The future for diagnostic tests of acute kidney injury in critical care: Evidence synthesis, care pathway analysis and research prioritisation.

Protocol

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The Leeds Teaching Hospitals NHS
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The future for diagnostic tests of acute kidney injury in critical care: evidence synthesis, care pathway analysis and research prioritisation.

SUMMARY OF RESEARCH:

Design: Systematic review, care pathway analysis, model-based economic evaluation and value of information analysis.

Target population: (a) Patients admitted to critical care (level 3 care). (b) A sub-group of patients admitted to critical care following cardiac surgery.

Clinical setting: UK NHS.

Health technologies being assessed: In vitro diagnostic tests for the early identification or risk stratification of AKI.

Project aims:

1. To evaluate the potential for AKI diagnostics to enhance the NHS care of patients admitted to critical care
2. To identify the priorities for further diagnostics development and propose efficient designs for relevant future research.

Care pathway-specific outcomes:

1. Incidence, prevalence and time to onset of AKI in critical care
2. AKI disease natural history (morbidity, chronic kidney disease (CKD), dialysis and mortality)
3. Rate, duration and timing of renal replacement therapy
4. Critical care and hospital length of stay, hospital-specific resource use and hospital costs
5. Post-discharge healthcare resource use and costs (primary and secondary care), quality of life, patient-financial burden.

Diagnostic test-specific outcomes:

a. Pre-analytical, analytical and biological measurement properties.
b. Clinical validity (sensitivity and specificity) for diagnosis and severity of AKI and outcomes such as length of stay, duration of renal replacement therapy, subsequent morbidity, rates of CKD and survival.
c. Clinical efficacy, clinical effectiveness and cost-effectiveness of test-directed care vs. standard care including patient/carer/clinician acceptability.
d. Recommendations for efficient research design (value of information).
e. Challenges for implementation and budget impact

Data sources: Outcomes will primarily be informed by the literature identified by the systematic review. Additional data will be sought from prospective UK-based datasets describing the care pathway and healthcare resource use. We already have agreement in principle to use data from an established registry of critical care patients and two recent UK clinical trials conducted in appropriate patient populations.

Statistical and economic analysis: The care pathway will be modelled using probabilistic decision analytic simulation techniques. Meta-analysis of diagnostic test properties will be conducted where multiple comparable studies are identified. Research recommendations will rely on value-of-information analysis.

Project timetable: The study will start in October 2014 with duration of 15 months.

Project Team Details

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PROJECT OBJECTIVES:

1. **To describe the care pathway followed by patients who are admitted to critical care and are at risk of AKI, represented as a decision analytic model.**
2. **To identify, through systematic review, candidate diagnostic tests for the early detection, risk stratification or therapy personalisation of AKI**
3. **To systematically review and meta-analyse the evidence on diagnostic properties, clinical validity and clinical utility of identified AKI diagnostics**
4. **To identify decision points in the care pathway that might be influenced by the diagnostic tests.**
5. **To evaluate the potential clinical and cost-effectiveness of the diagnostic tests, given their potential to change the care pathway.**
6. **To characterise uncertainties in the evidence, prioritise tests for development and identify efficient research designs.**

THE PROBLEM

The relevance of acute kidney injury as a major problem for public health has been recently emphasised in guidance issued by NICE (National Institute for Health and Care Excellence, 2013a). NICE estimate that acute kidney injury costs the UK National Health Service £434-620 million every year – more than breast, lung, and skin cancer combined (Taylor, 2011). Moreover, according to NICE, adequate care of acute kidney injury could avoid 42,000 deaths every year.

Acute kidney injury (AKI) occurs in 30-70% of critically ill patients most commonly associated with multi-organ failure secondary to hypotension and sepsis. Patients who develop AKI have worse clinical outcomes with a mortality rate greater than 50% which, despite advances in modern medicine, has remained unchanged for the last 30 years. Patients who develop severe AKI requiring renal replacement therapy (RRT) have a further increase in their risk of death (Thakar et al., 2009).

