RISK prediction for acute kidney injury in acute medical admissionS in the uK :

The RISK study

A prospective national, multi-centre study to collate data on all acute medical admissions in participating centres in order to develop a national risk assessment for AKI in secondary care.

Study protocol version 3.4
Study personnel and contact details

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Members of the UKKRC Acute Kidney Injury Clinical Study Group
https://www.kidneyresearchuk.org/research/acute-kidney-injury-clinical-study-group
### Synopsis

<table>
<thead>
<tr>
<th>Title</th>
<th>Risk Prediction For Acute Kidney Injury In Acute Medical Admissions In The UK</th>
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<td>Short title</td>
<td>The RISK study</td>
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<tr>
<td>Chief investigator</td>
<td>Professor Lui Forni</td>
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<tr>
<td>Objectives</td>
<td>To collect clinical and biochemical data in unselected medical admissions from which risk prediction tools for the development of acute kidney injury (AKI) will be derived</td>
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<tr>
<td>Study design</td>
<td>Multicentre, prospective observational study</td>
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<tr>
<td>Setting</td>
<td>Medical admission units (secondary care)</td>
</tr>
<tr>
<td>Sample size estimate</td>
<td>n/a</td>
</tr>
<tr>
<td>Number of participants</td>
<td>To be determined by number of medical admissions within study period</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>Patients aged ≥18yrs presenting to the acute admissions unit/MAU/AMU at time of the defined study date (study day starting at 8:00 hrs, and ending at 07:59 hrs)</td>
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<tr>
<td>Interventions</td>
<td>None</td>
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<tr>
<td>Duration of study</td>
<td>The study will collect data on all admissions over a 24hr period plus outcomes measured at 7days or hospital discharge, whichever occurs sooner</td>
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<td>Outcomes</td>
<td>Occurrence of AKI in the first 7 days in patients who do not have AKI on admission to hospital</td>
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<tr>
<td>Summary of statistical plan</td>
<td>Logistic regression analysis will be used to identify predictors of development of AKI within 7 days of admission. Regression coefficients associated with each variable will be used to build risk prediction scores. The calibration of the risk scores will be assessed by the Hosmer-Lemeshow goodness-of-fit test. Discrimination will be assessed using the area under the receiver operating characteristic curve (AUC)</td>
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Introduction:

Acute kidney injury (AKI) is common in hospital in patients with a reported incidence of between 10 – 20% but can be as high as 70% in the critically ill. Much of the early data examining the outcome of patients with AKI focused on the critically ill but increasing evidence has highlighted the fact that patients with AKI regardless of clinical setting have worse outcomes. This is reflected not only in terms of mortality risk but also an increase in the development of chronic kidney disease with its associated complications. Recently, the NCEPOD report suggested that there should be robust assessment of contributory risk factors towards AKI. Parallels can be drawn with the mortality risk scores currently used in acute medical assessment units such as NEWS but it is not known whether the adoption of a purely physiological based score is applicable in predicting those at risk of developing AKI.

Several studies have tried to address this problem by using electronic systems to generate automatic alert warnings for patients with a rise in serum creatinine. Such alert systems highlight a rise in creatinine after insult (i.e. aiming to improve detection after the onset of AKI) but do not inform as to the patients at risk of developing AKI (at a timepoint in the near future). The risk of development of AKI has been studied in specific patient groups predominantly in surgical and burns patients, but few attempts have been made outside of critical care to try to identify patients at risk of developing AKI when admitted to hospital as acute medical emergencies. Attempts have been made to utilise electronic health records to produce a risk stratification model but this is not easily applied at the bedside and does not employ any physiological parameters. One study, albeit in a single centre, has described a AKI prediction score but this may not be applicable throughout the UK.

