1. Title Page

Title	Metamizole and Acute Kidney Injury Events in Postoperative Settings (M-AKI)
Research question & Objectives	To determine if the use of metamizole in postoperative pain management setting causes an increased risk of acute kidney injury in hospitalised patients compared to opioids and NSAIDs.
Protocol version	V2
Last update date	27/05/2026
Contributors	**Primary investigator contact information:** Daniel Fernández-Llaneza **Contributor names:** Izak Yasrebi-de Kom, Daniala L. Weir, Ameen Abu-Hanna, Giovanni Cinà, Joanna E. Klopotowska
Study registration	**Site:** HMA/EMA RWD Catalogues **Identifier:** EUPAS1000000740
Sponsor	**Organization:** Dutch Research Council (Nederlandse Organisatie voor Wetenschappelijk Onderzoek, NWO) **Contact:** Joanna E. Klopotowska
Conflict of interest	n/a

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2. Abstract

Metamizole (dipyrone) was first introduced commercially in 1922 as an effective non-opioid analgesic and antipyretic, indicated for moderate to severe pain, particularly in postoperative settings. In the Netherlands, it is recommended by the Dutch Association of Anaesthesiologists (Nederlandse Vereniging voor Anesthesiologie, NVA), as a suitable alternative for patients who cannot take non-steroidal anti-inflammatory drugs (NSAIDs). While the haematological safety of metamizole, particularly its association with agranulocytosis, has been extensively debated, its potential contribution to acute kidney injury (AKI) remains poorly studied. This is especially concerning given its widespread use in the postoperative setting in the Netherlands, but also other European countries such as Germany. Therefore, this study will evaluate whether metamizole administered in postoperative settings increases the risk of AKI in a major academic hospital in the Netherlands to provide evidence to inform clinical practice.

We will use data from electronic health records (EHR) of patients who were hospitalised at the Amsterdam University Medical Centre (Amsterdam UMC), which includes longitudinal date-stamped outpatient and inpatient information on social demographics, laboratory measurements, healthcare utilisation, medication administrations, and medical diagnoses. We will carry out a cohort study with a new user active comparator design, where metamizole new-users will be compared against opioid new-users and NSAIDs new-users within the hospitalisation period.

3. Amendments and updates

Version date	Version number	Section of protocol	Amendment or update	Reason
13 May 2025	V1	First draft	n/a	n/a
01 Jul 2025	V1.1	Second draft	Update after comments from the rest of the team	n/a
24 Sep 2025	V1.2	Third draft	Last review prior to starting the formal analysis	n/a
11 Jun 2026	V2	Fourth draft	Introduction of two new exclusion criteria: 1) non-invasive diagnostic procedures, minimally invasive procedures or kidney-related surgeries, 2) invasive respiratory support, 3) Childbirth	Non-invasive diagnostic procedures or minimally invasive procedures do not entail significant pain which requires analgesic treatment in a postoperative pain management setting. Kidney-related surgeries might transiently impact kidney function, rendering AKI diagnosis unreliable. Childbirth and postpartum period can influence creatinine measurements and render the identification of AKI difficult. Childbirth DCM has now become available. Inspection of propensity score distribution revealed a subset of patients on invasive respiratory support have high likelihood of being administered opioids only. Given that this constitutes a

				structural positivity violation they would bed from the analysis.
			Removed bariatric surgery from the confounders list.	Bariatric surgery is not carried out within Amsterdam UMC premises and therefore is not relevant for this study,
			Amendment to intercurrent event (ICEs) list	Pre-renal AKI/haemodynamic instability events considered as ICEs. Post-renal and intrinsic AKI aetiologies are highly unlikely in a postoperative setting. Childbirth is included as an intercurrent event together with pregnancy.
			Addition of new drugs in treatment arms	Opioid use in postoperative setting goes beyond the ones recommended in the hospital guideline. Thus, tramadol, fentanyl, pethidine, and tapentadol have been added. Acetaminophen use at baseline will be reported as a descriptive statistic.
			Clarified baseline serum creatinine definition and added missingness as a backstop criterion. Added exclusion criterion on missing baseline serum creatinine.	There are multiple ways baseline serum creatinine can be defined and a heuristic is needed to estimate it. Missing baseline serum creatinine (if present, for CKD patients) does not allow diagnosis of AKI as per KDIGO 2012 guideline on AKI. Therefore, patients without baseline creatinine were excluded.
			Changing of nomenclature for analyses.	Causal contrast names and estimand numbering changed to improve accuracy in naming. All analyses are intention-to-treat and we distinguish them with different ICE handling strategies hypothetical and/or treatment policy.
			Removed prevalence rule for variable selection.	Prevalence criterion is not considered to be relevant for variable selection any longer, because confounding potential is determined by a variable's association with both exposure and outcome and not by how common it is in the study population.
			Specified how Charlson's Comorbidity Index was estimated when not directly available.	There are different ways (and sets of ICD codes) reported for estimating the Charlson's Comorbidity Index .
			Extended definition of variables of interest (i.e., confounders) by including laboratory measurements.	Including laboratory measurements (where applicable) for defining confounders increases sensitivity.
			Figure and table updates.	Figure updates were designed to improve clarity, precision, and

				consistency in nomenclature. In addition, patient attrition counts were updated to reflect current study status. Table on counts, AKI events and crude incidence stratified by treatment arm and their corresponding single drugs was also updated accordingly.
			Added reference to ASA score.	Anchoring the score to its original reference for better contextualisation.
			Provided further details on how multiple imputation will be done and the downstream handling for propensity scores estimation.	Additional details provided on its implementation and auxiliary variables added.
			Updated propensity score weighting 'post-processing': truncation and isotonic calibration for IPTW and truncation for IPCW.	Homogenised approach across analyses and added clarifications where needed.
			Nomenclature standardisation and description elaboration.	'Combination analgesic treatments' is a more accurate description of the patterns observed, thus 'multimodal analgesia' was dropped. 'Drug-drug interactions flagged for AKI' were rephrased as 'potentially nephrotoxic drug-drug interactions' for the sake of clarity. Target trial emulation framework, estimands framework, primary and secondary analyses tables, and follow-up tables were further elaborated and edited to ensure thorough and accurate description of the intended analysis.

Milestones

Table 1 Milestones

Milestone	Date
Feasibility counts	8 May 2025
Draft 1 of protocol complete	24 September 2025
Registration of protocol	29 September 2025
Protocol amendments based on preliminary analyses	11 June 2026
Study progress report 1	
Study progress report 2	
Final report of study results	

4. Rationale and background

What is known about the condition: Acute kidney injury (AKI) is defined as a sudden decline in kidney function identified via increased serum creatinine levels or reduced urine output. Over the past decades, AKI has been linked with poor health outcomes even at milder stages and occur approximately in 20% of hospitalised adults. It is estimated that 19-26% of AKI events in hospitalised patients is caused by drugs.

What is known about the exposure of interest: Metamizole (dipyrone) is used as an analgesic in the postoperative pain management setting, and, in the Netherlands, it is recommended for use in patients with a contraindication to NSAIDs. Its international status regarding regulatory approval remains controversial due to the risk of agranulocytosis, a potentially fatal adverse drug event. It is suspected that metamizole may also be causative for AKI, but current evidence is still scarce and with methodological limitations. Evidence from randomised clinical trials suggests that metamizole has a similar kidney prostaglandin-inhibitory profile to non-selective NSAIDs such as naproxen and diclofenac, although it does not appear to impair significantly glomerular filtration rate in healthy or patients with cirrhosis over short treatment periods. Paracetamol, by contrast, is a considerably weaker inhibitor of kidney prostaglandin synthesis and is therefore considered the safer analgesic option with respect to kidney function, particularly in patients at elevated kidney risk such as those with liver cirrhosis.

Gaps in knowledge: the causal relationship between metamizole use and acute kidney injury remains controversial.

What is the expected contribution of this study? To provide further evidence on the acute kidney injury potential of metamizole in postoperative pain management setting.

5. Research question and objectives

Table 2 Primary and secondary research questions and objective

A. Primary research question and objective

Objective:	To estimate the effect of metamizole on the risk of hospital-acquired acute kidney injury compared with (1) opioids and (2) NSAIDs.
Hypothesis:	Metamizole use increases the risk of acute kidney injury compared to opioids and may have a similar or lower risk compared to NSAIDs, when accounting for the natural course of treatment and patient outcomes in routine secondary care.
Population ***(mention key inclusion-exclusion criteria):***	First ever inpatient administration of metamizole users in a postoperative pain management setting (i.e., up to 7 days after surgery). Patients who were prescribed metamizole up to 14 days prior to surgery were excluded, as they were likely to be prevalent users. Patient admissions on combined analgesic treatment (i.e., multiple analgesics given together) up to one hour after treatment initiation were excluded, because it was considered that these medications were intended to be given together. Patients with acute kidney injury or acute kidney disease episodes up to seven days prior to surgery were excluded. Patients who had acute dialysis 14 days prior to exposure or on chronic dialysis were excluded.
Exposure:	Metamizole (dipyrone)
Comparator:	1) NSAIDs 2) Opioids
Outcome:	Acute kidney injury (AKI, all stages) as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) using serum creatinine measurements.
Time ***(when follow up begins and ends):***	Follow-up for the cohort began one hour after initiation of therapy with metamizole (or comparator), this to allow a grace period in which intended combination analgesic treatments therapy could be initiated (i.e., time zero). Follow-up continued until the earliest of: first-ever acute kidney injury during hospital stay, or hospital discharge, 14 days after treatment initiation, and end of study period (administrative censoring). Patients were followed up regardless of changes in treatment status (i.e., treatment discontinuation, dose adjustments, any switches/add-ons), consistent with a treatment-policy approach. Exposure to metamizole was evaluated any time from surgery end until 7 days after, which was considered to be postoperative pain management setting.
Setting:	Inpatient care.

Main measure of effect:	risk difference (primary estimand), risk ratio (supplementary estimand)

a. Estimands framework

Estimand Attribute	Estimand 1 (primary estimand)	Estimand 2 (supplementary estimand)	Estimand 3 (supplementary estimand)	Estimand 4 (supplementary estimand)
Population	Adults hospitalised in Amsterdam UMC for ≥24 hours between January 1, 2019 and December 31, 2025 in a postoperative pain management setting (i.e., 7 days after surgery).			
Treatment Conditions	Intervention group: first-ever systemic administration of metamizole. Control group: first-ever systemic administration of opioids (i.e., morphine, buprenorphine, oxycodone, piritramide, fentanyl, methadone, tramadol, pethidine, hydromorphone, and tapentadol). In-class rotation, switches, add-ons or dose adjustments during follow-up are considered part of the same initial treatment strategy and do not constitute treatment changes.		Intervention group: first-ever systemic administration of metamizole. Control group: first-ever systemic administration of non-steroidal anti-inflammatory drugs (i.e., aceclofenac, dexketoprofen, diclofenac, phenylbutazone, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meloxicam, nabumetone, naproxen, etoricoxib, parecoxib, celecoxib, piroxicam, propyphenazone, tiaprofenic acid, high-dose acetylsalycilic acid, and diflusinal). In-class rotation, switches, add-ons or dose adjustments during follow-up are considered part of the same initial treatment strategy and do not constitute treatment changes.	
Endpoint	First-ever inpatient acute kidney injury (AKI, all stages), based on KDIGO serum creatinine criteria			
Summary Measure	Risk difference	Risk ratio	Risk difference	Risk ratio
Intercurrent events and strategies to handle them*	Same for both treatment conditions. Intercurrent events (ICE): 1) Postoperative clinical events: a. Receipt of kidney replacement therapy (i.e., chronic or acute dialysis, and kidney transplantation): treatment policy. b. Postoperative pre-renal AKI /haemodynamic instability events (e.g., sepsis, arrhythmias, cardiomyopathies, myocardial infarction, and hypovolaemia): treatment policy.† 2) Out-of-class treatment switch/add-on (i.e., to a different comparator drug): treatment policy. 3) Documentation of pregnancy or childbirth: treatment policy. 4) Use of prohibited medications (i.e., selected drugs with AKI potential): treatment policy. 5) Administration of potentially nephrotoxic drug-drug interactions: treatment policy. 6) In-hospital death: while alive. Post-operative intrinsic AKI aetiologies (e.g., thrombotic microangiopathy, and thromboembolism) and post-renal AKI aetiologies (e.g., mechanical obstruction) were considered but deemed highly unlikely in the postoperative context. Intrinsic interstitial/nephrotoxic insult is one of the metamizole-AKI mechanisms and is therefore not an intercurrent event. Under the while alive strategy, the post-ICE outcome (AKI) is no longer of interest. No IPCW is modelled for this, given that AKI cannot occur thereafter.			