The diagnosis of AKI currently relies on a rise in serum creatinine and/or a decrease in urine output, both of which are considered relatively poor biomarkers. Serum creatinine remains a non-specific marker of AKI being a product of muscle metabolism and does not indicate the site of the injury or distinguish between pre-renal (functional process) and intrinsic (damage process) AKI. The generation of creatinine is dependent on muscle mass and is therefore a very poor marker of kidney function particularly in malnourished patients or patients with liver disease. It is recognised that a person could lose 50% of their kidney function before the creatinine rises above the normal range. The rise in serum creatinine is delayed in relation to the onset of the injury and the magnitude of rise does not correlate with the severity of injury. Likewise creatinine does not correlate well with recovery of kidney function. More specific serum and urinary biomarkers of AKI are needed urgently in clinical practice (Murray et al., 2013).

WHY THIS RESEARCH IS IMPORTANT

More recently it has been recognised that chronic kidney disease (CKD) occurs in 40% of survivors of AKI in critical illness and results in significant morbidity and expense. It is estimated that up to 10% of patients will not recover sufficient kidney function and will remain on RRT (Chawla et al., 2011). Chronic kidney disease in the UK costs £1.45 billion per year (Kerr et al., 2012). It is therefore important to identify patients' at risk or who are developing AKI to reduce the insult and ameliorate the severity of the injury and therefore reduce its short and long term consequences. It was reported that patients in 2009-2010 who experienced an episode of AKI in the UK stayed in hospital an average of 4.7 days longer than patients without AKI (Taylor, 2011). Acute kidney injury represents an important patient safety issue as recognised by NHS England and is a significant financial burden on healthcare services. There is great potential to prevent AKI and reduce its severity and hence the medical and financial burden to the NHS.

The development of better biomarkers to detect AKI would also benefit patients at risk outside of the intensive care unit (ICU). Not all hospitals in the UK have renal units and the facility to deliver RRT. In these hospitals patients who develop severe AKI requiring RRT may have to be transferred to the ICU for RRT alone which inappropriately utilises a precious NHS resource. Earlier detection of AKI with the potential to stratify prognosis would allow for prompt transfer of patients to the correct environment for their care.

Biomarker-based in-vitro-diagnostics (IVDs) offer an opportunity for early diagnosis, risk stratification and monitoring, enabling earlier specialist referral, targeted intervention or intensification of therapy where indicated by the test. There is evidence that early RRT can improve outcomes from AKI including reduced duration of RRT, reduced length of hospital stay, reduced rates of CKD and long term RRT (Kellum and Lameire, 2012). There are a number of pharmaceutical interventions in late-phase development that will increase the opportunity for targeted intervention in the coming years. Previous therapeutic interventions have been unsuccessful due in part to a very crude approach to the diagnosis of AKI and a failure to understand its complexity without appropriate biomarkers.

WHY THIS RESEARCH IS NEEDED NOW

Currently there is no robust evidence-base to guide when to initiate RRT and this is determined empirically dependent upon the clinical context and utilising creatinine as a marker of severity of AKI. There is an on-going research effort internationally to discover and develop biomarkers and diagnostics for AKI. The extent to which such tests can influence the clinical decisions and change the current management of patients admitted to critical care remains unknown. There is an urgent need to evaluate the extent to which AKI diagnostics have the potential to influence outcomes through change in clinical practice. If a model-based analysis demonstrates that AKI diagnostics can potentially change practice in a way that results in more cost-effective care then there will be value in further investment in a development and evaluation programme.

The sizeable waste within the historical research process has recently been highlighted (Macleod et al., 2014). Academic and commercial communities are at the start of a new era of diagnostics development for AKI. There is a time-limited opportunity to design this UK research programme efficiently and with appropriate up-front prioritisation. The Office of Health Economics have also recently highlighted that progress in personalised medicine is slower than some had expected, partly because of the science and partly because of insufficient economic incentives, particularly for investing in molecular diagnostics (Towse et al., 2013). It is clear that more efficient development strategies are needed and this grant proposes to lay the foundation for a UK development strategy for the development of diagnostics for AKI.