The aim of this study is to investigate the relative contributions of patient admission physiology (respiratory rate, heart rate, arterial pressure, temperature, oxygen saturation, conscious level and where known urine output) together with biochemical parameters and known co-morbidities (i.e. patient related risk factors) to devise a practical, robust scoring system. It is hoped that this would be easily calculable and can rapidly identify patients at risk of developing AKI following admission.
Study aims:

1. Assessment of the prevalence of AKI (defined as KDIGO stage 1-3) in acute admissions admitted to acute medical assessment units throughout the UK.
2. Assessment of physiological risk factors for AKI within this patient group.
3. Assessment of laboratory measured risk factors for AKI within this patient group.
4. Assessment of pharmacological risk factors for AKI within this patient group.
5. Assessment of patient and renal outcomes within 7 days of admission.

From this, derivation of new risk scores and validation of existing risk scores to predict patients at increased risk of developing AKI after hospital admission will be performed.

Methods:

Prospective multi-centre observational study in a cohort of patients presenting to UK medical assessment units over a single 24hr period. All participating centres will be asked to collect data for a single 24 hour period during a designated study week, dates to be finalised after attainment of ethical and R+D approvals. A comprehensive data set will be collected for each patient admitted to the MAU during the chosen 24hr period, and this will be supplemented by a smaller dataset that will describe outcomes up to day 7. Outcomes will include the recording of prevalence of AKI at time of the index study day, and development of AKI stage 1-3 (according to KDIGO) with a maximum follow up until either hospital discharge, or day 7 after the index study day. Data collection will only include that which is generated as part of routine care. No additional interventions or measurements for research purposes will be made.

Outcomes:

Primary outcome:

- Occurrence of AKI in the first 7 days in patients who do not have AKI on admission to hospital

Secondary outcomes

- Incidence of community acquired and hospital acquired AKI in general medical admissions
- Maximum AKI stage
- AKI-RRT if needed
- ICU admission
- Renal function at hospital discharge
- Length of hospital stay
- Mortality within hospital stay

**Inclusion criteria:**

1. Patients presenting to the acute admissions unit/MAU/AMU at time of the study data (date starting at 8:00 hrs, and ending at 07:59 hrs)
2. Age ≥18 years

**Exclusion criteria:**

None

**Data collection**

**AMU/Hospital Data (collected once per site):**

- Teaching Hospital or District General
- Total Number of Beds
- Are Nephrology Services on site?
- If not, is there a visiting nephrologist?
- Number of AMU Beds
- Does the AMU contain a level 2 care area?
- Does the AMU include a coronary care unit?
- Is there an electronic AKI detection system in place and functioning?
- Does the AMU employ an AKI risk assessment/AKI risk model?
- Does the trust have an outreach service?
- If there is an outreach service are they actively involved in patients with AKI?

**Data on the patients present in the AMU at time of the study date (collected per patient):**

We propose to collect only those data that are generated as part of routine hospital care. Therefore, we anticipate that whilst there will be some data items that will be collected in almost every patient, there will be some others that are not generated as part of routine care (some biochemical variables for example). We do not propose that additional testing should be performed, rather an option for ‘data not available’ be recorded, as the frequency of which data points are available will in itself inform the generation of risk tools with clinical utility.
Core details:

- Age
- Gender
- Race (for CKD-EPI/MDRD)
- AKI present within first 24hrs of admission – yes/no
- Baseline creatinine. For those patients without AKI on admission, the first serum creatinine in stay will be taken as baseline to assess for rise in creatinine within the next 7 days as per KDIGO criteria (risk prediction modelling). For those patients with definite AKI on admission, baseline will be taken as per current AKI detection system. If admission serum creatinine is elevated to above reference value range AND no previous value exist to use as baseline, data will be collected and a retrospective judgement made at time of data analysis as to whether AKI was present on admission (if not, admission creatinine will be taken as baseline and patient will be entered into pre-specified risk prediction modelling).
- Serum creatinine at time of hospital admission
- Highest serum creatinine during 7 days post admission

Admission data:

- Admission date hospital
- Referred from home or emergency department
- Reason for admission and main admission diagnosis (medical, emergency surgical, elective surgical, to be expanded)

Physiological Data on admission (first recorded in MAU):

- Presenting Tympanic Temperature
- Presenting heart rate
- Presenting blood pressure (Systolic, Diastolic and Mean)
- Presenting respiratory rate
- O₂ saturations (and inspired oxygen concentration FiO₂)
- Presenting AVPU score
- Urine output if known during first six hours of admission

Laboratory Data (first results in hospital stay):

- Biochemistry:
  - Serum creatinine concentration
- Serum urea
- Sodium
- Potassium
- Chloride
- Corrected serum calcium
- Serum phosphate
- Magnesium
- Uric Acid
- Bilirubin
- AST
- ALT
- Y-GT
- Ammonia
- pH
- Lactate
- Plasma bicarbonate
- Albumin
- Base deficit (If known)
- Troponin
- BNP (or NT pro-BNP)
- CRP
- Urine Analysis
- Haematology:
  - Haemoglobin
  - White Blood Cell Count Absolute
  - Neutrophil Count
  - Lymphocyte Count (For Neutrophil:Lymphocyte Ratio)
  - Red cell dispersion width
  - INR
  - Platelet count
- Medication taken at admission (yes/no for each):
  - Loop Diuretic
  - Thiazide
  - K-Sparing Diuretic
  - Spironolactone
- ACE Inhibitor
- ARB
- Ca^{2+} Antagonist
- Hydralazine
- Alpha Blocker
- Beta-Blocker
- Insulin
- Metformin
- Other Oral Hypoglycaemic Agents
- Oral Steroids
- Immunosuppressant Therapy
- Active Chemotherapy
- NSAIDs
- Paracetamol
- Antidepressants
- Other (List)

- Known Co-Morbidities:
  - CKD (Stage 3a-5)
  - Previous AKI
  - Cirrhotic Liver Disease
  - Non-Cirrhotic Liver Disease
  - Type I DM
  - Type II DM
  - Known Proteinuria
  - Cancer Previously
  - Cancer undergoing active therapy
  - COPD
  - Hypertension
  - CCF
  - Peripheral vascular disease
  - Ischaemic heart disease

**Recording of data up to discharge, death or 7 days:**
- Daily serum creatinine concentration for calculation of AKI
- Patient admission to HDU
- Patient admission to ICU
- Need for NIV
- Need for RRT for AKI (Intermittent)
- Need for RRT for AKI (Continuous)
- Mortality and date of death

**Study duration**

The study will last for 7 days; the end of the study will be 7 days after the last centre commences data collection.

**Selection and withdrawal of patients**

All patients admitted to medical assessment units in participating centres will be included in the study.

**Expected duration of participant participation**

There will be no direct participation required from patients. Data collection will take place to include data at time of admission, and then record outcomes at hospital discharge or at 7 days, whichever is sooner.

**Ethical considerations and consent**

This study will be conducted according to the standards of International Conference on Harmonisation, Good Clinical Practice Guideline, Research Ethics Committee regulations, any applicable government regulations, Trust and Research Office policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Research Ethics Committee (REC) for approval of the study conduct. As this study is only collecting only data that is generated by routine clinical care, and all data will be fully anonymised at source, the REC will be asked to consider a waiver of individual patient consent. Waiver of consent is also an essential component of this study’s feasibility, as without this there would be a prohibitive restriction on sample size. However, during the data collection period, efforts would be made to publicise the occurrence of the study on all participating MAUs (e.g. posters/notices) and these would include instructions of how patients can opt out and avoid inclusion.

