# How Repeated Time To Event (RTTE) modelling of opioid requests after surgery may improve future post-operative pain management

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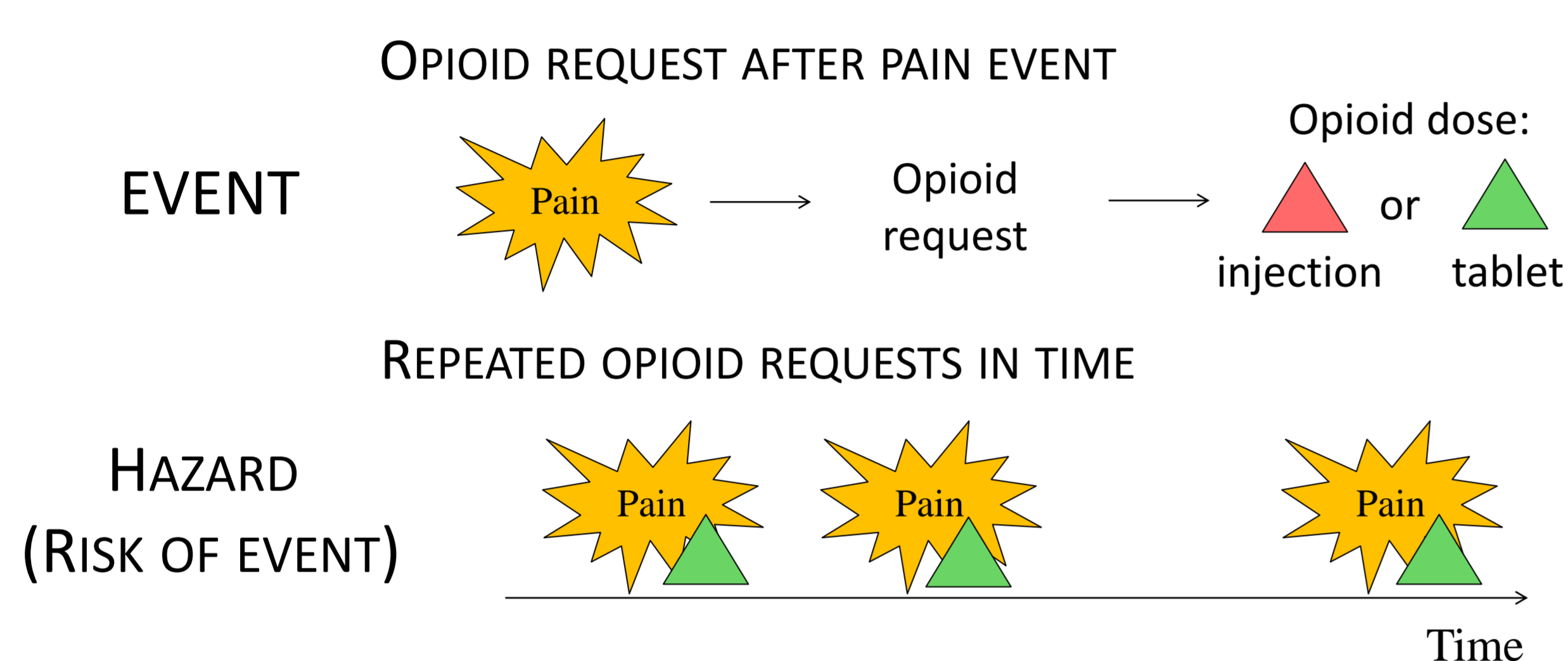
## Introduction