EXISTING RESEARCH

A number of different biomarkers have been investigated in small heterogeneous studies in critically ill patients with AKI including neutrophil gelatinase-associated lipocalin (NGAL), interleukin 18 (IL-18), kidney injury molecule-1 (KIM-1), liver fatty acid binding protein (L-FABP) and more recently the cell cycle arrest markers, Insulin-Like Growth Factor Binding Factor 7 (IGF BP-7) and Tissue Inhibitor of Metalloproteinases 2 (TIMP 2) (Murray et al., 2013). More data are required in well conducted trials to identify both improved patient outcomes and economic benefit to the NHS before their routine use can be recommended. It is unlikely that one biomarker will fit all and a panel of biomarkers will be required because of the heterogeneity of causes of AKI. However, a number of biomarkers have already been commercialised as in-vitro diagnostic test kits and are subject to active marketing campaigns, including IGF, BP7 and TIMP2 (NephroCheck™, Astute Medical); the NGAL Test (BioPorto/Alpha Laboratories); urine NGAL (Abbott Laboratories) and Triage NGAL Test (Alere). There is therefore a real risk that these biomarkers could be adopted by NHS laboratories and clinicians prior to the development of robust supporting evidence for clinical and cost-effectiveness.

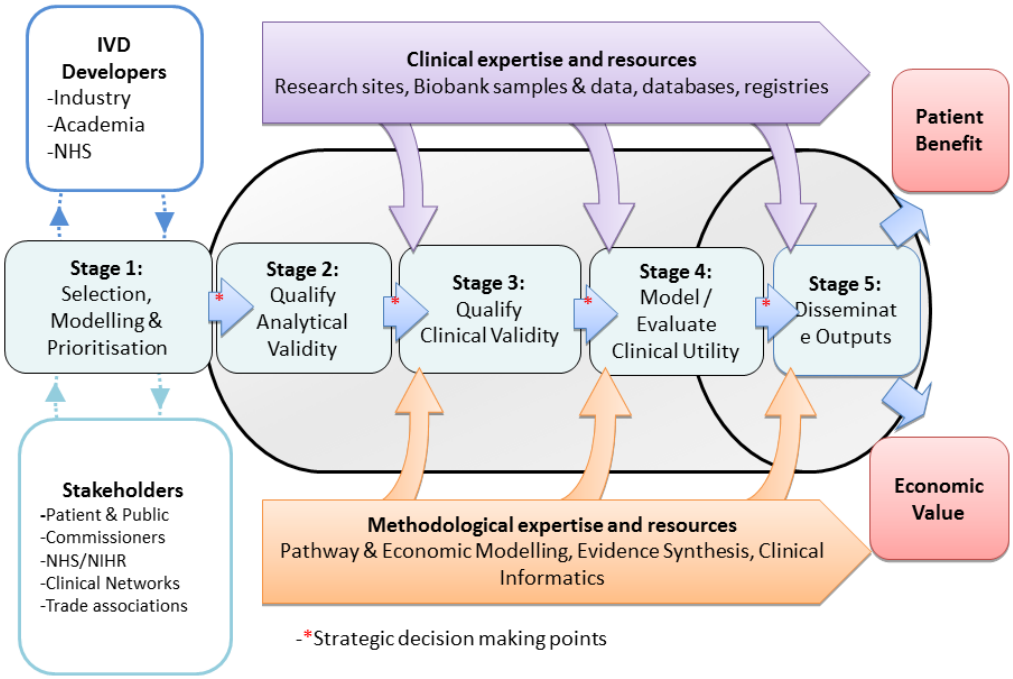
In 2013 a diagnostic test based on the NGAL biomarker was considered by the NICE Diagnostics Advisory Committee. They concluded that more research was needed prior to adopting NGAL, but that this was undoubtedly an area of considerable clinical need.

