DEFINING THE LONG TERM CONSEQUENCES OF ACUTE KIDNEY INJURY: THE AKI RISK IN DERBY (ARID) STUDY

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Trust(s) **where research will take place**	Derby Hospitals NHS Foundation Trust

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Study Summary

Title	Defining the long term consequences of acute kidney injury: the AKI Risk In Derby (ARID) study
Short Title	AKI Risk In Derby (ARID) study
Protocol Version Number and Date	**Version 1.4** **December 2015**
Methodology	Long term case-control study.
Study Duration	**Twelve** years and nine months. See section 3.1 for details.
Study Centres	Royal Derby Hospital
Objectives	To assess the effect of Acute Kidney Injury (AKI) on long term patient outcomes, specifically looking at the effect on progression of chronic kidney disease (CKD) and mortality rates. To identify clinical and biochemical markers that predict those at greatest risk of CKD progression
Number of Subjects/Patients	1084
Main Inclusion Criteria	Identified as AKI or Not AKI (NAKI) on iCM electronic reporting system Age ≥18 years and ≤85yrs Able to provide full informed consent
Statistical Methodology and Analysis	Descriptive statistics to summarise baseline variables. Kaplan-Meier curves to compare the primary endpoints. A Cox proportional hazard model to test the effect of AKI on primary endpoints adjusted for important co-factors.

1. Introduction

The described research study will be conducted in compliance with the protocol, the Research Governance Framework, International Conference on Harmonisation, Good Clinical Practice Guideline ICH/GCP, and all applicable Derby Hospitals NHS Foundation Trust Research Office requirements.

1.1 Background

Acute Kidney Injury (AKI) is very common in acutely ill patients and is associated with longer, more complicated hospital stays and worse patient survival. The RIFLE criteria and subsequent modification by AKIN now provide a widely accepted definition of AKI that is predictive of short term outcomes [1]. Mortality progressively increases with severity of AKI; the mortality rate of critically ill patients on the intensive care unit (ICU) who receive renal replacement therapy (RRT) ranges between 50-80% [1]. There is now an increasing recognition that episodes of AKI may also have profound longer term sequelae. There are some studies suggesting that AKI leads to chronic kidney disease (CKD) and increases the risk of end-stage renal failure requiring dialysis [2-7]. Clearly this is very important as CKD and dialysis in particular have major effects on patient well-being and symptomatology; it follows that survivors of AKI may also have a worse long term survival rate as compared to those who do not sustain AKI [3, 8, 9]. There are also huge health economic implications bearing in mind the annual cost of haemodialysis for just one patient is £30,000.

However, the majority of studies in this area are retrospective and many include only specific patient groups such as ICU patients who required RRT, those undergoing surgical procedures or following coronary angioplasty. Furthermore, several of the published studies are historical and do not use the current diagnostic criteria for AKI [2, 4, 10, 11]. It is therefore unclear as to whether an association really exists between AKI and long term outcomes in a general hospitalised population who form the largest group of patients sustaining AKI. In addition, it remains to be seen whether associations between AKI and outcomes are causal, and whether patients at higher risk of subsequent adverse outcomes can be identified to allow targeting of follow up and more intensive management to those with the greatest clinical need. This will also inform the design of future interventional research studies.

The progression of CKD is determined by several factors but progressive tubular damage and inflammation both lead to fibrosis [12]. Tubular injury and inflammation are also key in the development and propagation of AKI; biomarkers of tubular damage such as neutrophil gelatinase-associated lipocalin (NGAL) and circulating markers of inflammation such as interleukin-6 (IL-6) both correlate with the onset and severity of AKI [13, 14]. Although there are initial data suggesting NGAL can predict progression of

CKD [15], these data are limited and it is uncertain how these factors interact to affect CKD progression that follows episodes of AKI.

There is therefore a need to examine the long term effects of AKI on patient outcomes in a prospective, UK based study that includes patients across the entire severity spectrum of AKI and across a broad range of clinical scenarios and specialities.

2 Study Objectives

The objectives of the study are to determine the long term effects of AKI on progression of CKD and mortality rates by comparing outcomes in hospitalised patients with similar characteristics who did and did not sustain AKI.

We also seek to define profiles of patients (using clinical parameters, biomarker profiles or a combination of both) that allow identification of those at highest risk of CKD progression.