* Intercurrent events are post-baseline events (or post-randomisation events in randomised trials) that affect the interpretation or existence of outcome data. These events frequently affect receipt of treatment (e.g., treatment switching or treatment discontinuation) or preclude existence of the outcome (e.g., death, if it is not defined as part of the outcome).
† Postoperative AKI is often multifactorial, with overlapping and concurrent pathophysiological metamizole-associated AKI. For such insights, studies combining clinical data with human kidney tissue analyses are needed, which goes beyond the aim of this study.
Abbreviations: AKI, acute kidney injury; ICE, intercurrent event; KDIGO, kidney disease improving global outcomes

B. Secondary research question and objective

Objective:	To estimate the effect of metamizole on the risk of hospital-acquired acute kidney injury, compared with (1) opioids and (2) non-steroidal anti-inflammatory drugs (NSAIDs).
Hypothesis:	Under conditions where no intercurrent or censoring events occur at random (i.e., kidney replacement therapy, out-of-class switch/add-on, documentation of pregnancy, administration of potentially nephrotoxic drug-drug interactions, in-hospital death, use of prohibited medications [i.e., selected drugs with AKI potential]), metamizole use increases the risk of acute kidney injury compared to opioids, and has a comparable or lower risk to NSAIDs.
Population ***(mention key inclusion-exclusion criteria):***	First ever inpatient administration of metamizole users in a postoperative pain management setting (i.e., up to 7 days after surgery). Patients who were prescribed metamizole up to 14 days prior to surgery were excluded, as they were likely to be prevalent users. Patient admissions on combined analgesic treatment (i.e., multiple analgesics given together) up to one hour after treatment initiation were excluded, because it was considered that these medications were intended to be given together. Patients with acute kidney injury or acute kidney disease episodes up to seven days prior to surgery were excluded. Patients who had acute dialysis 14 days prior to exposure or on chronic dialysis were excluded.
Exposure:	Metamizole (dipyrone)
Comparator:	1. NSAIDs 2. Opioids
Outcome:	Acute kidney injury (AKI, all stages) as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) using serum creatinine measurements.
Time ***(when follow up begins and ends):***	Follow-up for the cohort began one hour after initiation of therapy with metamizole (or comparator), this to allow a grace period in which intended combination analgesic treatments therapy could be initiated (i.e., time zero). Follow-up continued until the earliest of: first-ever acute kidney injury during hospital stay, hospital discharge, 14 days after treatment initiation, end of study period, receipt of kidney replacement therapy, out-

	of-class treatment switch/add-on, documentation of pregnancy, administration of potentially nephrotoxic drug-drug interactions, in-hospital death, and use of prohibited medications (i.e., selected drugs with AKI potential). Patients were followed up regardless of changes in dose adjustments and postoperative clinical events. However, all other intercurrent events were handled using a hypothetical approach. Exposure to metamizole was evaluated any time from surgery end until 7 days after, which was considered to be postoperative pain management setting.
Setting:	Inpatient care.
Main measure of effect:	risk difference (primary estimand), risk ratio (supplementary estimand)

b. Estimands framework

Estimand Attribute	**Estimand 5 (primary estimand)**	**Estimand 6 (supplementary estimand)**	**Estimand 7 (supplementary estimand)**	**Estimand 8 (supplementary estimand)**
Population	Adults hospitalised in Amsterdam UMC for ≥24 hours between January 1, 2019 and December 31, 2025 in a postoperative pain management setting (i.e., 7 days after surgery).			
Treatment Conditions	Intervention group: first-ever systemic administration of metamizole. Control group: first-ever systemic administration of opioids (i.e., morphine, buprenorphine, oxycodone, piritramide, fentanyl, methadone, tramadol, pethidine, hydromorphone, and tapentadol). In-class rotation, switches, add-ons or dose adjustments during follow-up are considered part of the same initial treatment strategy and do not constitute treatment changes.		Intervention group: first-ever systemic administration of metamizole. Control group: first-ever systemic administration of non-steroidal anti-inflammatory drugs (i.e., aceclofenac, dexketoprofen, diclofenac, phenylbutazone, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meloxicam, nabumetone, naproxen, etoricoxib, parecoxib, celecoxib, piroxicam, propyphenazone, tiaprofenic acid, high-dose acetylsalycilic acid, and diflusinal). In-class rotation, switches, add-ons or dose adjustments during follow-up are considered part of the same initial treatment strategy and do not constitute treatment changes.	
Endpoint	First-ever inpatient acute kidney injury (AKI, all stages), based on KDIGO serum creatinine criteria			
Summary Measure	Risk difference	Risk ratio	Risk difference	Risk ratio
Intercurrent events and strategies to handle them*	Same for both treatment conditions. Intercurrent events (ICE): 1) Postoperative clinical events: a. Receipt of kidney replacement therapy (i.e., chronic or acute dialysis, and kidney transplantation): treatment policy. b. Postoperative pre-renal AKI/haemodynamic instability events(e.g., sepsis, arrhythmias, cardiomyopathies, myocardial infarction, and hypovolaemia): treatment policy.† 2) Out-of-class treatment switch/add-on (i.e., to a different comparator drug): treatment policy.			

Estimand Attribute	Estimand 5 (primary estimand)	Estimand 6 (supplementary estimand)	Estimand 7 (supplementary estimand)	Estimand 8 (supplementary estimand)
	3) Documentation of pregnancy or childbirth: treatment policy. 4) Use of prohibited medications (i.e., selected drugs with AKI potential): treatment policy. 5) Administration of potentially nephrotoxic drug-drug interactions: treatment policy. 6) In-hospital death: while alive. Post-operative intrinsic AKI aetiologies (e.g., thrombotic microangiopathy, and thromboembolism) and post-renal AKI aetiologies (e.g., mechanical obstruction) were considered but deemed highly unlikely in the postoperative context. Intrinsic interstitial/nephrotoxic insult is one of the metamizole-AKI mechanisms and is therefore not an intercurrent event. Under the hypothetical strategy, censoring at the ICE is non-administrative, since post-ICE outcomes remain of interest but are unobserved. Because this censoring is likely informative, IPCW is required.			

* Intercurrent events are post-baseline events (or post-randomisation events in randomised trials) that affect the interpretation or existence of outcome data. These events frequently affect receipt of treatment (e.g., treatment switching or treatment discontinuation) or preclude existence of the outcome (e.g., death, if it is not defined as part of the outcome).

† Postoperative pre-renal AKI/haemodynamic instability events (e.g., sepsis, arrhythmias, cardiomyopathies, myocardial infarction, and hypovolaemia), intrinsic AKI aetiologies (e.g., thrombotic microangiopathy, and thromboembolism), and post-renal AKI aetiologies (e.g., mechanical obstruction). Notably, postoperative AKI is often multifactorial, with overlapping and concurrent pathophysiological metamizole-associated AKI. For such insights, studies combining clinical data with human kidney tissue analyses are needed, which goes beyond the aim of this study.

C. Target Trial Emulation Framework

Protocol Element		Target Trial Specification	Emulation with Observational Data
Causal Estimand	Eligibility criteria	**Inclusion criteria:** 1) Adults (≥18 years old at admission date) admitted to Amsterdam UMC for more than 24 hours; 2) Post-operative pain management setting. **Exclusion criteria:** 1) Non-invasive diagnostic procedures or minimally invasive procedures (i.e., imaging procedures, insertion/placements, puncture/drainage, ablation/destruction, non-surgical fracture immobilization procedures, diagnostic and minimally invasive endoscopic procedures, examinations and inspections, extractions/removals), because they do not require analgesic pain management, and kidney-related surgeries (i.e., nephrostomy, nephrectomy, kidney transplant removal, kidney biopsy), because they may induce serum creatinine fluctuations and render AKI diagnosis unreliable; 2) Kidney transplantation in the past year from index date, because it alters kidney physiology and the kidney function may remain unstable; 3) On chronic dialysis, because no significant remaining kidney function can sustain injury; 4) Acute dialysis episode within the past 14 days (as per ADQI 16 Working group) from index date, because kidney function may be unstable or patients may still be recovering from an unresolved kidney injury; 5) Pre-exposure AKI or AKD episodes seven days prior to or on index date; 6) Neither metamizole nor comparator use 14 days prior to treatment initiation, to represent 'new user' status (washout window); 7) Pregnant women, because pregnancy alters serum creatinine physiology and baseline kidney function; 8) Childbirth; 9) Patients with a treatment switch/add-on within one hour of the administration of a study analgesic (i.e.,	Same as target trial. Observation period between January 2019, 1 and December 2025, 31. **Inclusion criteria**: 1) Adults (≥18 years old at admission date) admitted to Amsterdam UMC for more than 24 hours as registered in Amsterdam UMC EHR systems; 2) Post-operative pain management setting: identified in the Procedures in the Operation Room DCM. **Exclusion criteria:** 1) Non-invasive diagnostic procedures or minimally invasive procedures, and kidney-related surgeries: identified in the Procedures in the Operation Room DCM using CBV codes. 2) No kidney transplantation: defined as absence of procedure codes or ICD-10 diagnosis codes. 3) Chronic dialysis is defined as two dialysis encounters at least 90 days apart with at least two dialysis encounters per week (i.e., dialysis measurements, procedure codes or ICD-10 codes) or the equivalent total (i.e., 25 encounters in any 90-day time window) or a registration of a diagnosis code pertaining to chronic dialysis. 4) Acute dialysis episode: defined as the presence of a dialysis encounter, procedure code or ICD-10 diagnosis code 14 days prior to inpatient metamizole administration. 5) No previous AKI or AKD episode: defined as per 2012 AKI KDIGO using serum creatinine criteria. 6) No metamizole or comparator use (as pertinent in each treatment strategy) identified with ATC code and internal codes when the ATC code was lacking. 7) Pregnancy: identified via pregnancy status as recorded by clinicians in the Pregnancy Detailed Clinical Model (DCM). A pregnancy is considered active if the recorded status falls within 294 days

Protocol Element		Target Trial Specification	Emulation with Observational Data
		metamizole, NSAIDs, or opioids), as this likely reflects combination analgesic treatments rather than true out-of-class switch/add-on; 10) Missing baseline serum creatinine; 11) Invasive respiratory support (i.e., extracorporeal membrane oxygenation [ECMO] and invasive mechanical ventilation).	(approximately 42 weeks) before index date. Alternatively, presence of pregnancy-specific procedures in the Procedures Delivered in the Operation Room DCM. 8) Childbirth: If childbirth occurs up to 42 days (6 weeks are considered as the postpartum period) before index date documented in the Childbirth DCM or Procedures Delivered in the Operation Room DCM. 9) Combination analgesic treatments therapy: defined as receiving more than one pain management strategy (i.e., opioids, NSAIDs or metamizole) within 1 hour of index administration (i.e., first-ever administration of opioids, NSAIDs or metamizole). 10) Baseline serum creatinine was assigned based on a rule-based hierarchical algorithm which involved using pre-hospitalisation outpatient serum creatinine measurements, first inpatient serum creatinine measurement or back-calculation following the CKD-EPI equation (without race) and using patients' demographic data. 11) Invasive respiratory support was identified using CBV codes. Unlike in the target trial, given that we implement these exclusion criteria based on ICD-10, ATC, CBV, internal codes or registrations, misclassification may occur. In addition, no prior AKI relies on a retrospective implementation of the KDIGO serum creatinine AKI criteria on serum creatinine measurements available in EHR data, whereas in the target trial it could be done using prospective serum creatinine monitoring.
	Treatment strategies	Systemic administrations are defined as any oral, parenteral or other administration routes as specified in *Supplementary Information*. (1) First-ever initiation of systemic inpatient administration of metamizole only, as-needed, according to therapeutic dosing guidelines.	Same as target trial, identified in the Medication Administration DCM with ATC codes and internal codes if ATC codes are missing. In the target trial, first-ever systemic initiation is enforced and ensures a clean exposure contrast, whereas in the emulation drug exposure is reconstructed based on

Protocol Element		Target Trial Specification	Emulation with Observational Data
		(2) Active comparator arms: a. Reference cohort (negative exposure): i. First-ever initiation of systemic inpatient administration of opioids (i.e., morphine, methadone, buprenorphine, oxycodone, piritramide, fentanyl, tramadol, pethidine, hydromorphone, and tapentadol), according to therapeutic dosing guidelines and postoperative pain management setting utilisation. b. Additional cohort (positive exposure): i. First-ever initiation of systemic inpatient administration of NSAIDs (i.e., aceclofenac, dexketoprofen, diclofenac, phenylbutazone, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meloxicam, nabumetone, naproxen, etoricoxib, parecoxib, celecoxib, piroxicam, propyphenazone, tiaprofenic acid, high-dose acetylsalicylic acid [i.e., ≥100 mg/day], and diflusinal), according to therapeutic dosing guidelines.	registrations as EHR data is re-used. Additionally, combination analgesic treatments need to be discarded.
	Treatment Assignment (unmasked)	Randomised, non-blinded.	Non-blinded and assumed to be randomised conditional on the measured confounders. Randomisation is emulated through inverse probability of treatment weighting (IPTW). Medications are assessed using the medication administration records and internal codes if ATC codes are missing.
	Start/end Follow-up	Follow-up starts at treatment administration initiation and is censored at *first*-ever occurrence of AKI during hospitalisation, post-operative clinical events (i.e., receipt of kidney replacement therapy, postoperative pre-renal/haemodynamic instability events), 14 days after treatment initiation, out-of-class treatment strategy switch/add-on (i.e., to a comparator drug), documentation of pregnancy, in-hospital death, drug-drug interactions, prohibited medications, hospital discharge, or administrative censoring	Same as target trial, follow-up also ends at hospital discharge. Kidney transplantation is identified with procedure or ICD-10 codes performed in the operation room. In-hospital death as recorded in Amsterdam UMC premises. While in the target trial, censoring occurs by design (e.g., administrative end of follow-up); in the emulation, censoring