RESEARCH METHODS

Technical background for the methodological approach

The NIHR Diagnostics Evaluation Cooperatives (DECs) focus on clinical areas or themes where evidence of the clinical validity, clinical utility, cost-effectiveness and care pathway benefits of IVDs has the potential to lead to improvements in healthcare services and the quality of life of NHS patients. The DECs bring together a wide range of experts and specialists from across the NHS and industry, including clinicians and other healthcare professionals, patients, NHS commissioners, researchers and methodologists. The NIHR DEC Leeds promotes efficient research design for new technologies within the NHS. In doing so it acknowledges from the start that the gold standard for demonstrating clinical utility and cost-effectiveness, and accepted by NICE, is a model-based economic evaluation informed where possible by randomised controlled trials. For any given clinical context, modelling will therefore commence at the very start of technology evaluation, during the process which selects and prioritises technologies for inclusion within the DEC research pipeline (Figure 1). By introducing a model early, it is possible to characterise the potential impact of a diagnostic test on the clinical pathway, clinical decision points and expected clinical end economic outcomes. The optimal case definition threshold (cut-point) for tests can be proposed for cost-effectiveness in addition to clinical validity alone. Models will be maintained and updated as IVD evaluation progresses, populated by meta-analysis of evidence generated both within and external to the DEC. Probabilistic modelling will be used to characterise areas of uncertainty in the evolving evidence between each phase of development; thus enabling iterative research design efficiency. Expected cost-effectiveness and value for the NHS can be established as well as commercial headroom for relevant manufacturers. It is possible to model the test cost under different commercialization scenarios (e.g. large centralized lab vs. local hospital lab provision) and its impact upon the value of alternative research activities can be estimated. The use of Bayesian decision modelling and value of information analysis will be a core method. As an example, the trade-offs between investment in a large RCT which can measure causal effects versus alternative cheaper or quicker study designs which may simple measure associations.

Figure 1. The DEC pipeline:



RESEARCH PLAN:

Phase 1: Systematic review
Phase 2: Evidence synthesis and meta-analysis
Phase 3: Care pathway analysis
Phase 4: Decision analytic model
Phase 5: Sensitivity analysis and value of information analysis
Phase 6: Dissemination (recommendations for research design and test prioritisation)

Phase 1: Systematic review

The project will involve a systematic review with three targeted searches to meet the following objectives:

Search 1: To identify candidate or in-development relevant diagnostic tests (horizon scanning) that could be used in critical care to identify AKI.

Search 1 will use a broad search strategy, inclusive of the grey literature. Communication will also be made with relevant academic groups and manufacturers, many of whom have agreed to collaborate. By implication, tests in development for AKI outside the setting of critical care will need to be included within the scope of this search under the assumption that they may be future candidates for use in critical care. Tests will be categorised by their role within the care pathway (see Figure 2 below) and their stage of development.

Search 2: To identify current evidence for analytic validity, clinical validity, clinical utility and cost-effectiveness of tests identified in search 1 for AKI.

On the basis of information identified by Search 1, focussed searches will be conducted to enable the extraction of test-specific parameters to be made available for subsequent evidence synthesis and parameterisation of the care pathway. In the event that large numbers of tests or biomarkers are identified the Specialist Advisory Group will advise on prioritisation.

On the basis of our scoping searches, this part of the search is likely to find relatively little in the way of existing studies on clinical utility, and only limited evidence of clinical validity for some diagnostic tests. Identification of analytical and pre-analytical factors will therefore be key to understanding the technical and clinical validity of a test. Such considerations are often overlooked until they present later in the pipeline as sources of bias or explanations for trial failure. It is vital to identify and quantify the impact of these factors early on in the evaluation process to enable, through decision modelling and simulation, an accurate estimation of the uncertainties associated with a test's performance. This is a core principle for this project.