3 Study Design

3.1 General Design

This is a long-term longitudinal observational case-control study. Basic blood tests to include measuring renal function, haemoglobin, albumin and proteinuria will be measured at study entry as well as 1 year, 3 years, **5 years and 10 years** after AKI (approximately 9months, 33months, **57 months and 117** months after recruitment). Samples will also be collected and stored at each of these time points for subsequent biomarker measurement; these will consist of inflammatory markers (IL-6, high sensitivity CRP) and plus a panel of biomarkers of tubular injury (to include NGAL and IL-18). Included patients will have baseline demographics, co-morbidity and acute illness details extracted from the hospital PAS system. AKI stage and baseline renal function (that prior to sustaining AKI) will be extracted from the electronic AKI reporting system currently in clinical use at the Royal Derby Hospital. This novel system identifies all episodes of AKI from every inpatient location and also reports severity as per AKIN staging; the diagnostic accuracy of this system has been confirmed and reported previously [16].

Patients receiving acute dialysis during the episode of AKI will be identified from renal unit and intensive care unit databases; the renal database (Vitaldata) will be used to identify those patients who subsequently require chronic renal replacement therapy (RRT). The Medical Research Information

Service (MRIS, an arm of the NHS Information Centre) will be used to accurately track survival data of participants to **ten** years after the AKI episode.

A pilot study, specifically designed to test this methodology and recruitment process is currently underway, and demonstrates that the proposed recruitment, consent and matching processes are both practicable and feasible (recruitment rate ~20%, with approximately 15 participants recruited per week).

3.2 Primary Study Endpoints

1. The risk of death in AKI group versus controls.
2. The risk of CKD progression in AKI group versus controls.

CKD progression will be defined as doubling of serum creatinine, eGFR<15mls/min or the initiation of renal replacement therapy (dialysis or transplantation).

3.3 Secondary Study Endpoints

1. Proportion of patients reaching renal endpoint (doubling creatinine/ESRF)
2. Mortality rates at each time point.
3. Length of hospital stay.
4. Estimated glomerular filtration rate (eGFR), serum creatinine and urine protein:creatinine ratio at each time point.
5. Comparison of causes of death between AKI group and controls
6. Comparison of levels of biomarkers of tubular injury (a panel to include NGAL and IL-18) and markers of inflammation (IL-6, hs-CRP) in those with and without progression of CKD.

4 Methods

The methods are the same as for the pilot study; the only change is that we propose to collect an additional blood sample for storage and subsequent analysis at each time point.

4.1 Subject Selection and Withdrawal

4.1.1 Inclusion Criteria

- Age ≥18 years and ≤85yrs
- In-patient serum creatinine measurement detected by iCM electronic AKI reporting system

Exclusion Criteria

- Inability/refusal to give informed consent to participate.
- Language barrier that prevents informed postal consent.
- Death during the same hospital admission that AKI occurred.
- Receiving palliative care

4.2 Subject Recruitment and Screening

There will be two methods of patient recruitment. For the majority of patients, the recruitment will occur as in the pilot study and is detailed in section 4.2.1. For a specific group of patients with liver disease, we propose a modified method of recruitment to adapt to the challenges of participant engagement in this particular patient group; this is detailed in section 4.2.3.

All patients will be identified via the AKI electronic reporting system. This system will electronically identify all patients that have sustained AKI or been screened for possible AKI but who did not sustain it. This database is currently used internally to monitor trends and assess effectiveness of clinical care. We will apply for specific ethical approval from the National Information Governance Board (approval for the same methodology already in place for the pilot study) to allow the identification of potential participants from this database, even though their inpatient care may have been delivered by another clinical team.

4.2.1 Group A – main study

All patients with AKI will be screened for inclusion into the study, as well as those patients tested for possible AKI but who did not sustain it. Patients will not be approached until at least two months after they have recovered from their acute illness, by which time the majority of patients will have returned home.

Recruitment, matching and consent

Patients who meet the inclusion criteria will be contacted via post and invited to participate. The control group will be matched to AKI patients on a 1:1 basis in terms of baseline eGFR (within the same CKD stage but as closely as possible) and age ± 5yrs. In addition they will be recruited from a similar inpatient setting. Due to the proposed three year follow up, patients over 85yrs will be excluded as the reduced life expectancy due to age alone in these patients may affect the outcome measures of mortality.