Protocol Element		Target Trial Specification	Emulation with Observational Data
		(i.e., December 2025, 31), whichever occurs first.	also may also happen due to hospital discharge or lack of serum creatinine monitorisation. In the target trial, follow-up is guaranteed until day 14, regardless of discharge status. In contrast, in the emulation, follow-up ends at discharge, which may shorten observation time and introduces the risk of informative censoring.
	Primary outcome	AKI within a 14-day risk window after exposure. Acute kidney injury was defined as per 2012 AKI KDIGO criteria using serum creatinine criteria.	Same as target trial. Baseline serum creatinine is defined using a rule-based hierarchical algorithm. First, as the median serum creatinine between 7 to 365 days prior to hospital admission as suggested by Siew et al. or, in its default, the heuristics suggested by Joyce et al. were followed (admission serum creatinine>back-calculation using CKD-EPI (2009) with an eGFR derived from age and sex).
	Causal contrasts	Intention-to-treat (i.e., the effect of being assigned to a particular treatment). Estimands with two different strategies for handling intercurrent events (ICEs): treatment policy ICE handling strategy; hypothetical ICE handling strategy (except for AKI aetiologies, given that postoperative AKI is often multifactorial, with overlapping and concurrent pathophysiological mechanisms which may require studies combining clinical data with human kidney tissue analysis that are beyond the aim of this study).	Observational analogue of intention-to-treat effect (i.e., the effect of *initiating* a particular treatment strategy) under two scenarios: 1) ignoring ICEs (treatment policy ICE handling strategy); 2) assuming ICEs do not occur/occur at random across arms (hypothetical ICE handling strategy), except for AKI aetiologies;
Identifying Assumptions		Treatment policy ICEs handling strategy. Randomised treatment assignment: • Administrative censoring/loss-to-follow-up: end of study period, hospital discharge, and 14 days after start of follow-up. • Intercurrent/competing events/non-administrative censoring: postoperative clinical events (i.e., receipt of kidney replacement therapy, postoperative pre-renal AKI/haemodynamic instability events), out-of-class treatment switch/add-on (i.e., to a comparator drug), documentation of pregnancy, childbirth, prohibited medications, in-hospital death, administration of	Conditional exchangeability holds given baseline covariates used in the IPTW models. Baseline confounders: demographic (i.e., sex, age), healthcare utilisation (i.e., major surgery), comorbidities (i.e., prior AKI, cardiovascular disease, hypoalbuminaemia, sepsis, acute infections, chronic infections, Coronavirus disease 2019 [COVID-19], alcohol-related disorders, chronic kidney disease, liver disease, obesity, anaemia, chronic lung diseases, active cancer, diabetes mellitus, microangiopathics, vasculitides, renovascular disease, malignant hypertension, scleroderma, thrombosis of large arteries), medications (i.e., selected drugs with AKI potential, drug-drug interactions that cause AKI),

Protocol Element	Target Trial Specification	Emulation with Observational Data
	potentially nephrotoxic drug-drug interactions, and use of prohibited medications (i.e., selected drugs that cause AKI).	mechanical (i.e., benign prostatic hyperplasia, neurogenic bladder, intra/extra ureteric obstruction, retroperitoneal fibrosis, burns, and trauma, injuries and accidents), genetic (i.e., glucose-6-phosphate dehydrogenase deficiency), vascular (i.e., hypovolaemia), ASA score, baseline serum creatinine, and rhabdomyolysis. The different detailed clinical models (DCMs) used for identifying confounders are further specified in the *Supplement*. Stable Unit Treatment Value Assignment (SUTVA) and Consistency: patient treatment does not affect the risk of another patient's AKI risk. No risk of multiple versions. Consistency (well-defined interventions), as drugs are identified with ATC codes, only systemic administration routes are considered, same index date for start of follow-up, and no Combination analgesic treatments therapy. Positivity: non-zero probability of each treatment across covariate strata realised (i.e., covariate strata used in the weighting models) in the data. Independent censoring (IPCW): holds conditional on the observed covariate history and intercurrent events up to time *t*. Censoring is independent of potential outcomes given covariate history and intercurrent events up to time *t*. Correct model specification for the weighting/estimation steps.
	Hypothetical ICE handling strategy, except for postoperative clinical events related to postoperative pre-renal/haemodynamic instability events. Assumption of conditional exchangeability: same baseline confounders as per intention-to-treat effect.	Same as per intention-to-treat effect. Conditional exchangeability holds given baseline and time-varying covariates used in the IPTW models. Independent censoring (IPCW): holds conditional on the observed covariate history up to time *t*. Censoring is independent of potential outcomes given covariate history up to time *t*.

Protocol Element	Target Trial Specification	Emulation with Observational Data
Estimator	Adjusted cumulative incidence curves were computed to visualise differences between groups, after (lagged) applying inverse probability of censoring weighting (IPCW) to account for selection bias due to censoring (and other ICEs), and inverse probability weighting (IPTW) to adjust for confounding, comparing metamizole with opioids and with NSAIDs. In-hospital death was consistently handled as a competing event across all analyses, directly account for in the cumulative incidence function, with no IPCW required for this. Propensity scores for IPCW were estimated using pooled logistic regression, and generalised propensity scores for IPTW were estimated using (multinomial) logistic regression. Under the treatment policy strategy, ICEs are allowed to occur, and are not censored at their occurrence. Stabilised IPCW are used to adjust for informative censoring due to loss to follow-up, where weights are constructed conditional on covariate history up to time *t* (including ICE history). Since ICEs are permitted under this strategy, censoring at their occurrence would be administrative, and therefore no ICPW is applied for them. Under the hypothetical handling strategy, ICEs are still of interest but unobserved, making censoring at the ICE non-administrative and potentially informative. (Lagged) IPCW will be applied both to loss to follow-up and applicable ICEs. For arm-specific potential drug-drug interactions (DDIs), a single-arm unstabilised weight will be applied to effectively eliminate the event, reflecting its near-zero probability in the remaining arms. For all other ICEs, stabilised weights will be used to reduce variance conditionally at random with respect to measured confounders and improving finite-sample performance. Subgroup analysis was carried out for CKD patients. Sensitivity analysis will be performed to assess dose-response relationship. Both treatment policy and hypothetical estimands are reported as risk differences and risk rations, with cumulative incidence estimated via the weighted Aalen-Johansen estimator in both cases.	As per target trial. Handling of missing data: multiple imputation (MI) where relevant under the missing at random (MAR). CKD patients were identified as per Fernández-Llaneza et al. *Clin Kidney J.* 2025; 18 (4).

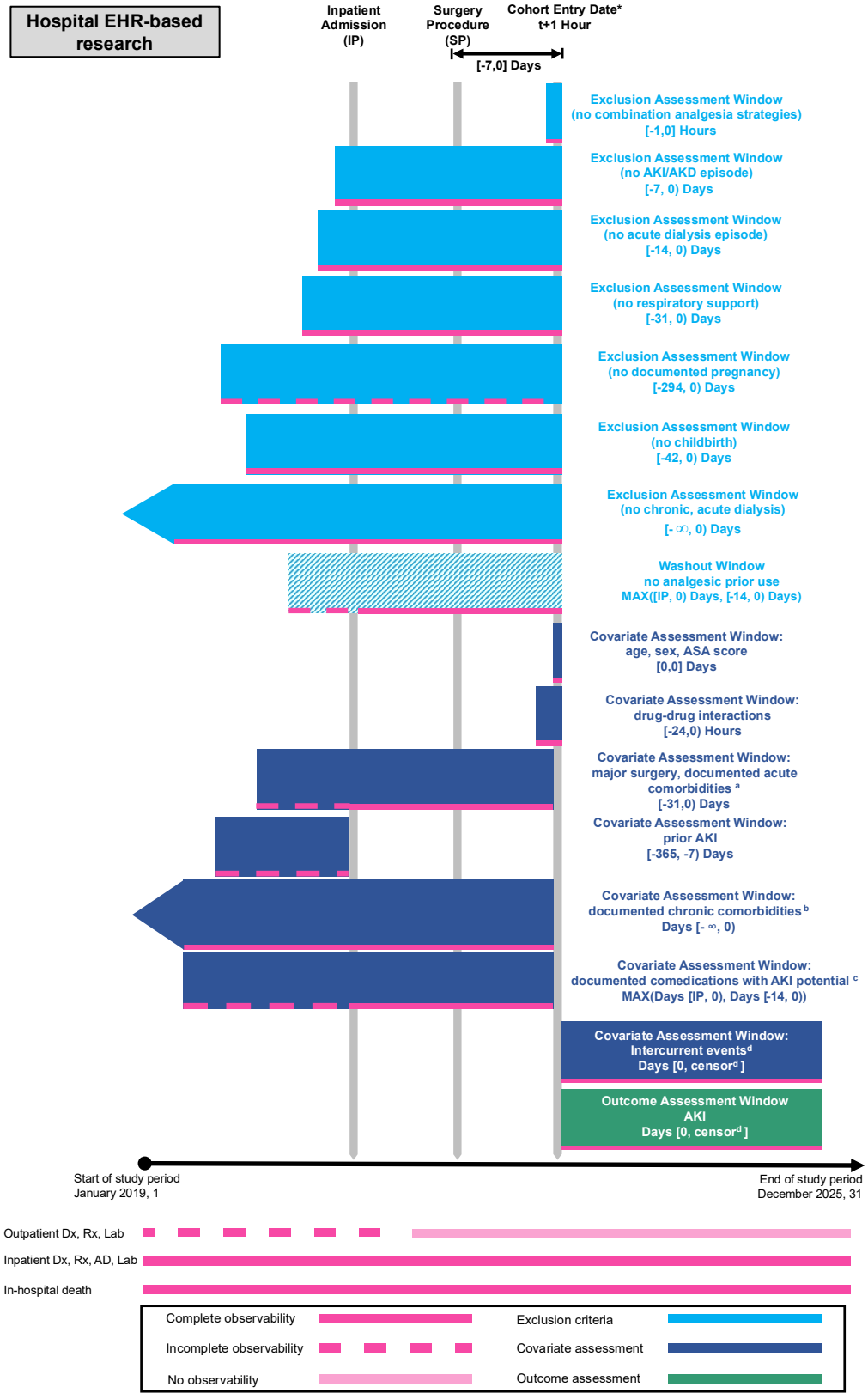
6. Research methods

6.1. Study design

Research design (e.g. cohort, case-control, etc.): New user active comparator cohort study

Rationale for study design choice: clear temporal relationship between exposure (initiation of metamizole) and outcome (i.e., incident AKI), incident exposure, and accurate risk estimation. This study design reduces risk of confounding by indication, prevalent user bias, and fits neatly into the target trial emulation framework.

6.2. Study design diagram



* *t* indicates treatment initiation

[a] Acute comorbidities: CVD (i.e., myocardial infarction), hypoalbuminaemia, sepsis, microangiopathics (HUS, TTP), vasculitides, acute infections, COVID-19, burns, trauma, and hypovolaemia. Identified via ICD-10 or CBV codes listed in the *Supplement*. ASA score is extracted from internal records. Baseline serum creatinine identified from laboratory results.

[b] Chronic comorbidities/genetic disorders/procedures: CVD, chronic lung diseases, cancer, liver disease, renovascular disease, malignant hypertension, scleroderma, glucose-6-phosphate dehydrogenase deficiency, anaemia, BPH, neurogenic bladder, intra/extra-ureteric obstruction, retroperitoneal fibrosis, alcohol-related disorders, obesity, thrombosis of large arteries, and rhabdomyolisis identified via ICD-10 codes listed in the *Supplement*. Charlson's Comorbidity Index was estimated following Deyo's definition.