Analytical and validation factors associated with the physical measurement of a biomarker, including sensitivity, specificity, precision, parallelism, recovery, selectivity, limit of quantitation (LOQ) and vulnerability to interferences will be sought where appropriate, and reviewed in line with current FDA best practice guidelines and CLSI standards. Pre-analytical variables that may influence the quality, integrity or composition of samples, including biological factors (e.g. within-patient variability, sample timing, medical history, diet and lifestyle) and technical factors (e.g. sample collection, processing, shipping and storage conditions) will be obtained and reviewed in line with the BRISQ reporting standards.

Search 3: To identify information describing the clinical care pathway and standard care for AKI in critical care, including investigation, clinical management, interventions, healthcare resource use, morbidity, mortality, quality of life and other relevant outcomes descriptors.

Search 3 will seek literature describing the care pathway in real-world NHS practice and will focus on clinical guidelines, observational studies, registry-based analyses, epidemiological studies, service evaluations, clinical audit quality of life studies, survivorship studies and cost analyses.

Search strategy

The search strategies will be designed by JW based on existing guidelines with advice from Specialist Advisory Group on clinical terms in order to capture published papers plus grey literature. A number of manufacturers have already agreed to provide unpublished data.

Individual searches for test validity, clinical utility and cost studies will be constructed with consideration of published guidance for retrieving diagnostic accuracy (de Vet 2008, Benyon et al., 2013) and cost-effectiveness studies (Glanville 2010). Sensitive searches will be developed using keywords (e.g. “acute renal failure”, “neutrophil* gelatin* associ* lipocal*”) and subject headings for concepts; Acute kidney injury (MeSH Acute Kidney Injury/), intensive care ((MeSH Intensive Care/), known candidate biomarkers (MeSH Insulin-Like Growth Factor Binding Proteins/), validity (MeSH Predictive Value of Test/), unknown biomarkers (exp *Biological Markers/). All searches will be run on MEDLINE, EMBASE, The Cochrane Library, HMIC (all OVID), MEDION database, the Web of Science Science Citation Index and Conference Proceedings (Thomson Reuters). Unpublished (grey) literature will be sought from databases which include conference proceedings, working papers and registries of on-going trials such as ClinicalTrials.gov. Searches for cost effectiveness will be run on additional economic databases including RePEC, NHSEED (CRD). The manufacturers of relevant diagnostic technologies will also be contacted for information about unpublished studies. Non-English language papers will be included where a translation of the study data is possible in the project timescale and budget. Records found will be stored and managed in an EndNote library.

Review strategy

The reviews will be led by EM. References identified by the literature searches will be appraised in two stages. Titles and abstracts of all identified studies will be screened for inclusion by one reviewer with a random sample (25%) independently screened by a second reviewer. The full-text of studies not definitely excluded at that stage will be obtained and independently assessed by two reviewers to determine whether they meet the inclusion criteria. Differences of opinion will be discussed until a consensus is reached; the opinion of a third reviewer will be sought where necessary. All decisions will be coded and recorded in an EndNote library. At the outset of the review, a training session (run by EM) will be held to ensure that each reviewer is aware of and understands the explicit inclusion and exclusion criteria, thereby facilitating standardisation in screening and selection.

We will undertake a hand search of the reference lists of all included papers to identify any potentially relevant papers not identified by the literature search. Additional papers identified in this way will be subjected to the review process outlined above.

Data extraction and quality assessment will be undertaken by one reviewer using a standardised proforma. A random sample (10%) will be reviewed and validated by a second reviewer. A training session and pilot will be held prior to the commencement of data extraction to review the proforma and criteria for quality assessment, and ensure that each included study is dealt with appropriately. Data will be stored in an Access database.

Methodological Quality checklists, such as those proposed by the NHS Centre for Reviews and Dissemination will be used to appraise study quality. Diagnostic test-specific approaches based on the QUADAS (or QUADAS-2) and/or STARD tools will also be used (Whiting et al., 2011; Bossyut et al., 2003).