Amount of opioid required by patients after surgery is often used as a surrogate measure for pain intensity in post-operative pain. However, the dynamic development of pain intensity over time is often ignored when investigating new analgesic treatments for post-operative pain[1].
Repeated Time To Event (RTTE) modelling[2] offers a novel approach to the study of opioid requests, which may increase understanding of pain breakthrough patterns in severe surgeries and improve pain management.
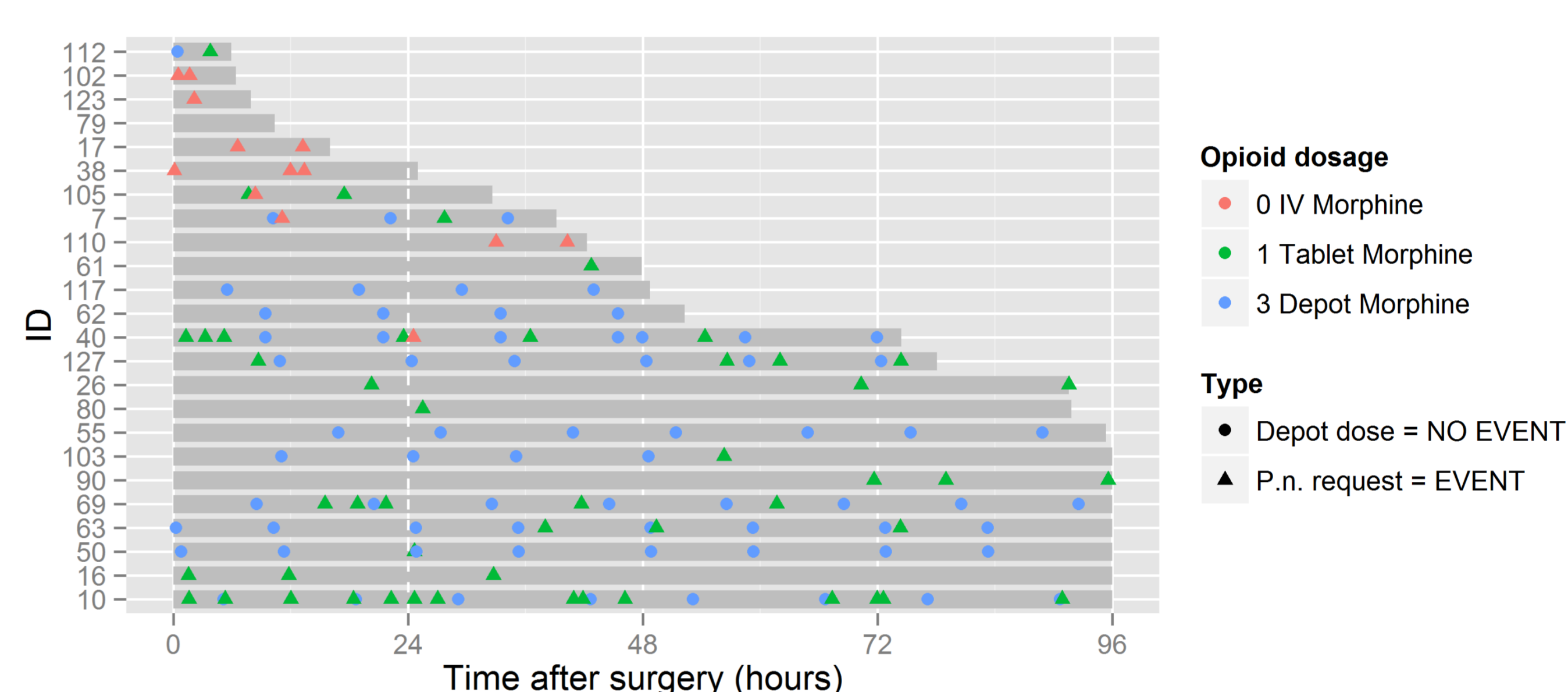
## Aim

To analyse the potential of RTTE modelling of opioid requests in post-operative pain by evaluating:
1. *Opioid request hazard in different surgery types*
2. *Analgesic effect on opioid request hazard*