Potential subjects will receive a letter of invitation along with a comprehensive patient information sheet. Interested patients will be asked to telephone a number at the Royal Derby Hospital during which patient identity will be affirmed using standard data protection questions. After confirmation that the patients are in possession of the information required to provide valid consent, they will be sent a consent form that they will sign and return in a pre-paid envelope, retaining a copy for themselves (see section 4.2.2 for more details of the consent process). If patients do not wish to participate they will be asked to confirm this by telephoning the same number. This methodology has been piloted and has been shown to be very successful in more than 300 patients to date, with very positive feedback from participants.

Each patient will be assigned a unique study number that will be used to identify all data collected for the study. This will be allocated upon recruitment. A key of patient identity and study numbers will be kept on a password-protected Trust server in a password-protected file. Any information passed onto the Medical Research Information Service will be in encrypted form. A recruitment log will be maintained and the patients' GPs will be informed of their participation in the study by letter.

4.2.2 Postal consent

The process of obtaining 'remote', valid consent is well recognised and established in specialities such as gastroenterology (for guidelines as endorsed by the British Society of Gastroenterology that conform to Department of Health recommendations see http://www.bsg.org.uk/clinical-guidelines/endoscopy/guidelines-for-postal-consenting-for-outpatient-endoscopic-procedures.html). Previous work in this area has shown that more than 90% of patients give valid consent with this system, with almost all of the remainder providing valid consent after an opportunity for further discussion, usually about very specific points [17]. This process is particularly suited to situations where a large number of patients require consent for a procedure that is of very low risk of complications – this situation applies completely to this study protocol in which there are no potential risks to patient safety. To ensure that consent is valid, patients have to be fully informed about the procedure/study and the benefits and risks it may entail – this does not mandate a face-to-face interview and in this study will be accomplished by the patient information sheet with an option to contact the ARID research team if patients wish to discuss any points in more detail. This process also ensures ample time is given for assimilation and consideration of information. Consent will be confirmed during a telephone interview with all patients who express an interest in participation. This step will also provide an opportunity to ratify patient identity using standard data protection questions. The consent form is only a formal documentation that this decision making process has taken place, and the signed form will be returned to the ARID office in a pre-paid envelope that will then form a record of this process.

Consent will specifically include certain identifiable information being passed on to the Medical Research Information Service. Information that they would require would be the participants full name, date of birth, NHS number and address.

4.2.3 Group B – patients with liver disease

Recruitment, matching and consent

Many patients with cirrhosis in the UK are alcoholics and intravenous drug users. They tend to live a chaotic lifestyle with fluid residential addresses and limited access to telephone facilities. We therefore propose an alternative recruitment method to include this important patient group and facilitate participation. Patients will still be identified via the electronic AKI system but those who had their inpatient care delivered by the gastroenterology team will be screened for cirrhosis (using established definitions). Patients will not be approached until they have recovered from their acute illness.

Patients with cirrhosis and who meet the inclusion criteria will be approached on the ward prior to discharge and invited to participate by one of the research team. The control group will be matched to AKI patients on a 1:1 basis in terms of baseline eGFR (within the same CKD stage but as closely as possible) and age ± 5yrs. In addition they will be recruited from a similar inpatient setting. Due to the proposed three year follow up, patients over 85yrs will be excluded as the reduced life expectancy due to age alone in these patients may affect the outcome measures of mortality.

Potential subjects will receive a letter of invitation along with a comprehensive patient information sheet which they can read for 24 hours. After addressing any concerns or queries, interested patients will be asked to sign a consent form that they will sign and return to a member of the research team prior to discharge, retaining a copy for themselves. If patients do not wish to participate they will be asked to confirm this and will continue to receive standard of care.

Each patient will be assigned a unique study number that will be used to identify all data collected for the study. This will be allocated upon recruitment. A key of patient identity and study numbers will be kept on a password-protected Trust server in a password-protected file. Any information passed onto the Medical Research Information Service will be in encrypted form. A recruitment log will be maintained and the patients' GPs will be informed of their participation in the study by letter.

Consent will specifically include certain identifiable information being passed on to the Medical Research Information Service. Information that they would require would be the participants full name, date of birth, NHS number and address.

4.3 Withdrawal of Subjects

Patients will be withdrawn only if they withdraw their consent.

All patients will be included in the analyses except for those in the control group who subsequently sustain AKI during the study period, who will be excluded.