Studies at risk of bias will not be excluded from the review, but an appraisal of the strength of existing evidence will be reported, and the review findings interpreted in light of this.

Review of cost-effectiveness literature

In addition to the databases identified above, targeted systematic searching will take place in the specialist health economic database NHS EED and the economic working papers resource IDEAS (REPEC). Economic evaluation search filters developed by the NHS CRD and utility and cost-specific search strategies designed by the NICE DSU will be used as a basis for the search strategy. The results of the searches will be stored in an Endnote database. The review strategy will mirror that of the effectiveness review. The quality of each paper will be assessed using a modified version of the Drummond et al checklist (Drummond, 2005). For papers reporting economic evaluations alongside clinical trials or cost-effectiveness models, the Drummond checklist will be supplemented with reference to the Good Practice Guidance produced by the ISPOR Task Force on Economic evaluations alongside clinical trials (Caro et al., 2012).

Phase 2: Evidence synthesis

The aim of this phase is to combine the findings from phase 1 and enable summary estimation of the relevant metrics outlined above. The exact format of evidence synthesis will depend on the nature and format of information identified by the literature review. For example, effect estimates from clinical utility studies will be combined using meta-analysis. In the absence of high quality comparative studies, meta-analysis of diagnostic test properties including analytical and clinical validity will be central to the analysis. Test-specific parameters will be required to be sensitive to variation between analytic platform, manufacturer and specific assay. It is likely that many tests will be at a relatively early stage in development, in which case their impact on the care pathway will need to be modelled (in phase 4) using extrapolation via surrogate endpoints. For example, confidence intervals around sensitivity and specificity may need to be estimated from data on analytic and pre-analytic properties of the tests.

Meta-analyses for diagnostic test accuracies are evolving rapidly as a methodology (Bipat et al., 2007; Phillips et al., 2010; Simel and Bossuyt, 2009) and recent additions to the literature will be considered prior to the commencement of any analyses. However, the technique of hierarchical regression meta-analysis proposed by Moses et al and developed further by Rutter and Gatsonis will most likely be used (Moses et al., 1993; Rutter and Gatsonis, 2001). This is a fully Bayesian approach which has the advantage of unifying the sensitivity analyses (assessment of uncertainty in the estimates) with the modelling step whilst allowing predictions of test accuracies in future trials via the posterior predictive distribution. This methodology will then naturally inform the models in phase 4. Sources of heterogeneity that will be considered include the QUADAS quality rating, previous diagnostic approach, study size, technology used, age of patients, and country. The definition of a reference case (or true positive outcome) for diagnostic property assessment has varied between studies – this will present a challenge for cross-study comparison. The definition will therefore be finalised after consultation with the literature and the Specialist Advisory Group and will be subject to sensitivity analysis.

Phase 3: Care pathway analysis

In line with established methods for model-based cost-effectiveness analysis, the first step will be to define standard care for patients at risk of and experiencing AKI in critical care (Bossuyt and McCaffery, 2009; Caro et al., 2012). An illustrative care pathway is shown in Figure 2. The pathway model will be used as the basis for phase 4 by enabling characterisation of:

- Key decision points at which tests change the process of care
- Mechanisms for changing the process of care
- Relationships and down-stream knock-on effects that may be influenced by tests.
- Key surrogate endpoints.

Endpoints and specific clinical events that will be considered include:

a. Incidence, prevalence and time to onset of AKI in critical care
b. AKI disease natural history (morbidity, chronic renal failure, chronic dialysis and mortality)
c. Rate, duration and timing of RRT
d. Critical care and hospital length of stay, hospital-specific resource use and hospital costs
e. Post-discharge healthcare resource use and costs (primary and secondary care), quality of life, patient-financial burden.

The information required to define the care pathway will be derived from systematic literature search number 3 and through consultation with the Specialist Advisory Group and patient representatives.

