentration of 9.3 ng/mL.[6] More recently, Xiberras *et al.* applied RTTE modelling to describe morphine pharmacodynamics in children after paediatric cardiac surgery, confirming the generalisability of the Gompertz framework and inter-event hazard modification across age groups.[7]

To date, no published RTTE-PKPD model exists for adult patients undergoing elective abdominal surgery. This is a population with a distinct trajectory of postoperative pain, diverse surgical approaches, and a different multimodal analgesic context. This study addresses that gap by developing the first validated RTTE-PKPD model for rescue

analgesic administration in adults undergoing elective abdominal surgery, incorporating published population PK parameters to link morphine exposure to the hazard of rescue analgesia.

2. Objectives

Primary Objective

To quantify the hazard of requiring rescue analgesic administration during the first 48 hours following elective abdominal surgery using repeated time-to-event (RTTE) modelling.

Secondary Objectives

- To characterise the time-course of the baseline hazard for rescue analgesia, including circadian variation and the influence of preceding analgesic events.
- To quantify the pharmacodynamic relationship between predicted morphine plasma concentration (derived from published population PK parameters applied to individual dosing histories) and the reduction in hazard for rescue analgesia.
- To identify patient-level covariates, including age, sex, BMI, surgical approach (open vs. laparoscopic), surgical duration, ASA classification, and baseline chronic analgesic use, which independently influence the hazard for rescue analgesia.
- To assess the internal predictive performance of the final RTTE-PKPD model using simulation-based evaluation methods.
- To use model-based simulations to explore the potential impact of optimised analgesic dosing strategies on postoperative pain control after abdominal surgery.

3. Methods

3.1 Study Design

A single-centre prospective observational cohort study of adult patients undergoing elective abdominal surgery under general anaesthesia. Postoperative analgesic administration and pain score data will be collected for 48 hours from the time of surgery completion (defined as skin closure). No modification of clinical care will be made as part of this study.

The study will be conducted in accordance with the Declaration of Helsinki and the Malaysian Guidelines for Good Clinical Practice (2nd edition). Ethics approval will be obtained from the Medical Research and Ethics Committee, Universiti Malaya Medical Centre prior to patient enrolment.

3.2 Study Population

Inclusion Criteria

- Adult patients aged 18–75 years
- American Society of Anesthesiologists (ASA) physical status I–III
- Elective open or laparoscopic abdominal surgery under general anaesthesia
- Expected postoperative ward or high-dependency unit (HDU) stay of ≥ 48 hours
- Ability to provide written informed consent in Bahasa Malaysia or English
- Ability to comprehend and self-report pain using the Numerical Rating Scale (NRS, 0–10)

Exclusion Criteria

- Chronic opioid therapy, defined as regular opioid use for ≥ 4 weeks prior to surgery
- Severe hepatic impairment (Child–Pugh Class B or C) or severe renal impairment (eGFR < 30 mL/min/1.73 m²)
- Known allergy or hypersensitivity to morphine or any opioid analgesic
- Cognitive impairment (documented diagnosis of dementia or delirium), language barrier, or communication deficit precluding reliable NRS self-report
- Documented history of substance use disorder (including opioid use disorder)
- Withdrawal of informed consent at any point

3.3 Postoperative Analgesia Protocol

All patients will receive a standardised multimodal analgesia protocol commencing in the perioperative period and continuing for the 48-hour study observation period.

Scheduled Non-Opioid Analgesics

- Paracetamol 1 g intravenously (IV) every 6 hours, unless contraindicated by hepatic impairment (dose reduced to 500 mg every 6 hours if weight < 50 kg or mild hepatic impairment)
- NSAIDS unless contraindicated (contraindications include: eGFR < 60 mL/min/1.73 m², active peptic ulcer disease, cardiovascular risk score ≥ moderate)

Rescue Analgesic Regimen

- All participants will receive intravenous morphine via a patient-controlled analgesia (PCA) device (programmed lockout interval: 5 minutes; bolus dose: 0.05 mg/kg; no background infusion; 4-hour ceiling dose: 0.4 mg/kg) as the sole postoperative rescue analgesic for the 48-hour observation window. This standardised regimen eliminates inter-patient variability in rescue analgesic type and delivery route, and ensures all analgesic exposures contribute to the pharmacodynamic model.
- Prior to surgery, a trained research nurse will instruct each participant on PCA use and the Numeric Rating Scale (NRS; 0 = no pain, 10 = worst imaginable pain). Participants will be instructed to assess their pain intensity immediately before each PCA demand and to self-record the NRS score on a standardised bedside pain diary at the time of each button press.

