OBSERVATIONAL STUDY TO EVALUATE THE EPIDEMIOLOGY OF SURGICAL-INDUCED ACUTE KIDNEY INJURY

ACRONYM

EPIS-AKI

Supported by Baxter, endorsed by ESA

Responsible Institution:
Department of Anesthesiology, Intensive Care and Pain Medicine
University Hospital Muenster
Albert-Schweitzer-Campus 1, A1
48149 Muenster
Germany

Coordinating Investigator:
Univ.-Prof. Dr. med. Alexander Zarbock
University Hospital Muenster
Department of Anesthesiology,
Intensive Care and Pain Medicine
Albert-Schweitzer-Campus 1, A1
48149 Muenster
Germany

Study code:

01-AnIt-19

Version 1.2
Date: 2020-06-29

Study Contact:
E-mail: epis-aki@ukmuenster.de
Hotline: +49 251 83 47282
Fax: +49-(0)251-83 40501

1.1 Synopsis

Study-ID	01-AnIt-19
Title of the trial	Observational study to evaluate the **EPI**demiology of **S**urgical-induced **A**cute **K**idney **I**njury
Acronym	EPIS-AKI
Responsible institution	Department of Anesthesiology, Intensive Care and Pain Medicine Albert-Schweitzer-Campus 1, A1 48149 Muenster
Medical condition	Complications after surgery
Principal investigator	**Univ.-Prof. Dr. med. Alexander Zarbock** Department of Anesthesiology, Intensive Care and Pain Medicine; University Hospital of Muenster; Albert-Schweitzer-Campus 1, A1; 48149 Muenster; Phone: +49 251/83-47252; Fax: +49 251/83-40501; Email: zarbock@uni-muenster.de
Medical project management	**Priv.-Doz. Dr. med. Melanie Meersch** Department of Anesthesiology, Intensive Care and Pain Medicine; University Hospital of Muenster; Albert-Schweitzer-Campus 1, A1; 48149 Muenster; Phone: +49 251/83-47282; Fax: +49 251/83-40501; Email: meersch@uni-muenster.de
Study coordinator	**Dr. oec. troph. Carola Wempe** Department of Anesthesiology, Intensive Care and Pain Medicine; University Hospital of Muenster; Albert-Schweitzer-Campus 1, A1; 48149 Muenster; Phone: +49 251/83-47267; Fax: +49 251/83-40501; Email: wempe-c@anit.uni-muenster.de
Trial type	International prospective, observational, multi-center, cross-sectional cohort study
Participating centers	This clinical trial will be carried out as an international multicenter observational cohort trial in Europe and the USA. If necessary, further qualified trial sites may be recruited to the trial. The listing of trial sites, principal investigators, sub-investigators, and further trial staff, will be kept and continuously updated in a separate list. The final version of this list will be attached to the final report of the clinical trial.
Biometry **(biometric evaluation)**	Laura Kerschke Institute of Biostatistics and Clinical Research University of Muenster Schmeddingstr. 56 48149 Muenster Phone: +49 251/83-53607 Email: laura.kerschke@ukmuenster.de
Funding	Unrestricted research grant from Baxter
Objective(s)	Acute kidney injury (AKI) is a severe clinical complication with increasing incidence and is associated with adverse short- and long-term outcomes resulting in a major health care burden worldwide. The introduction of consensus classification systems has enhanced the awareness for AKI. The evaluation of an accurate occurrence rate for AKI is of great importance for health policy, quality initiatives as well as for designing

	clinical trials. However, analyzing AKI from existing databases is often limited by missing data elements, especially the inclusion of the urine output criteria. Missing data and the use of different definitions before the consensus classification are the reasons for large variations in reported occurrences of surgical induced AKI. The primary objective is to prospectively evaluate the incidence of AKI within 72 h after extended surgical procedures that require admission to an observation unit (e.g., ICU, IMC, PACU) using the latest consensus definition for AKI (Kidney Disease: Improving Global Outcomes criteria) and a standardized data collection instrument and to assess the dependence of AKI on preoperative and intraoperative factors. Secondary objectives: to determine the effects of pre- and intraoperative factors on the occurrence of AKI, to determine the impact of AKI on postoperative outcomes including use of renal replacement therapy, all-cause mortality (ICU and hospital) as well as the length of stay (ICU and hospital) and a combination of endpoints summarized as $MAKE_{90}$ (major adverse kidney events at day 90).
Key inclusion and exclusion criteria	***Inclusion criteria:*** 1. Age ≥ 18 years 2. Major surgeries with a duration of at least 2 h 3. Planned or unplanned admission to the ICU, IMC or PACU after surgery 4. Written informed consent ***Exclusion criteria:*** 1. Pre-existing AKI 2. AKI within the last 3 months 3. End stage renal disease with dialysis dependency 4. Kidney transplant
Primary trial objective	The primary objective of the EPIS-AKI trial is to prospectively evaluate the incidence of AKI within 72h after extended surgical procedures in hospitals using the latest consensus definition for AKI according the KDIGO criteria.