[c] Comedications with AKI potential with a frequency ≥1% in the SmPC: losartan, gentamicin, piperacillin and beta-lactamase inhibitor, vancomycin, amphotericin B, mitomycin, carboplatin, cisplatin, sirolimus, lithium, abacavir, cidofovir, foscarnet, ganciclovir, valganciclovir, zoledronic acid, hydrochlorothiazide, tacrolimus, ciclosporin). Drugs are identified via ATC codes.

[d] Intercurrent events: in-hospital death, postoperative clinical events (i.e., receipt of kidney replacement therapy, pre-renal AKI aetiologies, other intrinsic AKI aetiologies), identification of pregnancy, out-of-class treatment switch/add-on, potential drug-drug interactions that cause AKI, prohibited medications (i.e., drugs with AKI potential), administrative censoring or 14 days from treatment initiation.

Design based on framework from Wang SV, Schneeweiss S. A Framework for Visualizing Study Designs and Data Observability in Electronic Health Record Data. Clin Epidemiol. 2022 Apr 29;14:601-608. doi: 10.2147/CLEP.S358583

Figure 1. Pharmacoepidemiologic design diagram

6.3. Setting

7.3.1 Context and rationale for definition of time 0 (and other primary time anchors) for entry to the study population

Time 0 is defined as one hour after study analgesic medication administration (i.e., metamizole, opioids or NSAIDs) in a postoperative pain management setting, this to allow a grace period in which intended combination analgesic therapy could be initiated.

Table 3 Operational Definition of Time 0 (index date) and other primary time anchors

Patients entered the base cohort based on initiation of pain relief medications (i.e., analgesics) like metamizole or a comparator drug (i.e., opioids or NSAIDs) after surgery. This allowed identification of patients in a postoperative pain management setting.

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting [1]	Code Type [2]	Diagnosis position	Incident with respect to...	Measurement characteristics / validation	Source of algorithm
Inpatients in postoperative pain management setting	Date of incident administration of study analgesic (i.e., metamizole, NSAIDs, opioids)	Multiple	Incident	[-14,0] days	IP	n/a	n/a	Analgesic (systemic formulations)	No validation study	Investigator review of ATC and internal codes

[1] IP = inpatient admission, n/a = not applicable

[2]See appendix for listing of clinical codes for each study parameter

7.3.2 Context and rationale for study inclusion criteria:

All adult patients (≥18 years old) admitted to Amsterdam UMC for more than 24 hours were included as inpatients. Outpatient episodes in the same setting were considered for baseline covariates such as comorbidities and medication use

Table 4. Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Inpatient admission	Trajectory ≥24 hours	Before selection of index date	[-∞,0] Days	IP	n/a	n/a	Metamizole-exposed patients; Opioids-exposed patients; NSAIDs-exposed patients.	n/a	n/a
Adult	Age ≥18 years	Before selection of index date	[0,0]	IP	n/a	n/a	Metamizole-exposed patients; Opioids-exposed patients; NSAIDs-exposed patients.	n/a	n/a
Postoperative pain management setting	All surgeries performed within Amsterdam UMC, (excluding diagnostic procedures, minimally diagnostic procedures or kidney-related surgeries)	Before selection of index date	[-7,0] Days	IP	n/a	n/a	Metamizole-exposed patients; Opioids-exposed patients; NSAIDs-exposed patients.	n/a	n/a

[1] IP = inpatient admission, OP = outpatient episode, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

7.3.3 Context and rationale for study exclusion criteria

We excluded the following patients: kidney transplant recipients, those on chronic dialysis, those who received acute dialysis, patients with recent AKI or AKD, individuals with prior analgesic use of the treatment medication, women documented as pregnant, and those on multimodal analgesia prior to baseline. Kidney transplant recipients were excluded due to potentially unstable kidney function. Patients on chronic dialysis and acute dialysis episodes fourteen days prior to time zero were excluded either because they may lack sufficient residual kidney function to sustain an injury or may still be recovering from unresolved kidney injury. Those with recent AKI or AKD were excluded to avoid including patients with prevalent elevations in serum creatinine. Pregnant women were excluded, because pregnancy alters serum creatinine physiology and baseline kidney function. Combination analgesic treatments identified within the first hour of exposure administration are excluded, in order to assess patients exposed to exclusively one analgesic agent. It is considered that clinicians planned to give the medications simultaneously and the existing lag between medication administration and registrations is attributed to delays in the clinical setting. A 14-day washout period was applied to ensure new-user status.

Table 5. Operational Definitions of Exclusion Criteria

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
kidney transplantation		After selection of index date	[-365,0] days	IP/OP	ICD-10, CBV (local Dutch codes)	Any	Metamizole-exposed patients; Opioids-exposed patients; NSAIDs-exposed patients.	No validation study	n/a
chronic dialysis	Two dialysis measurements separated by 90 days with 2 dialysis measurements per week (or the equivalent of 25 encounters within that time window) or the registration of a relevant diagnosis code.	After selection of index date	[-∞,0]	IP/OP	ICD-10, CBV (local Dutch codes)	Any	Metamizole-exposed patients; Opioids-exposed patients; NSAIDs-exposed patients.	No validation study	Fernández-Llaneza et al. *Clin Kidney J.* 2025; 18 (4)
acute dialysis		After selection of index date	[-14,0] days	IP/OP	ICD-10, CBV (local Dutch codes)	Any	Metamizole-exposed patients; Opioids-exposed patients; NSAIDs-exposed	No validation study	Chawla et al. *Nat Rev Nephrol.* 2017; 13 (4):241-267

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
							patients.		
AKI or AKD episode	Derived from serum creatinine measurements. AKI: as per KDIGO guidelines, if serum creatinine increases by ≥26.5 µmol/L over 2 days or increased by 1.5-fold from baseline over 7 days. Recovery defined AKD: if the most recent eGFR to hospitalisation is less than 60 mL/min/1.73 m^2, and the preceding measure at least 3 months before is greater than or equal to 60 mL/min/1.73 m^2, or there was no preceding serum creatinine or eGFR measurement and albuminuria was absent or not measured prior to index date.	After selection of index date	[-7,0] days	IP/OP	n/a	n/a	Metamizole-exposed patients; Opioids-exposed patients; NSAIDs-exposed patients.	No validation study	KDIGO guidelines for AKI (2012); Levey. *Nephron*. 2022, 146 (3): 302-305; James MT, et al. *JAMA Netw Open*. 2019, 2 (4):e191795
documentation of pregnancy	Pregnancy status	After selection of index date	[-294,0] days	IP/OP	CBV	n/a	Metamizole-exposed patients; Opioids-exposed patients; NSAIDs-exposed patients.	No validation study	
childbirth		After selection of index date	[-64,0] days	IP/OP	CBV	n/a	Metamizole-exposed patients; Opioids-exposed patients; NSAIDs-exposed patients.	No validation study	

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
combination analgesic treatments therapy (pain relief treatment rotation/switch/add-on)	Combination analgesic treatments therapy are considered to occur up to one hour after the first (postoperative) analgesic administration, as this is considered likely to reflect a specific treatment strategy.	After selection of index date	[-1,0] hours	IP	ATC, internal codes	n/a	Metamizole-exposed patients; Opioids-exposed patients; NSAIDs-exposed patients.	No validation study	Investigator review of medication names
invasive respiratory support	Invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)	After selection of index date	[-31,0] days	IP	CBV	n/a	Metamizole-exposed patients; Opioids-exposed patients; NSAIDs-exposed patients.	No validation study	Investigator defined

[1] IP = inpatient, OP = outpatient, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

6.4. Variables

7.4.1 Context and rationale for exposure(s) of interest

The exposure of interest is metamizole use, defined as first-ever inpatient administration occurring between surgery and up to seven days after surgery. A 14-day follow-up after initiation is used to allow sufficient time for the detection of AKI, ensure that all patients have a uniform observation period and reduce risk of immortal time bias.

Two active comparators are selected:

- Opioids, which are expected to have minimal AKI potential;
- Non-steroidal anti-inflammatory drugs (NSAIDs), which are known to increase AKI risk and serve as a relevant clinical comparator.

This exposure definition supports new-user, active-comparator design, minimising confounding by indication and aligning with real-world clinical practice.

Algorithm to define duration of exposure effect:

Exposure will be classified as first-ever use of metamizole, opioids, or NSAIDs in the postoperative period, as defined above. No stockpiling or refill-based assumptions are required, as this study focusses on inpatient medication records with medication administration timestamps.

Table 6. Operational Definition of Exposure

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type[2]	Diagnosis position[3]	Applied to study populations:	Incident with respect to...	Measurement characteristics/ validation	Source of algorithm
Exposure: metamizole	systemic administration	[-14,0)	[IP, SP]	IP	ATC, internal codes	n/a	Inpatients in postoperative pain management setting	Metamizole	No validation study	Investigator review of medication names
Comparator 1: opioids	systemic administration of morphine, methadone, buprenorphine, oxycodone, piritramide, fentanyl, tramadol, pethidine, hydromorphone, and tapentadol	[-14,0)	[IP, SP]	IP	ATC, internal codes	n/a	Inpatients in postoperative pain management setting	Any medication in comparator 1	No validation study	Investigator review of medication names
Comparator 2: NSAIDs	systemic administration of aceclofenac, dexketoprofen, diclofenac, phenylbutazone, flurbiprofen, ibuprofen, indomethacin, ketoprofen, meloxicam, nabumetone, naproxen, etoricoxib, parecoxib, celecoxib, piroxicam, propyphenazone, tiaprofenic acid, high-dose acetylsalycilic acid (≥100 mg/day) or diflusinal	[-14,0)	[IP, SP]	IP	ATC, internal codes	n/a	Inpatients in postoperative pain management setting	Any medication in comparator 2	No validation study	Investigator review of medication names

[1] IP = inpatient admission, SP = surgery procedure, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

7.4.2 Context and rationale for outcome(s) of interest

The primary outcome of interest is AKI (all stages) occurring during hospitalisation, defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria from 2012, based on changes in measured serum creatinine. This outcome is clinically meaningful, well-standardised, and captured in hospital electronic health records from Amsterdam UMC, where outpatient and inpatient data is routinely collected.

Acute kidney injury is a frequent and serious complication in postoperative patients, which is associated with increased morbidity, long-term damage of kidney function, and prolonged hospitalisations. Non-steroidal anti-inflammatory agents are known to contribute to AKI through kidney damage and dysfunction. On the other hand, opioids are not known to cause AKI, but they have been associated with respiratory depression and addiction as adverse drug events. Metamizole (dipyrone) is an alternative non-opioid analgesic often thought to have a different kidney safety profile.

Thus, outcome was selected to address a clinically and pharmacologically relevant safety question. This is important given the debate regarding the balance between analgesic efficacy and kidney safety in the postoperative setting.

Table 7. Operational Definitions of Outcome

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
Acute kidney injury	Using serum creatinine measurements only as recorded in laboratory measurements. Baseline serum creatinine will be defined as 7 to 365 days prior to admission.	Yes	binary	[-7,0) days	IP	n/a	n/a	Inpatients in postoperative pain management setting	Variable depending on setting. Most studies conducted in emergency settings or ICU. 68% PPV, 79% sensitivity, 94% specificity 94% (Jonsson et al. Eur J Intern Med. 2019 60:78-82). Other examples in Hall PS et al. The future for diagnostic tests of acute kidney injury in critical care: evidence synthesis, care pathway analysis and research prioritisation. Health Technol	KDIGO (2012) guideline for AKI; Siew et al. 2012. 7 (5): 712-9 (baseline serum creatinine)

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source of algorithm
									Assess. 2018 22 (32):1-274	

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] See appendix for listing of clinical codes for each study parameter
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

7.4.3 Context and rationale for follow up

The assessment window for the outcome of AKI is 14 days following first-ever inpatient administration of an analgesic (i.e., metamizole, opioids or NSAIDs). Acute kidney injury tends to develop in 7 days or less and there is a time-lag between kidney function and serum creatinine of around 2 days. Fourteen days are allowed to detect the outcome, capturing both acute onset and delayed presentations (e.g., cumulative effects).

The lookback window is of 1 year prior to treatment initiation, to capture healthcare utilisation potential confounders.

Table 8. Operational Definitions of Follow Up

Primary analysis

Follow up start	Day 1, one hour after first analgesic administration	
Follow up end[1]	**Select all that apply**	**Specify**
Date of outcome	Yes	acute kidney injury
Date of death	Yes	in-hospital death
Other intercurrent events	No	postoperative clinical events (i.e., receipt kidney replacement therapy, postoperative pre-renal/haemodynamic instability events), documentation of pregnancy, administration of potentially nephrotoxic drug-drug interactions, use of prohibited medications (i.e., selected drugs with AKI)
End of observation in data	Yes	end of study period

Day X following index date *(specify day)*	Yes	day 14
End of study period (specify date)	Yes	December 31, 2025
End of exposure *(specify operational details, e.g. stockpiling algorithm, grace period)*	No	in-class treatment discontinuation is disregarded; follow-up continues.
Date of add to/switch from exposure *(specify algorithm)*	No	switch/add-on to out-of-class analgesic (i.e., to a comparator drug)
Other date *(specify)*	Yes	hospital discharge date

[1] Follow up ends at the first occurrence of any of the selected criteria that end follow up.