The care pathway will look at all-comers to critical care, all of whom are at risk of AKI. The only pre-planned subgroup analysis will look at the special population of patients admitted to critical care following cardiac surgery. This subgroup has been chosen because patients are at particular risk of AKI and are universally managed in a controlled environment with strong potential for management changes to be made in response to diagnostic tests. A post-cardiac surgery population is likely to be relatively more homogenous and have a more clearly defined care pathway with rich published data describing clinical outcomes of interest. These characteristics make it an attractive population for planning further research within.

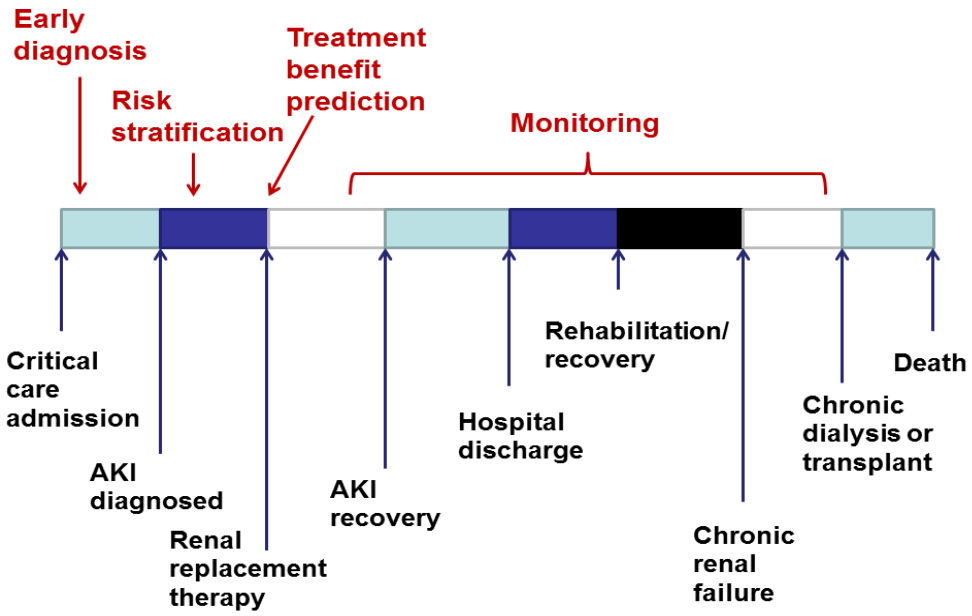
In addition to the published literature, we have approval to use three patient-level datasets that can be used to obtain information on the care pathway and resource use during the inpatient stay of patients admitted to critical care with and without AKI:

1. The OSCAR trial recruited 795 patients in critical care, collecting detailed daily data on the process of care and resource use. Clinical and QoL outcomes were collected for 1 year (Young et al., 2013).
2. The ERRICA trial recruited patients undergoing Coronary Artery Bypass Graft surgery (ERICCA) the trial included a biobank to look prospectively at the clinical validity of AKI biomarkers. Clinical and QoL outcomes were collected for 1 year (Hausenloy, 2013).
3. An international registry of AKI patients in critical care (“Epi-AKI”) which includes a UK cohort. Led by Professor Mehta of the University of San-Diego, the Registry was established following an international consensus meeting in 2007 with the objective of accurately characterising the care pathway clinical outcomes in critical care and during hospital stay (Mehta et al., 2007).