## RTTE modelling: Hazard describes risk of having pain events



Representative pattern of post-operative opioid requests (events) and preventive depot dosing (non-events) in patients undergoing Dynamic Hip Screw surgery (n=24).
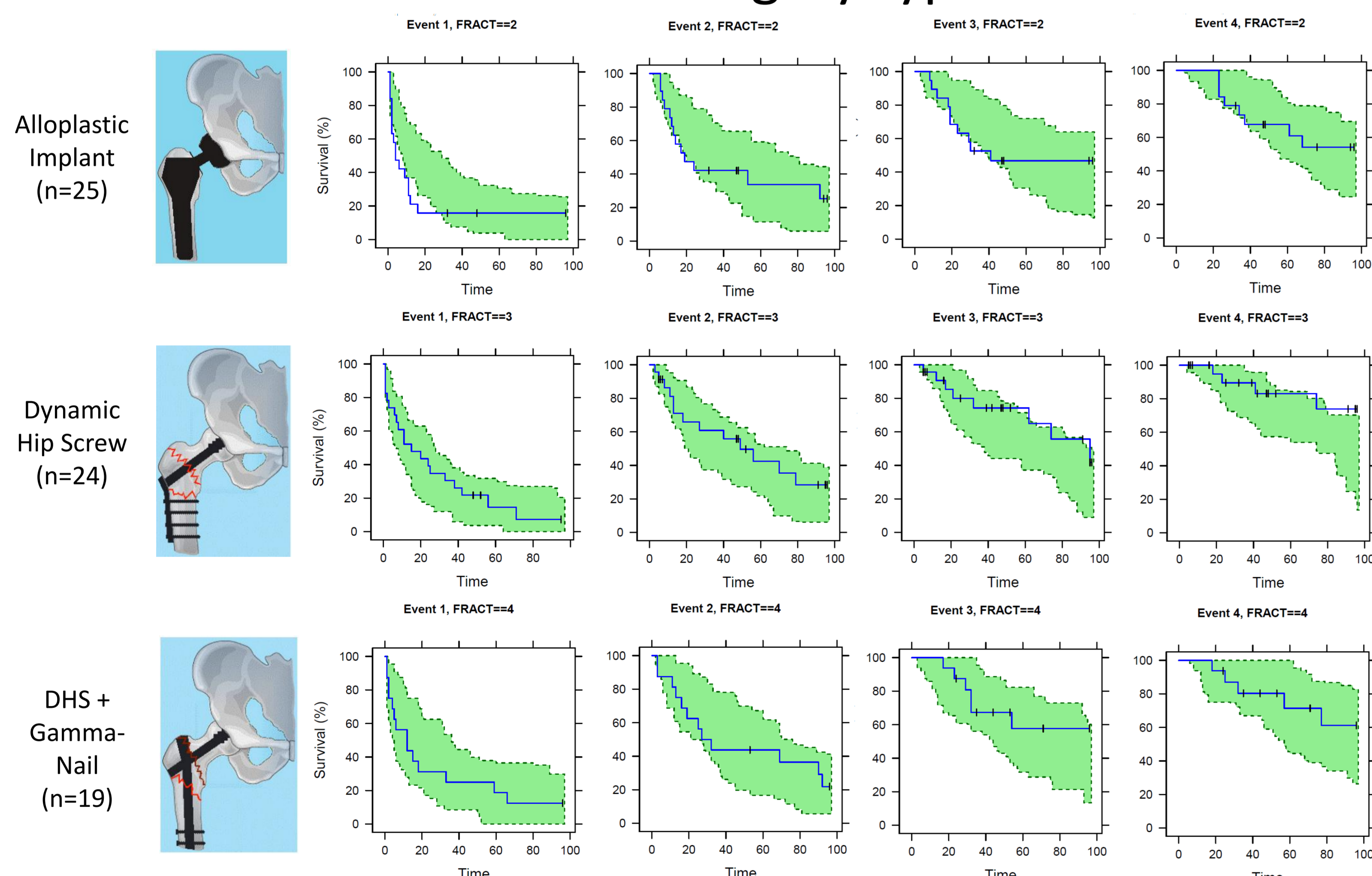
Opioids are ideally given only when needed. An opioid request is a sign of a pain breakthrough event. With RTTE modelling a hazard profile can be calculated that estimates the risk of pain events. Preventive depot dosing are not events.

## RTTE hazard distinguishes pain event patterns between surgery types



Visual Predictive Checks (VPC) of 1st to 4th opioid request event after three surgery types with superposition of a simple weibull type hazard RTTE model. **The same model was fitted assuming no difference between surgery types.** Blue line is the Kaplan Meier survival curve of original data. Green interval is the prediction interval of the RTTE model. The VPCs show that **opioid request was not adequately described by the fitted model** when stratified for surgeries.