Secondary analysis (hypothetical effect)

Follow up start	Day 1, one hour after first analgesic administration	
Follow up end[1]	**Select all that apply**	**Specify**
Date of outcome	Yes	acute kidney injury
Date of death	Yes	in-hospital death
Other intercurrent events	Yes	receipt kidney replacement therapy, documentation of pregnancy, administration of potentially nephrotoxic drug-drug interactions, use of prohibited medications (i.e., selected drugs with AKI)
	No	postoperative clinical events (i.e., postoperative pre-renal/haemodynamic instability events)
End of observation in data	Yes	end of study period
Day X following index date *(specify day)*	Yes	day 14
End of study period (specify date)	Yes	December 31, 2025
End of exposure *(specify operational details, e.g. stockpiling algorithm, grace period)*	No	in-class treatment discontinuation is disregarded; follow-up continues.
Date of add to/switch from exposure *(specify algorithm)*	Yes	switch/add-on to out-of-class analgesic (i.e., to a comparator drug)

Other date *(specify)*	Yes	hospital discharge date

7.4.4 Context and rationale for covariates (confounding variables and effect modifiers, e.g. risk factors, comorbidities, comedications)

We included indications and contraindications for metamizole use which are known to cause AKI based on the Informatorium Medicamentorum curated and maintained by the Royal Dutch Pharmacists Association (Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie), further referred as IM-KNMP, a clinical nephrology textbook, Het Acute Boekje, and information from Yasrebi-de Kom et al. In addition, direct risk factors for AKI (i.e., causes of the outcome) were included, as those may also influence the treatment decision when AKI is suspected (Brookhart et al.). Thus, comorbidities, comedications, healthcare utilisation, and social demographic covariates were considered.

Table 9. Operational Definitions of Covariates

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
age	at cohort entry	continuous	[0,0] days	n/a	n/a	n/a	Inpatients in postoperative pain management setting	n/a	n/a
sex	male, female	binary	[0,0] days	n/a	n/a	n/a	Inpatients in postoperative pain management setting	n/a	n/a
major surgery	Charlson's Comorbidity Index (CCI-Deyo)[a]>3 AND (post-surgery ICU up to 12 hours after surgery OR operative time>4 h). If no CCI was present in the CCI DCM, then it was calculated manually.	binary	[-31,0) days	ED, IP	n/a	n/a	Inpatients in postoperative pain management setting	For estimating the CCI, Sundararajan et al. J Clin Epidemiol. 57 (12):1288-94, and Quan et al. 2005. Med Care. 43 (11): 1130-9 were used	Investigator defined
prior AKI	Defined as per 2012 KDIGO AKI guidelines using serum creatinine measurements	binary	[-365.25,-7] days	IP	internal codes	n/a	Inpatients in postoperative pain management setting	n/a	2012 KDIGO AKI

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
cardiovascular disease (chronic)	peripheral vascular disease, heart failure, arrhythmias	binary	[-∞,0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management setting	Cardiac arrhythmias. Sensitivity: 39.0%, PPV: 93.4%, specificity: 99.2%, NPV: 85.3% Peripheral vascular disease. Sensitivity: 43.3%, PPV: 65.5%, specificity: 99.0%, NPV: 99.0%. Heart Failure. Sensitivity: 68.6%, PPV: 90.2%, specificity: 99.3%, NPV: 97.2% (Quan et al. 2008. Health Serv Res. 43 (4))	Quan et al. 2005. Med Care. 43 (11): 1130-9
cardiovascular disease (acute)	myocardial infarction	binary	[-31,0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management setting	sensitivity: 61.5%, PPV: 93.5%, specificity: 99.4%, NPV: 94.6% (Quan et al. 2008. Health Serv Res. 43 (4))	Quan et al. 2005. Med Care. 43 (11): 1130-9
chronic lung diseases	asthma, chronic obstructive pulmonary disease	binary	[-∞,0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management setting	sensitivity: 52.8%, PPV: 90.8%, specificity: 99.1%, NPV: 92.2%	Quan et al. 2005. Med Care. 43 (11): 1130-9

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
								(Quan et al. 2008. Health Serv Res. 43 (4))	
anaemia	Blood loss anaemia, deficiency anaemia; haemoglobin <5.5 mmol L^{-1}	binary	[-31,0) days	IP, OP	ICD-10, internal codes	any	Inpatients in postoperative pain management setting	Blood loss anaemia. Sensitivity: 17.8%, PPV: 32.0%, specificity: 99.6%, NPV: 99.1% (Quan et al. 2008. Health Serv Res. 43 (4))	Quan et al. 2005. Med Care. 43 (11): 1130-9; Bepalingen. Amsterdam UMC. 28 January 2025. https://amc.elabgids.nl/bepalingen/detail/308de37b-65fb-42f7-ae4c-b881e08e1a97 (accessed 4 Nov 2025)
active cancer		binary	[-∞,0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management setting		Quan et al. 2005. Med Care. 43 (11): 1130-9
hypoalbuminaemia	Defined as albumin blood levels <30 g/L	binary	[-31,0) days	IP, OP	n/a	n/a	Inpatients in postoperative pain management setting	Unknown	Laboratory results
sepsis		binary	[-31,0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management setting	Sensitivity: 71.9%, Specificity: 85.4%, PPV: 88.2%, NPV: 66.6%	Jolley RJ et al. 2015. BMJ Open. 5(12)
obesity	Defined as body mass index>30 kg/m^2	binary	[-∞,0) days	IP, OP	(laboratory measurements)	any	Inpatients in postoperative pain management setting	Unknown	Laboratory results

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
liver disease		binary	[-∞,0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management setting	Sensitivity: 40.6%, PPV: 85.4%, specificity: 99.6%, NPV: 96.9%. (Quan et al. 2008. Health Serv Res. 43 (4))	Quan et al. 2005. Med Care. 43 (11): 1130-9
renovascular disease	renovascular hypertension	binary	[-∞,0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management setting	No validation study	Investigator review of ICD-10 codes
malignant hypertension	Uncomplicated and complicated hypertension	binary	[-∞,0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management setting	Sensitivity: 68.3%, PPV: 93.1%, specificity: 97.8%, NPV: 87.7% (Quan et al. 2008. Health Serv Res. 43 (4))	Quan et al. 2005. Med Care. 43 (11): 1130-9
scleroderma	systemic sclerosis	binary	[-∞,0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management setting	No validation study	Investigator review of ICD-10 codes
thrombosis of large arteries		binary	[-∞,0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management setting	No validation study	Investigator review of ICD-10 codes
microangiopathics	haemolytic uremic syndrome, thrombotic thrombocytopaenic purpura	binary	[-31, 0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management setting	No validation study	Investigator review of ICD-10 codes
vasculitides	vasculitis	binary	[-31, 0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management	No validation study	Investigator review of ICD-10 codes

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
							setting		
COVID-19	Coronavirus disease 2019	binary	[-31,0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management setting	No validation study	Investigator review of ICD-10 codes
diabetes mellitus	With and without chronic complication	binary	[-∞,0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management setting	Diabetes with chronic complication. Sensitivity: 59.1%, PPV: 63.1%, specificity: 99.0%, NPV: 98.9%. Diabetes without chronic complication. Sensitivity: 75.8%, PPV: 88.5%, specificity: 98.7%, NPV: 96.8%. (Quan et al. 2008. Health Serv Res. 43 (4))	Quan et al. 2005. Med Care. 43 (11): 1130-9
acute infections	Inflammatory diseases of the central nervous system, intestinal infectious diseases, zoonotic bacterial diseases, sexual infections, spirochaetal diseases, rickettsioses, viral infections, mycoses, protozoal diseases,	binary	[-31,0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management setting	No validation study	Investigator review of ICD-10 codes

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
	helminthiases, pediculosis, acariasis, sequelae of infectious and parasitic diseases, acute upper respiratory tract infections, influenza and pneumonia, infections of skin and subcutaneous tissue								
chronic infections	HIV/AIDS, herpes, Epstein-Barr virus, chronic hepatitis B and hepatitis C, toxoplasmosis, cytomegaly, Lyme disease, Q fever, endocarditis, schistosomiasis, tuberculosis	binary	[-∞,0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management setting	HIV/AIDS. Sensitivity: 41.7%, PPV: 100%, Specificity: 100%, specificity: 99.7%. (Quan et al. 2008. Health Serv Res. 43 (4)) Chronic hepatitis B. Sensitivity: 74.3%, PPV: 86.6%. Chronic hepatitis C. Sensitivity: 77.6%, PPV: 93.8%. (Kuang A et al. 2024. 72 (4): 202744)	Quan et al. 2005. Med Care. 43 (11): 1130-9; Kuang A et al. 2024. 72 (4): 202744; investigator review of ICD-10 codes
glucose-6-phospate dehydrogenase deficiency	Genetic disorder	binary	[-∞,0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management setting	No validation study	Investigator review of ICD-10 codes
benign prostatic hyperplasia		binary	[-∞,0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management	No validation study	Investigator review of ICD-10 codes

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
							setting		
neurogenic bladder		binary	[-∞,0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management setting	No validation study	Investigator review of ICD-10 codes
intra/extra ureteric obstruction	hydronephrosis with ureteropelvic junction obstruction, hydronephrosis with ureteral stricture, hydronephrosis with renal and ureteral calculous obstruction	binary	[-∞,0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management setting	No validation study	Investigator review of ICD-10 codes
retroperitoneal fibrosis		binary	[-∞,0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management setting	No validation study	Investigator review of ICD-10 codes
alcohol-related disorders	alcohol abuse	binary	[-∞,0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management setting	Sensitivity: 52.2%, PPV: 83.7%, specificity: 99.2%, NPV: 96.3% (Quan et al. 2008. Health Serv Res. 43 (4))	Quan et al. 2005. Med Care. 43 (11): 1130-9
chronic kidney disease		binary	[-∞,0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain management setting	Sensitivity: 78.8%, PPV: 64.3%, specificity: 98.2%, NPV: 99.1%. (Quan et al. 2008. Health Serv Res. 43 (4))	Quan et al. 2005. Med Care. 43 (11): 1130-9 Fernández-Llaneza et al. Clin Kidney J. 2025; 18 (4)
trauma	Trauma, injuries, and accidents.	binary	[-31,0) days	IP, OP	ICD-10	any	Inpatients in postoperative pain	Sensitivity: 69.8% PPV: 84.2%	Investigator review of ICD-10 codes, and

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
							management setting	(Kuang et al. 2024. J Epidemiol Popul Health. 72(4):202744)	Kuang et al. 2024. J Epidemiol Popul Health. 72(4):202744
hypotension	Mean arterial blood pressure (MAP) <60 mmHg for at least two consecutive hourly measurements. MAP was calculated from median systolic and diastolic blood pressure measurements per hour. MAP was then calculated as per the formula in Lehman LW et al. Comput Cardiol (2010). 37:1095-1098.	binary	[-31,0) days	IP, OP	ICD-10, internal codes	any	Inpatients in postoperative pain management setting		Investigator review of ICD-10 codes, Nederlandse Internisten Vereniging. Het Acute Boekje (2017-2025). Hypovolemie en infuusvloeistoffen - Het Acute Boekje (accessed 4 November 2025)
hypovolaemia	urine sodium <30 mmol L^{-1}, urine osmolality >500 mOsm kg^{-1}, urine chloride <20 mmol L^{-1}, urine/creatinine ratio>1:10	binary	[-31,0) days	IP, OP	ICD-10, internal codes	n/a	Inpatients in postoperative pain management setting		Investigator review of ICD-10 codes, Nederlandse Internisten Vereniging. Het Acute Boekje (2017-2025). Hypovolemie en infuusvloeistoffen - Het Acute Boekje (accessed 4 November 2025)
burns	burns in respiratory tract, exposure to smoke, fire, and flames, contact with	binary	[-31,0) days	IP, OP	ICD-10	Any	Inpatients in postoperative pain management	Sensitivity: 43%-93% Specificity: 86%-99%	Mason et al. 2017. Burns. 43(2): 258-264.