Event Definition and Data Capture

- A *rescue analgesic event* is defined as each successful PCA activation resulting in drug delivery.
- Unsuccessful demands (those rejected during the lockout period) will be recorded separately and will not constitute analgesic events for the primary RTTE analysis, as they represent analgesic-seeking behaviour without drug exposure.
- The time and dose of every successful and unsuccessful demand will be automatically logged by the PCA pump. Pump data will be downloaded and reconciled with the bedside pain diary at the end of the 48-hour observation period by a research team member blinded to covariate data.

3.4 Data Collection

The following data will be collected for the first 48 hours following the end of surgery (T = 0).

Demographics and Surgical Characteristics

- Age, sex, body weight (kg), height (cm), BMI (kg/m²)
- Race/ethnicity
- ASA physical status classification
- Surgical diagnosis, procedure type (open vs. laparoscopic), and operative duration
- Anaesthetic technique (total intravenous anaesthesia vs. inhalational)

Analgesic Dosing History

- All analgesic agents administered: drug name, dose, route, and exact administration time (from the EMR/CRF)
- Pre-operative analgesic use: drug class, dose, and duration (from patient history and medical records)

Pain Scores

- NRS (0–10) at rest and on movement recorded at fixed timepoints: on arrival to PACU, every 15 minutes in PACU, and every 4 hours on the ward for 48 hours
- NRS recorded immediately before each rescue analgesic administration (to confirm the NRS ≥ 4 trigger)
- NRS recorded 15 minutes after each rescue dose (to document response)

Safety and Process Measures

- Side effects at each assessment: nausea/vomiting, sedation (Ramsay scale), pruritus, respiratory rate, SpO_2
- Time of PACU arrival, PACU discharge, and ward transfer
- Time to first out-of-bed mobilisation

Pharmacokinetic Data Strategy

Individual predicted morphine plasma concentrations at each time point will be derived by applying published population PK parameters for IV morphine in adult surgical patients to each patient's documented individual dosing history. [8]

3.5 Model Development

All modelling and simulation will be performed in NONMEM® version 7.5 (ICON Development Solutions, Dublin, Ireland) with Perl-speaks-NONMEM (PsN, version 5.3). R version ≥ 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria) will be used for all graphical output and secondary statistical analyses.

3.5.1 Structural Hazard Model

The hazard function h(t) describes the instantaneous risk of a rescue analgesic event at time t after surgery. Three candidate parametric base hazard distributions will be compared: constant, Weibull, Gompertz. Circadian (24-h periodic) components will be explored to capture day–night variation.

Model selection will be based on objective function value (OFV) comparison and clinical plausibility.

3.5.2 Drug-Effect Model

The pharmacodynamic effect of morphine on the hazard will be modelled using an exponential inhibitory function. An alternative Emax inhibitory model will also be evaluated for comparison. Model selection between the exponential and Emax parameterisations will be based on OFV comparison, parameter precision, and clinical interpretability.

3.5.3 Covariate Modelling

Candidate covariates will be pre-screened for correlation with individual parameter estimates (empirical Bayes estimates, EBEs) using Pearson's r or Spearman's ρ as appropriate.

A standard sequential stepwise approach will be used:

- Forward inclusion: $\Delta OFV \geq 3.84$ (corresponding to $p < 0.05$, χ^2 distribution, 1 degree of freedom)
- Backward elimination: $\Delta OFV \geq 6.63$ (corresponding to $p < 0.01$, χ^2 distribution, 1 degree of freedom) required for retention in the final model

Candidate covariates include age, sex, BMI, surgical approach (open vs. laparoscopic), surgical duration, ASA classification, baseline chronic analgesic use, and anaesthetic technique.

3.5.4 Model Estimation and Evaluation

- NONMEM 7.5 will be used with stochastic approximation expectation-maximisation and importance sampling.
- Model selection: likelihood ratio tests for nested models, Akaike information criterion (AIC) for non-nested models
- Goodness-of-fit will be evaluated using the following methods:
    - Kernel-based Visual Hazard Comparison (kbVHC): non-parametric kernel-smoothed hazard estimates from observed data will be superimposed on model-predicted hazard functions
    - Visual predictive checks (VPCs) for event occurrence.
- Non-parametric bootstrapping (n = 1000 resampled datasets with replacement) will be used to derive 95% confidence intervals for all model parameters, and to assess parameter stability and model robustness.

3.5.5 Sensitivity Analyses

- Stratified analyses by surgical approach (open vs. laparoscopic), given expected differences in postoperative pain severity and trajectory.
- Influence of analgesics co-administration on baseline hazard.