As this is an observational study it is not anticipated that any other ethical problems will arise. Children will not be included.
Study procedures
None

Randomisation
Not applicable

Statistical plan and sample size estimation
The sample size will be determined by the number of participating centres and number of admissions during the study period. Logistic regression analysis will be used to identify predictors of development of AKI within 7 days of admission. Regression coefficients associated with each variable will be used to build risk prediction scores. The calibration of the risk scores will be assessed by the Hosmer-Lemeshow goodness-of-fit test. Discrimination will be assessed using the area under the receiver operating characteristic curve (AUC); this approach will also be utilised to perform validation studies of existing risk scores. Sample size will determine statistical approach to validation cohort for novel risk scores. p values <0.05 will be considered as significant.

Data collection and information governance
Information about study subjects will be kept confidential and managed according to the requirements of the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care, Ethics Committee Approval and Trusts’ IM&T Policy.
Method of data collection: Coded data in paper case record forms (CRF). Each participant will be assigned a unique study number (combination of centre code and number allocated locally) and patient identifiable data will be stored in a single password protected file on a Trust server at each participating centre. Only the site principle investigator has access to the code lists.
Anonymised data will then be entered into an electronic CRF through a secured website at the University of Surrey under the auspices of the Clinical Informatics Research Group at the University of Surrey. The Research Group works within the research and Information Governance frameworks for health and social care in the United Kingdom, and is compliant with the University’s best practice standards. The University of Surrey is registered with the Information Commissioner’s Office Data Protection Register, and is compliant with the Data Protection Act, and other legislations. Data is then transferred to the University of Surrey via a secure network transfer. Only authorised researchers in the University of Surrey have access to this data, and do so as part of research projects.
approved by the RSC. The group at the University of Surrey have all undertaken Information Governance training, and the infrastructure of the research group has been deemed satisfactory as part of the NHS Information Governance Toolkit (IGT) for Hosted Secondary Use Team/Project, Version 12 assessment. Details of the departmental information governance policies and procedures can be found in: http://www.clininf.eu/about/informationgovernance.html. All data are strongly encrypted by a combination of symmetric and asymmetric encryption algorithms: Triple DES and RSA 1024 before transmission, and utilises public and private key pairs unique to each project. Data transfer will be conducted in accordance with the Research Group's standard operating procedures in data extraction, pseudonymisation, and transfer. All data processing and analysis in the present proposed study will be conducted within the secure IT environment of the Clinical Informatics Research Group, at the University of Surrey. The secure network is sited behind a firewall within the University's network, all inbounded connections are block, but outbounded connections are allowed. The server room, where the DHCMP secure server is housed, is located in floor 3 in a windowless internal space within the Faculty IT Support Office. No external access to the Server Room is available other than through the Faculty IT Support Office, entry to which is controlled by access reader system with additional access reader to the Server Room within. In addition, the Faculty IT Office and server room are protected by PIR (Passive Infrared) Sensors. Access to these areas is user restricted to IT staff, the Faculty Facility Manager, and Central IT for emergency operations, if IT staff are unavailable. Cleaners do not clean in these areas unless there are supervised by IT staff member.

Case Report Forms
Each participant will have a data collection form covering all study results, labelled with the unique study number. These will be completed in accordance with the principles of Good Clinical Practice.

Records Retention
All paper records will be stored in a locked filing cabinet within the Trust or Medical School for the duration of the study. Computer records will be stored in password-protected files on password-protected servers in the Trust. At the conclusion of the study all data will be archived and stored at each centre for 5 years.

Data handling
All missing data will be explained. Participating site staff will be asked not to leave a blank space on the CRF, but rather to enter “not done (N/D)” if a data is not available. Should an item not be applicable to the individual case, “not applicable (N/A)” will be recorded. All entries will be printed legibly in black ink. If any error is made in data entry, to correct the error, a single straight line will be drawn through the incorrect entry and the correct data entered above it. All such changes will be initialed and dated. Errors will not be erased or altered by any other method. For clarification of
illegible or uncertain entries, the clarification will be printed above the item, initialed and dated. Correction fluid will not be used.