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
	heat and hot substances, exposure to electrical current and radiation						setting	PPV: 49%-94% NPV: 85%-98% (Mason et al. 2017. Burns. 43(2): 258-264)	
baseline serum creatinine	Defined as the averaged outpatient serum creatinine between 7 to 365 days before admission	continuous	[IP-365,IP-7] days	IP, OP	(laboratory measurements)	n/a	Inpatients in postoperative pain management setting	Intraclass correlation coefficient with respesct to reference standard is 0.91 (95% confidence interval, 0.88-0.92)	Siew et al. 2012. 7 (5): 712-9 Joyce et al. 2019. 1;34(3):401-407
acute kidney injury		binary	[-365,-7] days	IP, OP	(laboratory measurements)	n/a	Inpatients in postoperative pain management setting		KDIGO (2012) guideline for AKI based on serum creatinine criteria
American Society of Anaesthesiology (ASA) score (ASA Statement, Anesthesiol Open 2026.)	Assesses the physical health status before surgery and anaesthesia with a scale from 1 (healthy) to 6 (brain-dead)	ordinal	[IP,0) days	IP	n/a	n/a	Inpatients in postoperative pain management setting	n/a	n/a
drugs with AKI potential – Agents acting on the renin-angiotensin-aldosterone system	losartan (frequent, 1-10%)	binary	max([-14, 0) days, [IP,0) days)	IP, OP	ATC	n/a	Inpatients in postoperative pain management setting	No validation study	Fernández-Llaneza et al. 2025, Drug Saf. 48(1): 43-58
drugs with AKI potential – Antibacterials for systemic use	gentamicin (very frequent, >10%), piperacillin and beta-lactamase inhibitor (frequent 1-10%) vancomycin (frequent 1-10%)	binary	max([-14, 0) days, [IP,0) days)	IP, OP	ATC	n/a	Inpatients in postoperative pain management setting	No validation study	Fernández-Llaneza et al. 2025, Drug Saf. 48(1): 43-58

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
drugs with AKI potential – antimycotics for systemic use	Amphotericin B (frequent 1-10%)	Binary	max([-14, 0) days, [IP,0) days)	IP, OP	ATC	n/a	Inpatients in postoperative pain management setting	No validation study	Fernández-Llaneza et al. 2025, Drug Saf. 48(1): 43-58
drugs with AKI potential – Antineoplastic agents	mitomycin (frequent, 1-10%), carboplatin (very frequent, >10%), cisplatin (very frequent, >10%), sirolimus (frequent, 1-10%)	binary	max([-14, 0) days, [IP,0) days)	IP, OP	ATC	n/a	Inpatients in postoperative pain management setting	No validation study	Fernández-Llaneza et al. 2025, Drug Saf. 48(1): 43-58
drugs with AKI potential - Antipsychotics	lithium (very frequent, >10%)	binary	max([-14, 0) days, [IP,0) days)	IP, OP	ATC	n/a	Inpatients in postoperative pain management setting	No validation study	Fernández-Llaneza et al. 2025, Drug Saf. 48(1): 43-58
drugs with AKI potential - Antivirals for systemic use	abacavir (very frequent, >10%), cidofovir (frequent, 1-10%), foscarnet (frequent, 1-10%)	binary	max([-14, 0) days, [IP,0) days)	IP, OP	ATC	n/a	Inpatients in postoperative pain management setting	No validation study	Fernández-Llaneza et al. 2025, Drug Saf. 48(1): 43-58
drugs with AKI potential - Bisphosphonates	zoledronic acid (frequent, 1-10%)	binary	max([-14, 0) days, [IP,0) days)	IP, OP	ATC	n/a	Inpatients in postoperative pain management setting	No validation study	Fernández-Llaneza et al. 2025, Drug Saf. 48(1): 43-58
drugs with AKI potential - Diuretics	hydrochlorothiazide (frequent, 1-10%)	binary	max([-14, 0) days, [IP,0) days)	IP, OP	ATC	n/a	Inpatients in postoperative pain management setting	No validation study	Fernández-Llaneza et al. 2025, Drug Saf. 48(1): 43-58
drugs with AKI potential - Immunosuppressants	tacrolimus (frequent, 1-10%), ciclosporin (frequent, 1-10%)	binary	max([-14, 0) days, [IP,0) days)	IP, OP	ATC	n/a	Inpatients in postoperative pain management setting	No validation study	Fernández-Llaneza et al. 2025, Drug Saf. 48(1): 43-58
administration of potentially nephrotoxic	Agents acting on the renin-angiotensin system and diuretics.	binary	max([-14, 0) days, [IP,0) days)	IP	ATC	n/a	Inpatients in postoperative pain	No validation study	IM-KNMP Fernández-

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
drug-drug interactions	They do not include any study analgesics. Note that all single drugs from these pharmacological classes are derived from the ones indicated in IM-KNMP		Intercurrent event: [0,14] days				management setting		Llaneza et al. 2025, Drug Saf. 48(1): 43-58
postoperative pre-renal AKI/haemodynamic instability events	use of any vasopressor, inotropic, or emergency haemodynamic management agent OR registration of sepsis, hypovolaemia, cardiomyopathy, acute MI, and arrhythmias.	binary	Intercurrent event: [0,14] days	IP	ICD-10, ATC	any	Inpatients in postoperative pain management setting	No validation study	
death	In-hospital death	binary	Intercurrent event: [0,14] days	IP	n/a	n/a	Inpatients in postoperative pain management setting	No validation study	
pregnancy or childbirth		binary	Intercurrent event: [0,14] days	IP	n/a	n/a	Inpatients in postoperative pain management setting	No validation study	
kidney replacement therapy	both chronic or acute dialysis and kidney transplant	binary	Intercurrent event: [0,14] days	IP/OP	ICD-10, CBV (local Dutch codes)	any	Inpatients in postoperative pain management setting	No validation study	Fernández-Llaneza et al. *Clin Kidney J.* 2025; 18 (4)
out-of-class treatment add-on/switch	change from one treatment arm to another	binary	Intercurrent event: [0,14] days	IP	ATC	n/a	Inpatients in postoperative pain management setting	No validation study	

[1] IP = inpatient admission, SP = surgery procedure, OP = outpatient episode, ED = emergency department, OT = other, n/a = not applicable

[2] See appendix for listing of clinical codes for each study parameter

[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)
[a] Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992 Jun;45(6):613-9

6.5. Data analysis

7.5.1 Context and rationale for analysis plan

We use multinomial logistic regression to estimate generalised propensity scores to apply inverse probability weighting (IPTW) to adjust for baseline confounding S. Yang et al. (2016). Pooled logistic regression was used to estimate propensity scores to apply (lagged) inverse probability of censoring weighting (IPCW) to adjust for selection bias and estimate effects with ICE occurring at random, where relevant. We apply weighted cumulative incidence estimators to estimate the cumulative incidence function (CIF) and then calculate risk difference (and risk ratio, as a supplementary outcome measure). The primary estimand of interest is handles all ICEs with treatment policy strategy.

Table 10. Primary, secondary, and subgroup analysis specification

A. Primary analysis

Hypothesis:	Metamizole use increases the risk of acute kidney injury compared to opioids and may have a similar or lower risk compared to NSAIDs, when accounting for the natural course of treatment and patient outcomes in routine secondary care.
Exposure contrast:	First-ever administration of metamizole vs. first-ever administration of opioids (comparator 1) First-ever administration of metamizole vs. first-ever administration of NSAIDs (comparator 2)
Outcome:	Acute kidney injury (using serum creatinine criterion only, all stages)
Analytic software:	R v4.2.2; Python 3.13.5
Model(s): *(provide details or code)*	Propensity score model: multinomial logistic regression modelling treatment assignment (i.e., metamizole, opioids, NSAIDs) as a function of baseline confounders. Stabilised inverse probability of treatment weights will be calculated from this model. Censoring model: a pooled logistic regression model will estimate the probability of remaining uncensored over time, where censoring occurs at hospital discharge due to right censoring in the absence of post-discharge outcome data. Censoring is assumed to be potentially informative with respect to the outcome. The model will condition on treatment, baseline and time-varying covariates, and pre-specified intercurrent events. Stabilised inverse probability of censoring weights (IPCW) will be derived from the fitted model and truncated at the 99th percentile. Weighting: inverse probability weights for treatment and censoring events will be combined multiplicatively to create composite weights. Outcome model: cumulative incidence curves will be generated for each treatment group using inverse probability weighting to adjust for confounding, and censoring. The estimator corresponds to a weighted Aalen-Johansen estimator

	that accounts for intercurrent events. Risk differences and risk ratios comparing cumulative incidences at 14 days will be calculated.
Confounding adjustment method	*Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.*
	To adjust for baseline confounding, we will estimate generalised propensity scores using a multinomial logistic regression model. The probability of receiving each treatment will be modelled conditional on a set of baseline covariates, including sociodemographic characteristics, comorbidities, healthcare utilisation, and concomitant medications (see Appendix E). Resulting propensity scores will be calibrated as described by van der Laan et al. (i.e., via isotonic regression) assuming that the model's ranking of treatment probabilities is monotonic and that the relationship between predicted and observed treatment probabilities is stable (representative) across the population. We then use the Hájek estimator to calculate IPTW. Finally, individuals with extreme propensity scores, defined as scores above the 99th percentile (through truncation), will be excluded to improve overlap and reduce the influence of outliers. The resulting stabilised inverse probability of treatment weights will be used to balance covariates across treatment groups and estimate marginal treatment effects.
Missing data methods	*Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.*
	Missing values will be imputed using the Multivariable Imputation by Chained Equations (MICE), assuming missing at random missingness mechanism. All confounders, the outcome AKI, and auxiliary variables (i.e., anaesthesia type, emergency admission, surgery department, surgery type, urgent surgery class) will be used for the substantive model. Random forest will be used as the algorithm for imputation. For the estimation of the causal contrast, the *within* strategy will be used, as specified in Nguyen et al. and Leyrat et al.
Subgroup Analyses	*List all subgroups*
	If sample size is sufficient, chronic Kidney Disease patients in Amsterdam UMC, as defined by Fernández-Llaneza et al. 2025, CKJ, 18(4), will be studied. CKD stage at administration date will be introduced as a confounder.

B. Secondary analysis

Secondary analysis 1

Hypothesis:	Under conditions where no intercurrent or censoring events occur at random (i.e., kidney replacement therapy, out-of-class switch/add-on, documentation of pregnancy, administration of potentially nephrotoxic drug-drug interactions, in-hospital death, use of prohibited medications [i.e., selected drugs with AKI potential]), metamizole use increases the risk of acute kidney injury compared to opioids, and has a comparable or lower risk to NSAIDs.
Exposure contrast:	First-ever administration of metamizole vs. first-ever administration of opioids (comparator 1) First-ever administration of metamizole vs. first-ever administration of NSAIDs (comparator 2)
Outcome:	Acute kidney injury
Analytic software:	R v4.2.2; Python 3.13.5
Model(s): *(provide details or code)*	Propensity score model: multinomial logistic regression, with the treatment (i.e., metamizole, NSAIDs, opioids) as the dependent variable and the confounders as independent variables. The selected confounders are those which affect both the exposure and the outcome or intercurrent event and outcome relationship. Stabilised inverse probability of treatment

	weights will be calculated from this model. Censoring model: pooled logistic regression models will be used to estimate the probabilities of remaining uncensored and not experiencing pre-specified intercurrent events over time, conditional on treatment and relevant baseline and time-varying covariates. Stabilised inverse probability weights will be constructed for censoring and selected intercurrent events to account for potential selection bias and will be truncated at the 99th percentile. For arm-specific drug–drug interaction events, unstabilised inverse probability of censoring weights will be applied to adjust for informative censoring under the corresponding pseudo-population. Weighting: inverse probability weights for treatment and censoring will be combined multiplicatively to create composite weights. Outcome model: cumulative incidence curves will be generated for each treatment group using inverse probability weighting with the composite weights to adjust for confounding, censoring, and intercurrent events. The estimator corresponds to a weighted Aalen-Johansen estimator that accounts for intercurrent events. The risk difference and risk ratio comparing cumulative incidences at 14 days will be calculated.
Confounding adjustment method	***Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.***
	To adjust for baseline confounding, we will estimate generalised propensity scores using a multinomial logistic regression model. The probability of receiving each treatment will be modelled conditional on a set of baseline covariates, including sociodemographic characteristics, comorbidities, healthcare utilisation, and concomitant medications (see Appendix E). Resulting propensity scores will be calibrated as described by van der Laan et al. (i.e., via isotonic regression) assuming that the model's ranking of treatment probabilities is monotonic and that the relationship between predicted and observed treatment probabilities is stable (representative) across the population. We then use the Hájek estimator to calculate IPTW. Finally, individuals with extreme propensity scores, defined as scores above the 99th percentile (through truncation), will be excluded to improve overlap and reduce the influence of outliers. The resulting stabilised inverse probability of treatment weights will be used to balance covariates across treatment groups and estimate marginal treatment effects.
Missing data methods	***Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.***
	Missing values will be imputed using the Multivariable Imputation by Chained Equations (MICE), assuming missing at random missingness mechanism. All confounders, the outcome AKI, and auxiliary variables (i.e., anaesthesia type, emergency admission, surgery department, surgery type, urgent surgery class) will be used for the substantive model. Random forest will be used as the algorithm for imputation. For the estimation of the causal contrast, the *within* strategy will be used, as specified in Nguyen et al. and Leyrat et al.
Subgroup Analyses	***List all subgroups***
	If sample size is sufficient, Chronic Kidney Disease patients in Amsterdam UMC, as defined by Fernández-Llaneza et al. 2025, CKJ, 18(4), will be studied. CKD stage at administration date will be introduced as a confounder.