This suggest that **pain events do not occur in similar patterns in different surgeries.**

## Analgesic effects can be modelled on RTTE hazard
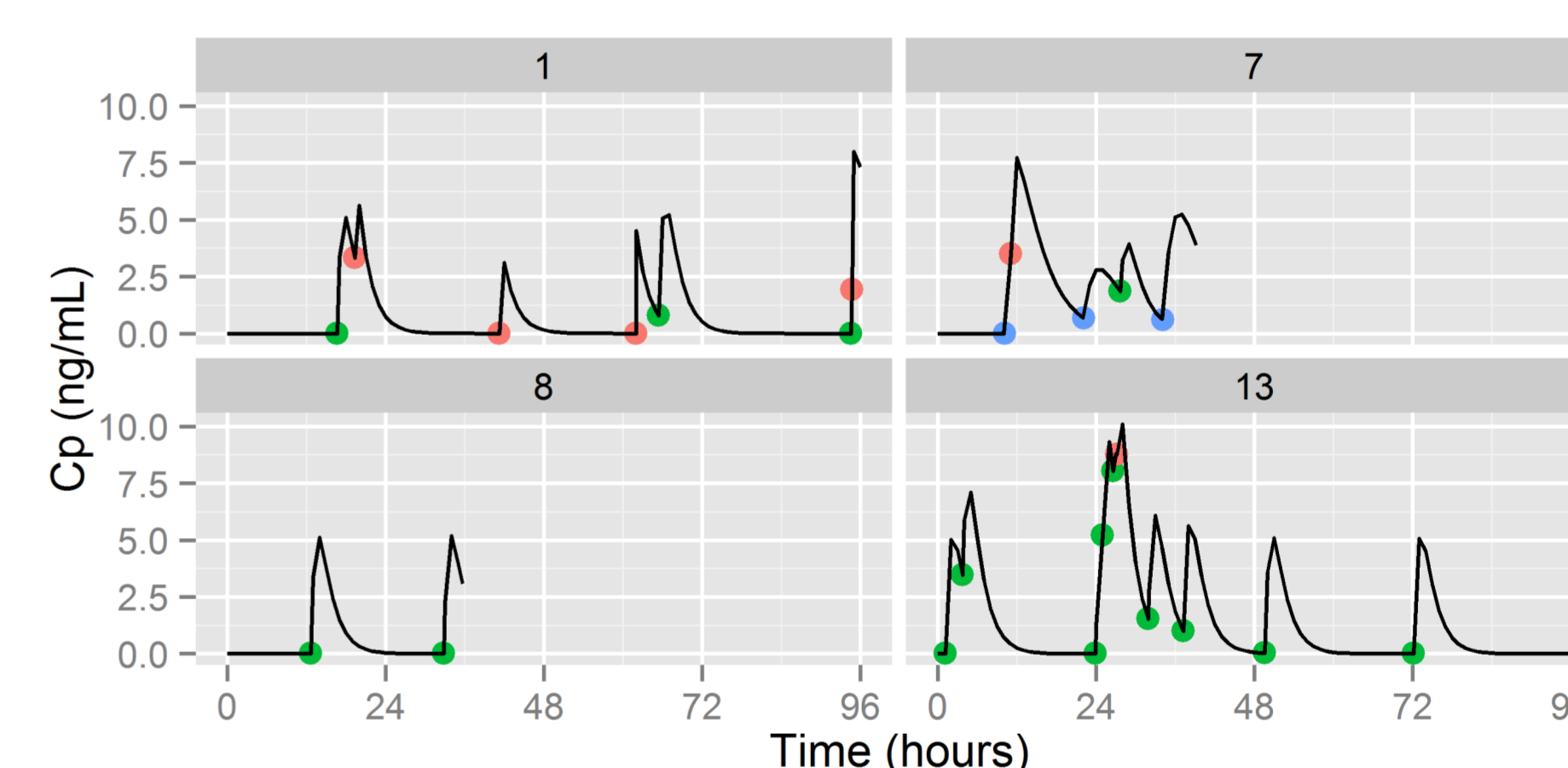


**1) Simulation of pharmacokinetic (PK) profiles**
Concentration of analgesics can be simulated using population PK models. Shown are four representative plots of PK morphine for patients based on recorded timing and dosing of opioids (requested and depot), simulated with an unpublished PK model for morphine (Lund et al 2013).