**Data quality assurance**

After data collection is complete, a random 5% sample of CRFs will be selected by the study statistician for review and validation against source data. This will be carried out by local investigators. The results of this will be used to extrapolate over quality of data capture and transfer. The study steering group will review these results and decide as to whether corrective or further actions are required.

**Safety and Adverse Events**

**Recording of Adverse Events**

All Adverse Events (AE) Serious Adverse Events (SAE) will be recorded according to R&D Procedure and Policy on Incident Reporting.

**When Adverse Events are Recorded**

As this is an observational study with no study procedures it is not anticipated that there will be any adverse events directly related to the study and no adverse event data for non-serious adverse events will be collected. Despite this, a process for dealing with any unexpected serious adverse events in the unlikely event they occur is still included. All such events will be communicated to the chief investigator. If a trial subject experiences a serious adverse event which in the opinion of the chief investigator is both related (resulted from administration of any of the research treatments or procedures) and unexpected then it will be reported to the Research Ethics Committee that gave a favourable opinion of the study and the sponsor within 15 days of the Chief Investigator becoming aware of the event using the NRES safety report form available from:

http://www.nres.nhs.uk/applications/after-ethical-review/safetyreports/safety-reports-for-all-other-research/

If the event fulfils the requirement of an IR1, it will also be reported according to local Trust Policy. The clinical course of each SAE will be followed until resolution, stabilization, or until it has been determined that the study participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome.
Study Monitoring Plan

The investigator will permit study-related monitoring, audits and inspections by the Ethics Committee, the Sponsor and the Research Governance Manager. This study will be monitored by the Research Governance Manager according to the Research & Development Office procedure for monitoring all non-commercial research. In line with the responsibilities set out in the Research Governance Framework, the Investigator will ensure that the research governance manager or other regulatory monitoring authority is given access to all study-related documents and study related facilities.

Study Finances

Funding Source

Local arrangements are in place to cover the costs of statistician time and secure web-based CRF. All other aspects of data collection are unfunded and will require interested clinicians to volunteer for this. There are non-financial incentives for participating – see section on ‘strategies to increase participation’.

Indemnity for the performance of the study

NHS indemnity will apply in the event of a claim by, or on behalf of, participants for negligent harm. There will be no special arrangements for non-negligent harm but the normal NHS Complaints mechanism will be available to all participants.

Sponsorship

Sponsorship will be arranged between the chief investigator and the Royal Surrey County Hospital Foundation Trust.

Publication Plan

A writing committee will be formed that will have primary responsibility for publication of the results. It is intended that the results will be presented at national and international nephrology conferences and published in high quality nephrology journals. Publications will be made under study group name (as opposed to individuals) and all contributors listed in manuscripts.
Strategies to increase centre participation

Professional society endorsement
This study now has the full backing of the UK Kidney Research Consortium and AKI Clinical Study Group, as well as support from the Society of Acute Medicine.

Allow access to the dataset for individual researchers who have actively contributed to data collection
Following completion of the study and publication of the primary results, all reasonable requests from any collaborator who contributed to data collection will be granted to perform additional analyses to answer their own research questions.

Acknowledgement of all contributors in any publications arising from this work
A Medline factsheet available here (https://www.nlm.nih.gov/pubs/factsheets/authorship.html) explains how an article can published under a study group or consortium name and then the personal names of the members of that group may be published in the article text. Such names are entered as collaborator names (also called investigator names) for the MEDLINE citation. A good example of how this can work is the ASTRAL trial in which all 475 collaborators received a Pubmed citation (N Engl J Med. 2009;361(20):1953-62, pubmed link: http://www.ncbi.nlm.nih.gov/pubmed/19907042).

Supporting documents
Case report form (CRF) version 1.6 (source data worksheet)
Supporting information for CRF/source data worksheet
Poster to display in clinical areas during study period

References
3. Ostermann M, Chang RW: Correlation between the AKI classification and outcome. Crit