Secondary analysis 2

Hypothesis:	Metamizole use increases the risk of acute kidney injury compared to opioids and may have a similar or lower risk compared to NSAIDs, when accounting for the natural course of treatment and patient outcomes in routine secondary care.
Exposure contrast:	First-ever administration of metamizole vs. first-ever administration of opioids (comparator 1) First-ever administration of metamizole vs. first-ever administration of NSAIDs (comparator 2)
Outcome:	Acute kidney injury (using serum creatinine criterion only)
Analytic software:	R v4.2.2; Python 3.13.5
Model(s): ***(provide details or code)***	Propensity score model: machine learning model (e.g., XGBoost) for treatment assignment (i.e., metamizole, opioids, NSAIDs) as a function of baseline confounders. Stabilised inverse probability of treatment weights will be calculated from this model. McCaffrey et al. and Piracchio et al. provide a good starting foundation for carrying these analyses. Censoring model: a pooled logistic regression model will estimate the probability of remaining uncensored over time, where censoring occurs at hospital discharge due to right censoring in the absence of post-discharge outcome data. Censoring is assumed to be potentially informative with respect to the outcome. The model will condition on treatment, baseline and time-varying covariates, and pre-specified intercurrent events. Stabilised inverse probability of censoring weights (IPCW) will be derived from the fitted model and truncated at the 99th percentile. Weighting: inverse probability weights for treatment and censoring events will be combined multiplicatively to create composite weights. Outcome model: cumulative incidence curves will be generated for each treatment group using inverse probability weighting to adjust for confounding, and censoring. The estimator corresponds to a weighted Aalen-Johansen estimator that accounts for intercurrent events. Risk differences and risk ratios comparing cumulative incidences at 14 days will be calculated.
Confounding adjustment method	***Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.***
	To adjust for baseline confounding, we will estimate generalised propensity scores using a multinomial logistic regression model. The probability of receiving each treatment will be modelled conditional on a set of baseline covariates, including sociodemographic characteristics, comorbidities, healthcare utilisation, and concomitant medications (see Appendix E). Resulting propensity scores will be calibrated as described by van der Laan et al. (i.e., via isotonic regression) assuming that the model's ranking of treatment probabilities is monotonic and that the relationship between predicted and observed treatment probabilities is stable (representative) across the population. We then use the Hájek estimator to calculate IPTW. Finally, individuals with extreme propensity scores, defined as scores above the 99th percentile (through truncation), will be excluded to improve overlap and reduce the influence of outliers. The resulting stabilised inverse probability of treatment weights will be used to balance covariates across treatment groups and estimate marginal treatment effects.
Missing data methods	***Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.***
	Missing values will be imputed using the Multivariable Imputation by Chained Equations (MICE), assuming missing at random missingness mechanism. All confounders, the outcome AKI, and auxiliary variables (i.e., anaesthesia type,

	emergency admission, surgery department, surgery type, urgent surgery class) will be used for the substantive model. Random forest will be used as the algorithm for imputation. For the estimation of the causal contrast, the *within* strategy will be used, as specified in Nguyen et al. and Leyrat et al.
Subgroup Analyses	*List all subgroups*
	N/A

Secondary analysis 3

Hypothesis:	Metamizole use increases the risk of acute kidney injury compared to opioids and may have a similar or lower risk compared to NSAIDs, when accounting for the natural course of treatment and patient outcomes in routine secondary care.
Exposure contrast:	First-ever administration of metamizole vs. first-ever administration of opioids (comparator 1) First-ever administration of metamizole vs. first-ever administration of NSAIDs (comparator 2)
Outcome:	Acute kidney injury (using serum creatinine and urine output criteria from KDIGO guidelines on AKI)
Analytic software:	R v4.2.2; Python 3.13.5
Model(s): ***(provide details or code)***	Propensity score model: multinomial logistic regression modelling treatment assignment (i.e., metamizole, opioids, NSAIDs) as a function of baseline confounders. Stabilised inverse probability of treatment weights will be calculated from this model. Censoring model: a pooled logistic regression model will estimate the probability of remaining uncensored over time, where censoring occurs at hospital discharge due to right censoring in the absence of post-discharge outcome data. Censoring is assumed to be potentially informative with respect to the outcome. The model will condition on treatment, baseline and time-varying covariates, and pre-specified intercurrent events. Stabilised inverse probability of censoring weights (IPCW) will be derived from the fitted model and truncated at the 99th percentile. Weighting: inverse probability weights for treatment and censoring events will be combined multiplicatively to create composite weights. Outcome model: cumulative incidence curves will be generated for each treatment group using inverse probability weighting to adjust for confounding, and censoring. The estimator corresponds to a weighted Aalen-Johansen estimator that accounts for intercurrent events. Risk differences and risk ratios comparing cumulative incidences at 14 days will be calculated.
Confounding adjustment method	***Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.***
	To adjust for baseline confounding, we will estimate generalised propensity scores using a multinomial logistic regression model. The probability of receiving each treatment will be modelled conditional on a set of baseline covariates, including sociodemographic characteristics, comorbidities, healthcare utilisation, and concomitant medications (see Appendix E). Resulting propensity scores will be calibrated as described by van der Laan et al. (i.e., via isotonic regression) assuming that the model's ranking of treatment probabilities is monotonic and that the relationship between predicted and observed

	treatment probabilities is stable (representative) across the population. We then use the Hájek estimator to calculate IPTW. Finally, individuals with extreme propensity scores, defined as scores above the 99th percentile (through truncation), will be excluded to improve overlap and reduce the influence of outliers. The resulting stabilised inverse probability of treatment weights will be used to balance covariates across treatment groups and estimate marginal treatment effects.
Missing data methods	*Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.*
	Missing values will be imputed using the Multivariable Imputation by Chained Equations (MICE), assuming missing at random missingness mechanism. All confounders, the outcome AKI, and auxiliary variables (i.e., anaesthesia type, emergency admission, surgery department, surgery type, urgent surgery class) will be used for the substantive model. Random forest will be used as the algorithm for imputation. For the estimation of the causal contrast, the *within* strategy will be used, as specified in Nguyen et al. and Leyrat et al.
Subgroup Analyses	*List all subgroups*
	N/A

Secondary analysis 4

Hypothesis:	Metamizole use increases the risk of acute kidney injury compared to opioids and may have a similar or lower risk compared to NSAIDs, when accounting for the natural course of treatment and patient outcomes in routine secondary care.
Exposure contrast:	First-ever administration of metamizole vs first-ever administration of diclofenac
Outcome:	Acute kidney injury
Analytic software:	R v4.2.2; Python 3.13.5
Model(s): *(provide details or code)*	Propensity score model: logistic regression modelling treatment assignment (metamizole vs. diclofenac) as a function of baseline confounders. Stabilised inverse probability of treatment weights will be calculated from this model. Censoring model: a pooled logistic regression model will estimate the probability of remaining uncensored over time, where censoring occurs at hospital discharge due to right censoring in the absence of post-discharge outcome data. Censoring is assumed to be potentially informative with respect to the outcome. The model will condition on treatment, baseline and time-varying covariates, and pre-specified intercurrent events. Stabilised inverse probability of censoring weights (IPCW) will be derived from the fitted model and truncated at the 99th percentile. Weighting: inverse probability weights for treatment and censoring events will be combined multiplicatively to create composite weights. Outcome model: cumulative incidence curves will be generated for each treatment group using inverse probability weighting to adjust for confounding, and censoring. The estimator corresponds to a weighted Aalen-Johansen estimator that accounts for intercurrent events. Risk differences and risk ratios comparing cumulative incidences at 14 days will be calculated.
Confounding adjustment method	*Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata*

	definition), other.
	To adjust for baseline confounding, we will estimate generalised propensity scores using a multinomial logistic regression model. The probability of receiving each treatment will be modelled conditional on a set of baseline covariates, including sociodemographic characteristics, comorbidities, healthcare utilisation, and concomitant medications (see Appendix E). Resulting propensity scores will be calibrated as described by van der Laan et al. (i.e., via isotonic regression) assuming that the model's ranking of treatment probabilities is monotonic and that the relationship between predicted and observed treatment probabilities is stable (representative) across the population. We then use the Hájek estimator to calculate IPTW. Finally, individuals with extreme propensity scores, defined as scores above the 99th percentile (through truncation), will be excluded to improve overlap and reduce the influence of outliers. The resulting stabilised inverse probability of treatment weights will be used to balance covariates across treatment groups and estimate marginal treatment effects.
Missing data methods	*Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.*
	Missing values will be imputed using the Multivariable Imputation by Chained Equations (MICE), assuming missing at random missingness mechanism. All confounders, the outcome AKI, and auxiliary variables (i.e., anaesthesia type, emergency admission, surgery department, surgery type, urgent surgery class) will be used for the substantive model. Random forest will be used as the algorithm for imputation. For the estimation of the causal contrast, the *within* strategy will be used, as specified in Nguyen et al. and Leyrat et al.
Subgroup Analyses	*List all subgroups*
	N/A

Table 11. Sensitivity analyses – rationale, strengths and limitations

	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Sensitivity Analysis 1 [treatment policy effect]	Metamizole exposure definition; comparing high dose (i.e., ≥3,000 mg/day) vs. low dose (i.e., <3,000 mg/day) as per Brinkman et al. 2025. Br J Clin Pharmacol; 1-8, instead of metamizole vs. opioids.	To test the consistency assumption and address whether a dose-response relationship exists between metamizole and AKI.	Increases granularity of the exposure definition; provides insight into a possible dose-response, supporting causal interpretation.	No universally accepted thresholds, increasing risk of exposure misclassification; smaller sample sizes within dose strata may reduce precision

6.6. Data sources

7.6.1 Context and rationale for data sources

Reason for selection: The Research Data Platform (RDP) contains data from electronic medical records (Epic) from Amsterdam UMC. Amsterdam UMC consists of two teaching hospitals in Amsterdam. The whole hospital trajectory for admitted patients is fully traceable and there is also availability of data related to outpatient specialist clinics.

Strengths of data source(s): The database contains longitudinal records from secondary care, where clinicians and nurses enter information using Epic's standardised electronic forms. All prescriptions and medication administrations from clinicians are recorded, medical diagnoses and procedures are captured via ICD-10 and CBV codes, laboratory measurements, medical history, lifestyle/clinical variables such as body mass index are also captured. After entry in the system, all diagnoses codes are curated by specialised medical coders.

Limitations of data source(s): The data source reflects inpatient and outpatient encounters captured in electronic health records in Amsterdam UMC and may miss elements of care received in primary care or other institutions.

Data source provenance/curation: Access to the data source is provided after authorisation by the Research Data Management board and is validated periodically by medical coders. The selected data source is used for research and documentation of data contents is provided.

Table 12. Metadata about data sources and software

	Data 1
Data Source(s):	Amsterdam UMC Electronic Health Records
Study Period:	2019 – 2025
Eligible Cohort Entry Period:	2019 – 2025
Data Version (or date of last update):	15 April 2026
Data sampling/extraction criteria:	via Research Data Platform
Type(s) of data:	electronic health records
Data linkage:	no external data linkage
Conversion to CDM*:	n/a
Software for data management:	RStudio 1.4.1106 and SQL Server Management Studio v19.2.56.2

*CDM = Common Data Model

6.7. Data management

Pseudonymised routinely collected EHR data of patients admitted to Amsterdam UMC were re-used. Laboratory findings were extracted from two laboratory information systems: GLIMS and LabTrain. All data was extracted retrospectively on 31st December 2023 covering hospital admissions between January 2019, 1 and December 2023, 31. Amsterdam UMC uses EHR system of EPIC© Epic Electronic Health Record [Computer software]., *Madison, WI: Epic; Madison, WI*. Data extractions from the EHR system are facilitated by Research Data Management team of Amsterdam UMC via Research Data Platform and according to a Standard Operating Procedure "*Reuse of care data for the purpose of research*". EHR data are organized in tables called Detailed Clinical Models (DCMs). Each DCM contains

variables compiled from various EHR tables, for example a DCM Problem List contains all registered problems per patient and admission linked to ICD-10 or ICD-9, as well as among others the status of the problem, date of registration, the provider number, location in hospital.

6.8. Quality control

This protocol was drafted in collaboration with experts in pharmacology, causality, pharmacoepidemiology, and medical informatics. Weekly meetings are held to discuss important topics on this study and potential updates of the study design and methodological challenges. Quality control on programming was checked by structuring the code independently, running and explaining it to peers and colleagues within the team.