4.3.1 When and How to Withdraw Subjects

Patients who withdraw their consent will be removed from the study immediately. They will continue to receive routine care through their GP.

4.3.2 Data Collection and Follow-up for Withdrawn Subjects

Patients who withdraw will be asked to allow data collected prior to the date of withdrawal to be retained for analysis. They will also be asked to allow outcome data, including clinical events and the

results of any kidney function tests arranged by the GP, to be collected for future analysis. If a participant declines this their data will be deleted.

Patients who fail to attend for blood tests will be contacted by telephone to determine whether or not they are willing to continue. Patients without access to a telephone will be contacted by letter. If no response is received to two letters sent one month apart, the patient will be assumed to have been lost to follow-up.

4.4 Prior and Concomitant Therapy

Details of the hospital admission during which the patients were initially identified (either with AKI or screened as NAKI) will be collected from coding data on the hospital's PAS system. This will include primary diagnosis, secondary diagnoses and co-morbidity (specifically diabetes, hypertension, cardiovascular disease, active malignancy and for the liver subgroup aetiology and severity of liver disease). The patient's highest AKI stage, length of hospital stay, and discharge creatinine will be recorded. Acute dialysis treatments and dialysis independence will be determined for those patients who require acute RRT during the course of AKI.

5 Laboratory Assays

Renal function (urea and electrolytes) will be obtained at recruitment (this will be 3mnths after the episode of AKI/NAKI). Then at 1 year, 3 years**, 5 years and 10 years** after AKI/NAKI (approximately 9mnths, 33mnths, **57 mnths and 117 mnths** post recruitment). These samples form part of routine clinical care for patients recovering after an episode of AKI or with CKD and would normally be performed by the General Practitioner. Participants will be asked not to eat meat for 12 hours prior to the blood tests (to avoid a potential effect on the creatinine assay) and will be able to have the samples taken at GP surgeries, community hospitals (including London Road) or RDH. Results will be available via the hospital results system.

5.1 Biomarker analysis

Samples of EDTA plasma/serum and urine will be separated and stored at each of the **five** sample collection time points (recruitment, 9mnths, 33mnths, **57 mnths and 117 mnths** post recruitment). This will not require any additional blood or urine from the patient. Samples will be returned as usual practice to RDH central pathology laboratory where the specific study code on the iCM-generated

request form will result in removal of an aliquot of 1ml of plasma/serum and urine for storage. These samples will be placed immediately into 24/7 alarmed secure freezers in the pathology department; if additional storage space is required this will be provided in similar freezers in the medical school. Batched analysis of samples would take place subsequently to include measurement of IL-6, hs-CRP and a panel of biomarkers to include NGAL and IL-18 (final panel to be decided at time of analysis as this is a rapidly changing field). Samples will not be stored beyond the duration of the study.

6 Randomisation

Not applicable

7 Study Procedures

No procedures other than the **five** blood and urine samples (detailed in section 5) are planned.

8 Statistical Plan

Statistical advice has been sought from Derby Hospitals NHS Foundation Trust Statisticians, Mr. Apostolos Fakis and Miss Sally Hinchliffe.

8.1 Sample Size Determination

The original sample size for the study was based on some assumptions and information published in two studies [10, 11] so in line with the statistical plan in version 1.2 of the protocol, the sample size calculation has been repeated using one year results from the pilot study. The new sample size calculation is based on percentage change in eGFR at one year, a surrogate for subsequent CKD progression (doubling of serum creatinine or progression to CKD stage 5/dialysis). A previous study reported that 21.4% of those who experienced a 20% fall in eGFR at one year progressed to initiation of RRT [18]. Results from the pilot study have shown that 13 patients experienced such a decline in eGFR at one year in the control group as compared to 29 in the AKI group. Therefore, the estimated proportion in the control group that will progress to a doubling of serum creatinine or progression to CKD stage 5 is 2.02% as compared to 4.41% of the AKI group. Assuming a 5% significance level and 80% power this means that 430 patients will be required per group. Assuming a drop-out rate of 26% then a total of 542 patients will be required in each group.