**2) Estimation of effect model**
The hazard is expected to decline with increasing analgesic concentrations. This could potentially be described by effect models such as shown to the right. Such models will **allow for detailed analysis of analgesic effects in post-operative pain** after severe surgeries.
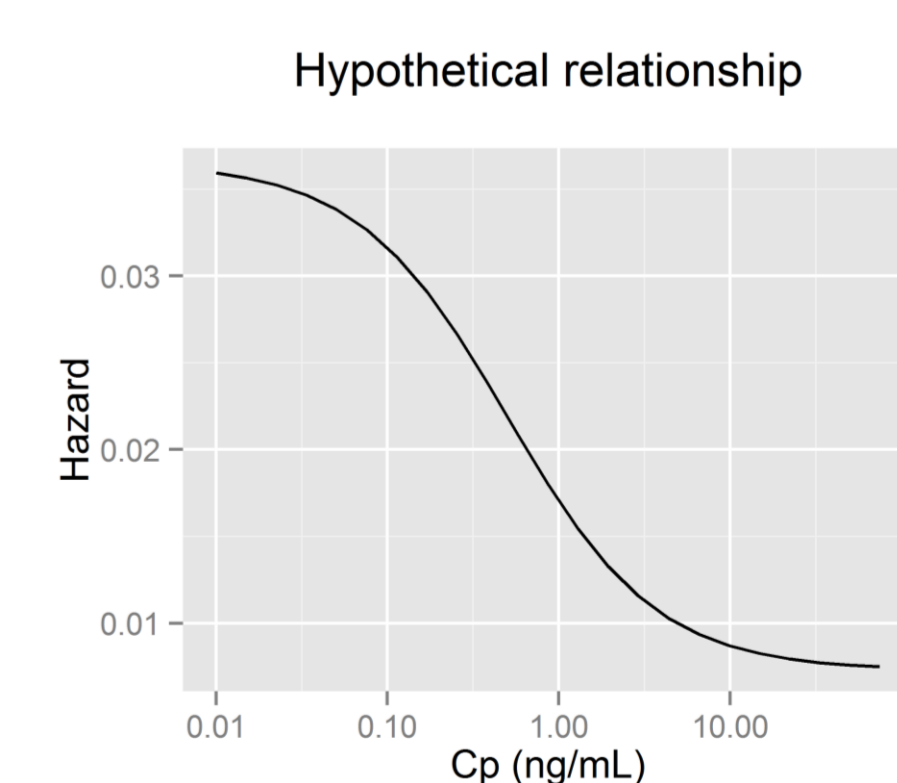


$$Hazard * \left(1 - \frac{Emax * Cp}{Cp + EC50}\right)$$

## Methods

68 patients (F:45,M:23, Age:76±15) were included from patients receiving surgery after hip fracture at Orthopaedic Ward, Aalborg University Hospital in the period May-Dec 2012. Opioid dosing times (estimated precision: ±5mins), formulations and doses were extracted from medical journals in the hospitalization period or until 96 hours after surgery. RTTE modelling and PK simulation was performed in NONMEM 7.2 with Pirana , PsN and Xpose- and ggplot2 libraries for R.

### References
[1] McQuay et al. 2008. Br J Anaesth. 101(1):69-76
[2] Plan et al. 2011. J Pharmacol Exp Ther. 339(3):878-85

## Conclusion

RTTE modelling of opioid requests in post-operative pain may improve future pain management by:
• Identification of surgery specific patterns in pain events
• Evaluation of concentration related effects of analgesics

**It is concluded that RTTE modelling of opioid requests has the potential to improve future pain management**