6.9. Study size and feasibility

Feasibility counts (see **Figure 2**) reveal a sample size of 57,294 patients administered metamizole, 31,197 patients administered NSAIDs, and 87,641 patients administered opioids in Amsterdam UMC. After implementing preliminary exclusion/inclusion criteria, the counts get down to 9,429 patients exposed to metamizole, 977 patients exposed to NSAIDs, and 87,641 patients exposed to opioids. When using serum creatinine as a criterion for identifying AKI following the KDIGO (2012) guideline, there are 343 AKI cases within 14 days of opioid initiation, 174 AKI cases within 14 days of metamizole initiation, and 25 cases within 14 days of NSAIDs initiation, respectively. The distribution of time from treatment initiation to administrative censoring seems comparable across arms (see **Figure 3**).

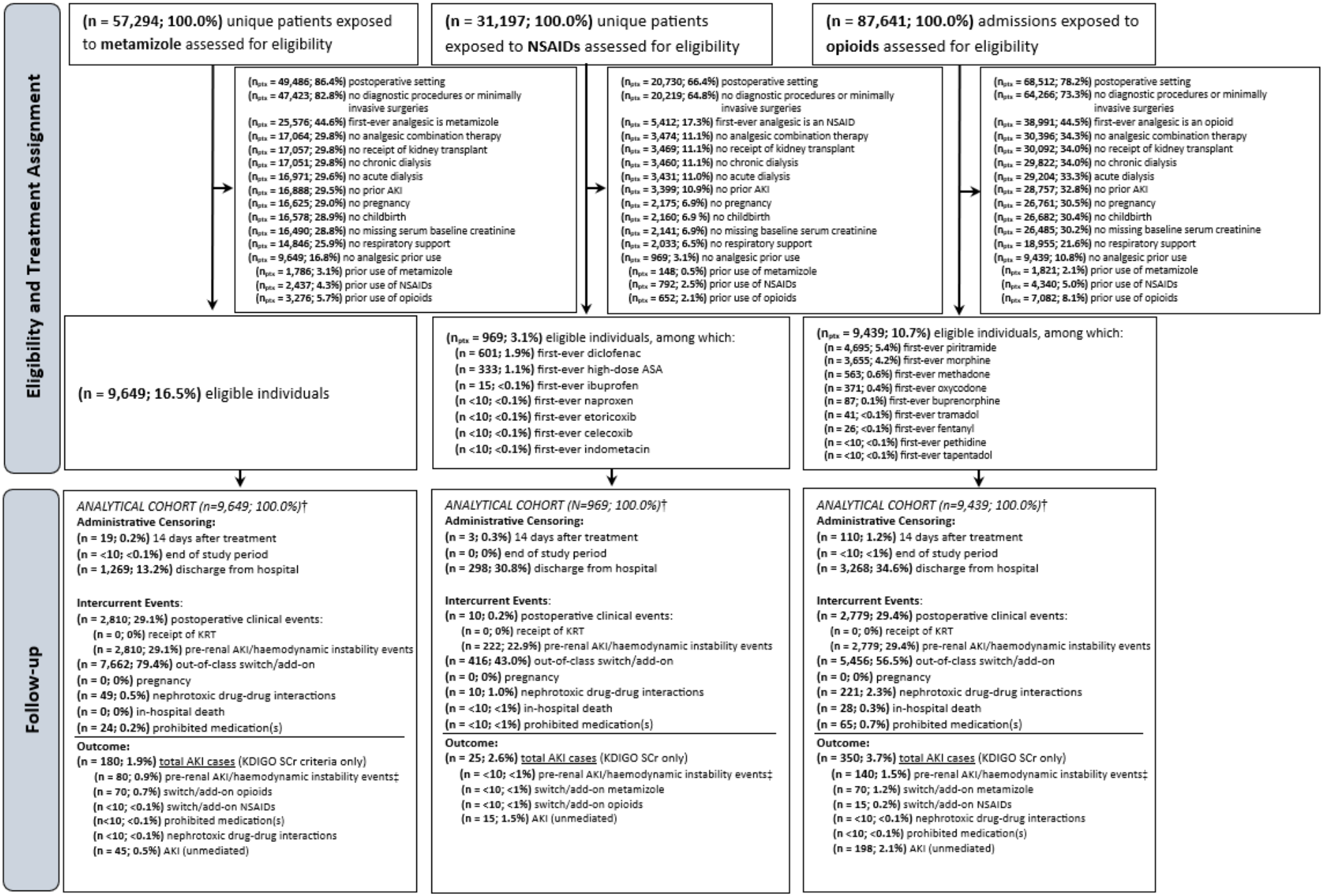


Figure 2. Preliminary attrition funnel for the three treatment arms.

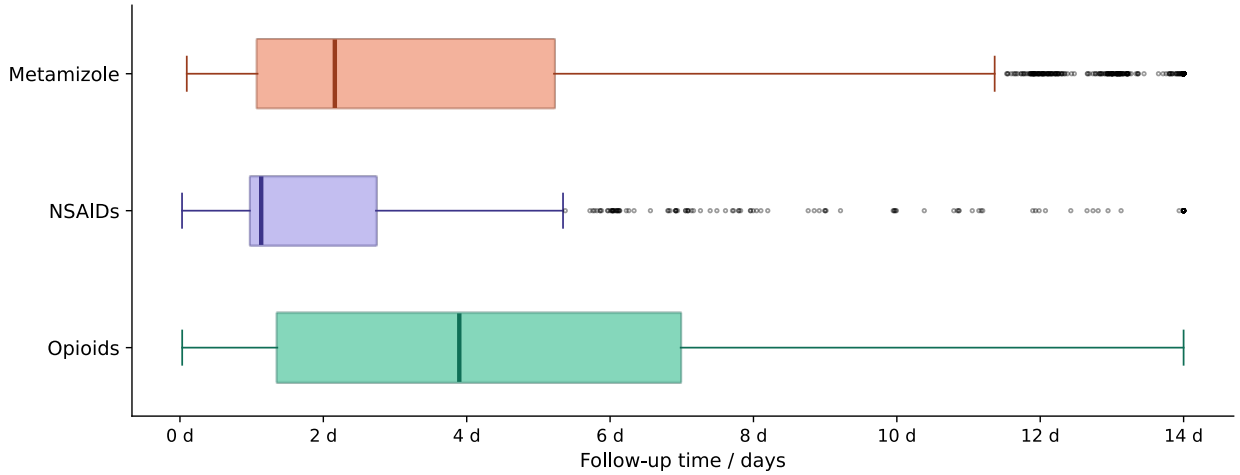


Figure 3. Boxplot displaying time distribution of administrative censoring per treatment arm after time zero.

As previously mentioned, existing evidence on metamizole AKI potential is scarce and there are few clinical trials and observational studies clearly reporting on this. Stueber et al. report an odds ratio of 1.62 (95% CI: 1.12-2.34) for dose per day (i.e., a 1.6-fold increase in the incidence of AKI per each additional gram of intravenous metamizole administered per day). Baseline risk for AKI (i.e., patients not exposed to metamizole) is estimated to be around 20% as per Susantitaphong et al. Following the formula from Zhang et al., we can convert the odds ratio to a risk ratio and risk difference:

$$RR = \frac{OR}{(1 - p_0) + (p_0 \times OR)} = \frac{1.62}{(1 - 0.2) + (0.2 \times 1.62)} \approx 1.44\ (95\%\ CI\colon 1.09 - 1.85)$$

$$RD = 0.20 \times (1.44 - 1) = 0.124\ (12.4\%\ absolute\ risk\ increase)$$

To calculate the sample size, given baseline AKI risk of p_0=0.20, p_1=RR*p_0=1.44*0.20=0.29, power (i.e., the probability of correctly rejecting the null when the alternative is true) of 0.80 and significance level (α) of 0.05:

$z_{1-\alpha/2}$=2.241; $z_{1-\beta}$=0.84

compute pooled mean $\bar{p} = \frac{0.20+0.29}{2} = 0.245$

For a binary outcome within a fixed window (e.g., 14 days), assuming equal allocation, the standard two-sample approximate formula is:

$$n \approx \frac{\left(z_{1-\frac{\alpha}{2}}\sqrt{2\bar{p}(1-\bar{p})} + z_{1-\beta}\sqrt{p_1(1-p_1) + p_0(1-p_0)}\right)^2}{(p_1 - p_0)^2} = \frac{\left(2.241 \times \sqrt{2 \times 0.245 \times 0.755} + 0.84 \times \sqrt{0.29 \times 0.71 + 0.20 \times 0.80}\right)^2}{(0.09)^2} \cong 432\ patients$$

About 432 patients would be needed per arm for each metamizole vs comparator comparison under α'=0.05 and 80% power. With three arms and equal allocation, a total of N = 432 x 3 = 1,269 patients would be required. This might be a conservative approach given that a Bonferroni correction has been applied. Under the stated assumptions, the study would be designed with approximately 1,296 participants (432 per arm). This pre-specified sample size of 432 patients per arm is achieved for the metamizole and opioids arms. The NSAIDs arm enrolled 403 patients, representing approximately 93% of the target sample size. As a consequence, comparisons between metamizole and NSAIDs will have marginally reduced statistical power relative to the planned 80%. Results from this comparison will be reported in alignment with the approach suggested by Hernán (2022) and will be interpreted with appropriate caution. This shortfall will be acknowledged as a limitation in the final study report.

Table 13. Distribution of single-drugs in treatment arms from hypothetical trial

Arm	Single drug	Unique patient counts after inclusion/exclusion criteria	Number of AKI cases* (based on SCr criterion only)	Crude incidence (%)
METAMIZOLE		**9,429**	**174**	**1.8**
NSAIDs	diclofenac	609	12	2.0
	ibuprofen	15	<10	<70
	naproxen	<10	0	0
	celecoxib	<10	0	0
	etoricoxib	<10	0	0
	indometacin	<10	0	0
	high-dose acetylsalicylic acid	333	12	3.6
	Grand total	**977**	**30**	**3.1**
OPIOIDS	piritramide	4,688	150	3.2
	morphine	3,599	140	3.9
	methadone	548	30	5.5
	oxycodone	367	15	4.1
	buprenorphine	84	<10	6.0
	tramadol	42	<10	9.5
	fentanyl	26	0	0
	pethidine	<10	<10	N/A
	tapentadol	<10	0	0
	Grand total	**9,336**	**343**	**3.7**

*without accounting for intercurrent events; rounded to the nearest 5 to protect patient confidentiality

7. Limitation of the methods

There are several potential limitations with the methods specified in this protocol and we outline some remediating strategies that we implemented.

1. The data was not collected for research and some important variables may not be collected or may be measured imperfectly.

    a. We have selected validated algorithms when possible
    b. We have considered outpatient data and medical history data for covariate assessment to reduce misclassification bias
    c. Serum creatinine measurements will be measured opportunistically rather than being systematically monitored
    d. We have designed a medication administration observation window of one hour to capture delay in registration of combination analgesic treatments (i.e., administration of more than one pain relief medication)
2. There will be no randomisation
    a. We have emulated the design of a target trial and present the estimands framework
    b. We have balanced compared groups with respect to confounding variables via IPTW
3. On treatment follow-up may be short in real-world practice, there is potential for informative censoring
    a. We have incorporated censoring weights
4. Some proposed secondary analyses may lack sufficient sample size
    a. Proposed a host of secondary and sensitivity analyses and in order of priority

8. Protection of human subjects

This study is part of a larger project called Leveraging real-world dAta to optimize PharmacotheRapy outcomes in multimorbid patients by using machine learning and knowledge representation methods (LEAPfROG project). The LEAPfROG project was exempted from requiring ethics approval (waiver W22_340 # 22.412) on September 2022, 22 by the Medical Ethics Committee of the Amsterdam University Medical Centres, University of Amsterdam, Amsterdam, the Netherlands, as it did not fall within the scope of the Dutch Medical Research Involving Human Subjects Act.

9. Reporting of adverse events

The proposed study is observational research that makes secondary use of data collected as part of routine care and does not involve any intervention or alteration in clinical care. Therefore, reporting of adverse events related to this study is not applicable. Safety evaluations for this study are limited to the specified safety outcomes stated in section 4.4.2.

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11. Appendices

See excel files.

Appendix A – Study Population Entry Criteria (exposure)

Appendix B – Administration Status

Appendix C – Administration Routes

Appendix D – Drug-, Diagnosis-, and Procedure-based Inclusion and Exclusion Criteria

Appendix E – Drug, Diagnosis-, and Procedure-based covariates

Appendix F – Outcome

Appendix G – Care Setting Description

Appendix H – Acetylsalicylic Dose

Appendix I – Drug Classes

Appendix J – Diagnostic Procedures, Minimally Invasive Procedures, and Kidney-related Surgeries

Appendix E – List of Covariates (Diagnoses, Procedures, Prescriptions)