4. Sample Size Considerations

Sample size is determined by two complementary factors: a minimum-events criterion and simulation-based power estimates from the literature.[5]

The final RTTE model is anticipated to include up to 7 fixed-effect parameters (baseline hazard, contagion, inter-event interval, morphine concentration, circadian effect, and 2 covariates). Applying a rule of 15 events per estimated parameter, a minimum of 105 observed PCA activations is required for stable parameter estimation.

Based on anticipated PCA utilisation in the abdominal surgery population, each enrolled patient is expected to generate approximately 7–10 successful activations over the 48-hour observation window. At the conservative lower bound (7 events/patient), 105 events are achieved with 15 patients; however, this figure applies only to event accumulation, not to the power to detect a clinically meaningful effect on inter-event hazard.

The primary power reference is the simulation by Juul et al. [5], which demonstrated that 50 patients yield 80% power to detect a 37% reduction in analgesic demand under an RTTE framework, compared with over 200 patients required under a Mann-Whitney approach.

Assuming up to 20% dropout or data incompleteness (device failure, protocol deviation, early discharge), the required enrolment would be 63 patients. Rounding up to 65 patients will provide a modest buffer and provide adequate representation across the expected range of baseline morphine consumption.

A pre-specified interim event-rate review will be conducted after the first 20 patients are enrolled. If the observed activation rate falls outside the 5–10 events per patient range, the sample size will be recalculated and the protocol amended accordingly before continuing enrolment.

5. Statistical Analysis Plan

Continuous variables will be summarised as mean (standard deviation [SD]) for normally distributed data and median (interquartile range [IQR]) for non-normally distributed data. Categorical variables will be reported as counts and percentages. Baseline characteristics will be compared between surgical subgroups (open vs. laparoscopic) using independent t-tests or Mann–Whitney U tests for continuous variables, and chi-squared or Fisher’s exact tests for categorical variables, as appropriate.

The primary analysis is the RTTE model described in Section 3.5. All estimated hazard ratios from the covariate model will be reported with 95% bootstrap confidence intervals and interpreted clinically.

Handling of missing data

Missing NRS observations (≤ 10% of scheduled timepoints) will be handled using last-observation-carried-forward (LOCF) for descriptive analyses. Missing rescue analgesic records are not anticipated, given that the records are logged in the PCA device's memory. Any unavoidable missing events will be treated as censored observations within the RTTE model framework.

6. Ethical Considerations and Regulatory Compliance

This study will be conducted in full compliance with the Declaration of Helsinki, the Malaysian Guidelines for Good Clinical Practice (2nd edition), and all applicable institutional policies and regulations. Ethical approval has been obtained from the Medical Research Ethics Committee (MREC), University Malaya Medical Centre (UMMC) prior to commencement of participant recruitment (MECID NO: 2026223-16373). The study has also been registered with the National Medical Research Register (NMRR) of Malaysia (NMRR ID-26-02772-RUY) and prospectively registered on ClinicalTrials.gov prior to the enrolment of the first participant, in accordance with the principles of the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) for prospective registration of studies involving human participants.

Written informed consent will be obtained from all participants prior to enrolment.

This is an observational study with no modification of clinical care. The analgesic protocol described in Section 3.3 reflects the standard of care at the study institution. Plasma blood sampling for pharmacokinetic purposes has been excluded from the study design to minimise procedural burden and participant risk. Therefore, the risks to participants are limited to those associated with standard postoperative clinical care and routine data collection.

7. Expected Outcomes and Impact

This study will develop the first validated RTTE-PKPD model for rescue analgesia in adults undergoing elective abdominal surgery. Specifically, the study aims to:

- Quantify the pharmacodynamic relationship between predicted morphine plasma concentration and the hazard of rescue analgesic administration, providing a mechanistic and quantitative foundation for model-informed analgesic dosing in abdominal surgery.
- Characterise the temporal structure of analgesic demand, including circadian variation and inter-event hazard modification, enabling the identification of high-risk time windows for pre-emptive dose adjustment.

- Identify patient subgroups at elevated baseline risk for uncontrolled postoperative pain (by sex, age, BMI, and surgical approach), supporting personalised analgesic protocols.
- Provide simulation-based evidence for optimising the timing and dosing of multimodal analgesic protocols in abdominal surgery, with direct applicability to clinical decision support systems.

The resulting model will serve as the quantitative foundation for future prospective model-informed analgesic dosing studies and potentially for integration into electronic clinical decision support tools for postoperative pain management.

References

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