Study endpoints	**Primary endpoint:**
	Occurrence of AKI within 72h after surgery according the KDIGO criteria
	Secondary endpoints:
	Secondary endpoints are:
	• Effect of preoperative risk factors on the incidence of post–operative AKI
	• Effect of predetermined intraoperative factors on the incidence of post–operative AKI
	• Biomarkers of AKI (urine for this endpoint will be collected in some centers)
	• Outcomes:
	  ○ Use of renal replacement therapy
	  ○ Length of ICU stay
	  ○ Length of hospital stay
	• Survival
	  ○ ICU mortality
	  ○ Hospital mortality
	• $MAKE_{90}$ (major adverse kidney events at day 90): combined endpoint consisting of:
	  ○ mortality
	  ○ renal replacement therapy
	  ○ persistent renal dysfunction defined as serum-creatinine ≥ 1.5 times as compared to baseline serum-creatinine

Number of subjects	To be analyzed in the trial: n=10,000

Time plan	First patient first visit (FPFV): 01/06/2020 Last patient first visit (LPFV): 30/06/2022 Last patient last visit (LPLV): 30/09/2022 Final study report: 31/12/2022
Statistical analysis	Statistical analyses will be performed according to the principles of the ICH-guideline E9 “Statistical Principles for Clinical Trials” using standard statistical software. Data will be summarized by standard descriptive statistical measures. Normally distributed variables will be reported as mean and standard deviation and non-normally distributed variables as median and lower and upper quartile. Categorical variables will be expressed as proportion. To quantify evidence of differences between groups given by categorical parameters, such as the type of surgery, statistical tests like t-tests, Mann-Whitney-U tests, Chi-square tests or Fisher’s exact tests will be used appropriate to the distributional characteristics of the endpoint. In the primary analysis the incidence of AKI will be estimated together with the exact corresponding two-sided 95% confidence interval according to Clopper-Pearson. To detect factors that might be correlated to the occurrence of AKI (e.g., type/length of surgery, use of blood products, morbidities), exploratory uni- and multivariable logistic regression analyses will be conducted. For secondary outcomes, point estimates and corresponding 95% confidence intervals will be derived. In further exploratory analyses, the association between secondary outcomes and the type of surgery will be analyzed using appropriate statistical methods. Additionally, subgroup analyses will be performed based on the type of surgery to identify variables that are correlated with the occurrence of AKI in each group. A two-sided p-value of < 0.05 will be considered as statistically significant.
Power calculation	The primary aim of the study is to estimate the incidence of post-surgery AKI and to derive the corresponding exact two-sided 95% confidence interval according to Clopper-Pearson. Depending on the type of surgery, AKI incidences of 1.8-39.3% are reported in existing literature. As the width of the confidence interval increases, the closer the observed incidence of post-surgery AKI equals 50%, a rate of 40% is assumed, as a conservative approach. Using this assumption, the width of the confidence interval based on a sample size of $n = 10{,}000$ patients and a confidence level of 95% is given by 0.019. Thus, with $n = 10{,}000$ patients, the incidence of post-surgery AKI can be estimated with at least this precision. The study also aims to detect factors that might be correlated to the occurrence of post-surgery AKI, as e.g. the type of surgery (i.e. cardiac, neurological etc.) and predefined preoperative and intraoperative factors. Therefore, further exploratory analyses such as uni- and multivariable logistic regression analyses will be conducted. Given the relatively large number of different types of surgeries, a sample size of $n = 10{,}000$ patients is sufficient to investigate the influence of this parameters on the occurrence of post-surgery AKI in a uni- and multivariable context.
Trial Registration	The trial is registered at ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT04165369).

2 Study Design

The EPIS-AKI trial is an international, prospective, observational, multi-center, cross-sectional cohort study including 10,000 patients undergoing extended surgical procedures.