8.2 Statistical Methods

Statistical analysis will be performed using SPSS v19.0 and Stata v11. Descriptive statistics will be used to summarise baseline variables in AKI and control groups. Univariate parametric or non-parametric analysis will be done to compare the two groups at baseline. Kaplan-Meier curves will be constructed to compare the primary endpoints, renal end-point and mortality between the two groups using the Log-Rank test. A Cox proportional hazard model will be used to test the effect of AKI on primary endpoints adjusted for age, gender, (race if possible), co-morbidity (diabetes, hypertension, malignancy, cardiovascular disease), baseline renal function, proteinuria, requirement for acute dialysis and multiple episodes of AKI. Conditional logistic regression will be performed for exploring the effect of AKI matched patients and secondary outcomes on the proportion of patients with CKD progression and on their mortality status at 12 months. Participants with cirrhosis will be included in the main analysis, but their co-morbid conditions will be accounted for in the statistical analysis.

8.3 Subject Population(s) for Analysis

All patients will be included in the analyses described above except for those in the control group who subsequently sustain AKI during the study period, who will be excluded. Depending on the frequency of this occurrence a separate 'intention to treat' secondary analysis may be performed. Data from patients who withdraw (and give consent) or who die will be included until the date of withdrawal or death.

9 Safety and Adverse Events

9.1 Recording of Adverse Events

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

9.2 When Adverse Events are Recorded

As this is an observational study with no study procedures other than venesection 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, it is important that this protocol includes a process for dealing with any unexpected serious adverse events in the unlikely event they occur. Serious adverse events that are considered expected in the investigator's judgement will be captured on a SAE log. 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 DHFT 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 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.

10 Data Handling and Record Keeping

10.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Data Protection Act, NHS Calldicott Guardian, The Research Governance Framework for Health and Social Care, Ethics Committee Approval and Trust IM&T Policy. Any information given as required for participant health status tracking to MRIS will be delivered in encrypted form.

Patient contact details including name, address and telephone number will be collected. This information will be retained to facilitate contacting the participants to arrange follow-up tests. Only the research team will have access to this database. It will be stored on a Trust password-protected server. A single hard copy will be stored in a locked filing cabinet in the data custodian’s office.

Each participant will be assigned a unique study number. The patient's name, date of birth and study number will be stored in a single password protected file on a Trust server. Only the research team will have access to this file. All data collected for the study will be entered into a separate database in which data will be labelled only with the study number. The participant's hospital number will be entered into this database but without any other identifiable details. Participants will not be identifiable from any publications arising from this study.

The Trust has a comprehensive registration with the Information Commissioner with research being registered under Purpose 4 of the Register; The Trust Data Protection Officer will be notified of all research studies in order to comply with the Trust IM&T Security Policy.
Dr Selby will act as "Custodian" of the data.

10.2 Source Documents

Source documents for this study will include:

- Case report form (results section)
- Laboratory results reports

10.3 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.

10.4 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 for 5 years in a secure storage facility in accordance with Trust policy.

Three copies of the consent from will be obtained. One will be retained by the participant and the others will be filed in the participant's hospital records and with the data collection form (in the TMF) respectively.

11 Study Monitoring, Auditing, and Inspecting

11.1 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 carried out at the Derby Hospitals NHS Foundation Trust. 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.

12 Ethical Considerations

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. The protocol will also be submitted to the National Information Governance Board for specific approval of the participant screening process.

All subjects for this study will be provided with an information sheet describing the elements of this study and sufficient information for subjects to make an informed decision about their participation in this study. See Attachments for a copy of the Information Sheet. The subject will complete and sign a consent form to indicate that they have given valid consent to participate.

As this is an observational study it is not anticipated that any ethical problems will arise. Children and vulnerable adults will not be included.

13 Study Finances

13.1 Funding Source

It should be noted that the anticipated costs of this project are low due to the straightforward protocol and local funds are already in place to allow project start-up. Funding has been secured in the form of a Research Grant from the BUPA Foundation.

13.2 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.

13.3 Sponsorship

Sponsorship will be arranged between the chief investigator and Derby Hospitals NHS Trust.

14 Publication Plan

Dr Selby 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.

15 References

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16 Attachments

- Invitation letter to AKI patients
- Invitation letter to non-AKI patients
- Participant Information Sheet
- Consent Form
- Patient letter to accompany consent form
- Letter to GPs
- Lay summary
- Peer reviews
- Case Report Form
- Invitation letter to AKI patients for liver patients
- Invitation letter to non-AKI patients for liver patients
- Participant Information Sheet for liver patients
- **Consent Form – for extended follow-up**
- **Participant letter for extended follow-up and Year3 sample collection**