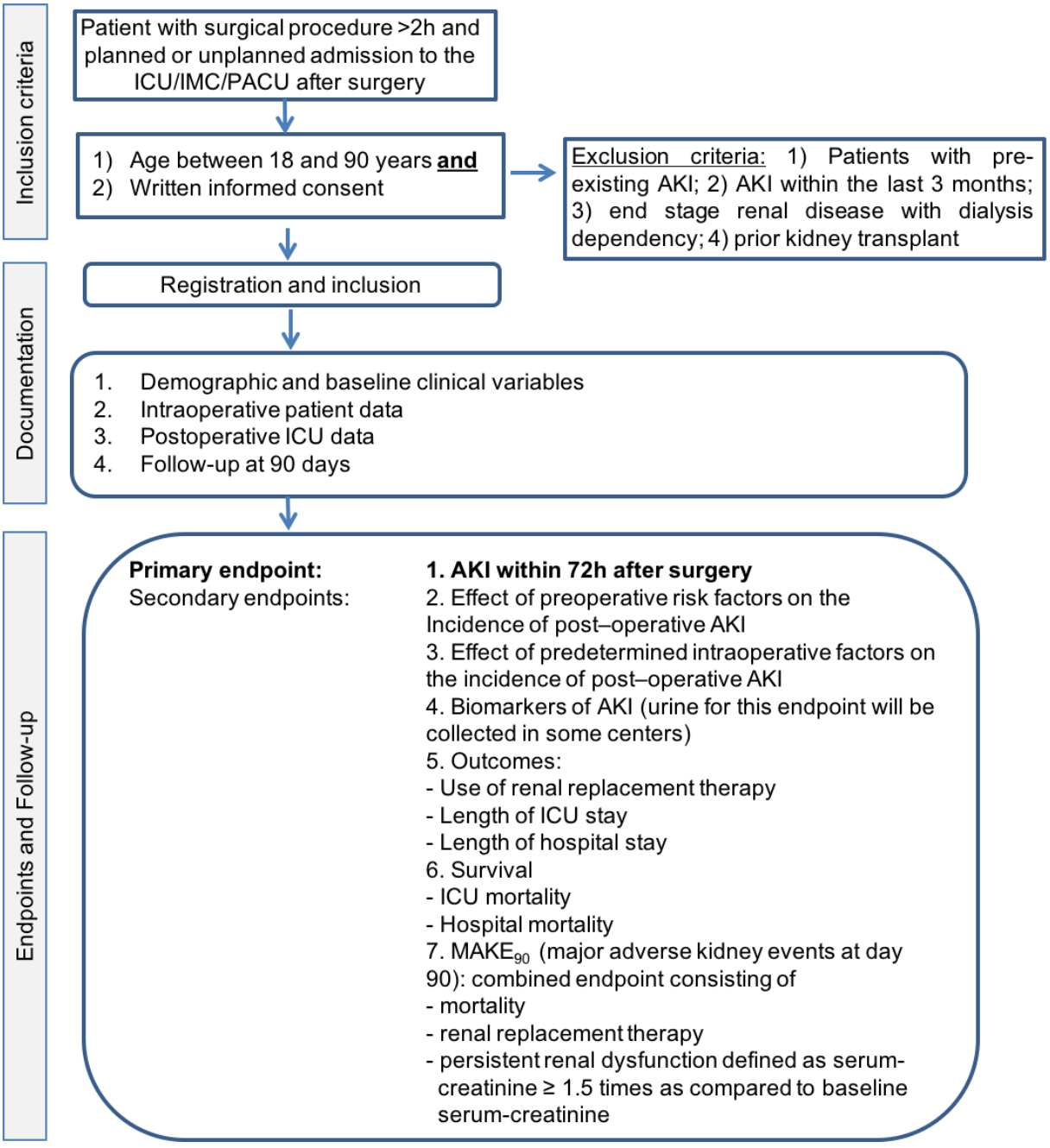

Figure 1: EPIS-AKI Trial Workflow.

Visit	**S**	**B**	**OD**	**Postop. days 1-3**	**Day 90**
	T1		**T2**	**T3**	**T4**
Inclusion and Exclusion criteria	X				
Demography Age, Gender, Race, Comorbidities (CKD, hypertension, diabetes, COPD), Medication (Diuretics, NSAIDs, ACEi/ARBs, Statins), ASA status, weight; BMI		X			
Admission diagnosis, source of admission		X			
Intraoperative data Surgical procedure (type, priority, duration, episodes of hypotension (MAP < 55mmHg for more than 5 minutes), blood loss, transfusion, fluid intake, urine output, use of colloids, use of nephrotoxic agents, use of vasopressors), if cardiac: CPB/ aortic X-clamp duration			X		
Postoperative data APACHE, SAPS, fluid status (fluid balance, fluid intake, urine output, blood loss, transfusion), postoperative complication (sepsis, hemodynamic instability)				X	
AKI Stage, Definition, RRT, use of nephrotoxic drugs				X	
Concomitant Medication Pressors, amphotericin, aminoglycosides, cyclosporine, tacrolimus, radiocontrast agents, diuretics				X	
Mortality					X
Length of primary stay (ICU, Hospital)					X
Serum-creatinine					X
Renal recovery					X
Number of days of RRT/RRT dependence					X
MAKE = major adverse kidney events					X

Abbreviations: S, Screening: B, Baseline; ACEi, angiotensin converting enzyme inhibitors; AKI, Acute Kidney Injury; APACHE, Acute Physiology And Chronic Health Evaluation; ARBs, angiotensin receptor blockers; ASA, American Society of Anesthesiology; CPB, cardiopulmonary bypass; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; NSAID, non steroidal anti-inflammatory drugs; RRT, Renal Replacement Therapy; SAPS, Simplified Acute Physiology Score