Although, wherever possible, outcomes will be informed by the literature identified by the systematic review and from the described datasets, patient representatives and clinical experts will be consulted in order to describe the care pathway and healthcare resource use. Part of this process will involve two focus groups which will be convened following the initial development of the care pathway description. Focus group 1 will comprise 8-10 clinical experts in the management of renal disease and critical care and other relevant specialties. Focus group 2 will comprise 5-8 patient and carer representatives with experience in critical care, acute renal failure, chronic renal failure and dialysis. Patient representatives will be recruited nationally through The National Kidney Foundation and Kidney Research UK. The aim of the focus groups will be primarily to explore what the care pathway will look like after diagnosis with AKI. Focus groups are particularly useful at such an exploratory phase of investigation for allowing participants to generate their own questions, frames and concepts and pursue their own priorities on their own terms (Kitzinger and Barbour, 1999). The key to such a technique is the use of group interaction to generate data exploring people’s experiences, opinions, wishes and concerns and as such different populations are most favourable. Our research team patient representative, Claire Corps, will be key to convening this group and will aid with communication along with David Meads, Elizabeth Mitchell and Karen Vinall-Collier who have experience in the elicitation of opinion and preferences in a

focus group setting. Focus group discussion will be transcribed in verbatim and analysed using thematic analysis by KV in consultation with DM and EM. Thematic analysis will be undertaken following the recommendations set by Braun and Clark as a means of 'identifying, analysing and reporting patterns (themes) within data (Braun and Clarke, 2006). The same focus groups will be used to elicit relevant probability parameters within the economic decision model where there is no quantitative published evidence to base these on. In addition to the focus groups, alternative methods for the elicitation of expert opinion may also be used. Any elicitation exercises will be designed in line with current recommendations, such as those laid out in the SHELF system developed by the University of Sheffield (http://www.tonyohagan.co.uk/shelf/), depending on the required information.

Figure 2. Exemplar clinical care pathway: AKI in critical care highlighting key decision points.



Phase 4: Decision analysis

A decision model will be developed, based on the care pathway developed in phase 3, to calculate expected costs and QALYs for the current AKI care pathway. The economic evaluation will follow contemporary methods for model-based economic evaluation such as those specified in the NICE guidance on the methods of technology appraisal and the ISPOR taskforce (Caro et al., 2012; National Institute for Health and Care Excellence, 2013b). The base-analysis will take an NHS and personal social services perspective with an additional analysis considering a societal perspective. The model structure will be defined with guidance from the Specialist Advisory Group. Input parameters will rely on evidence identified in the previous three phases with particular consideration given to the evidence requirements for the evaluation of diagnostic tests (Sutton et al., 2008). The model will most likely be a time-varying Markov model capturing the costs and benefits of a cohort passing through the clinical pathways from admission to critical care to death (lifetime horizon). However, the precise modelling technique will be determined after consultation and consideration will be given to the use of discrete event simulation or patient-level micro-simulation if necessary. The model structure will most likely comprise health states as outlined in Figure 2, with more detailed modelling around decision points influenced by the tests. Data sources to populate the model beyond hospital admission will be derived from the published literature, including quality of life estimates from published studies using the EQ-5D and population mortality from the Office of National Statistics or published registry data. Outcomes comparing current standard care with test-directed care will be presented as incremental cost-effectiveness ratios (ICERs) and net monetary benefit. Characterisation of uncertainty will rely on

probabilistic evaluation either by bootstrapping directly from data available or by Monte Carlo simulation.

The role of AKI diagnostic tests will be incorporated in the model at key decision points as indicated by the current evidence or recommendations of the Specialist Advisory Group. Divergence in the clinical pathway, consequent on test results will be modelled. Where possible, the consequences of sensitivity and specificity will be captured as follows:

- True positives: Receive appropriate management and derive consequent benefit.
- False positives: Receive inappropriate management and derive harm or use unnecessary resource.
- True negatives: Managed appropriately.
- False negatives: Managed incorrectly or with delayed intervention with relevant consequences.

Uncertainty in test properties and allocation to these groups will be captured within the probabilistic analysis.

Phase 5: Sensitivity analysis and value of information analysis

Current uncertainty will be captured around the expected clinical utility and cost-effectiveness of each test using probabilistic sensitivity analysis. Deterministic sensitivity analysis will also be conducted around alternative uses of the tests within the care pathway. For example, the potential for a test to change care when used in risk-stratification or for early diagnosis can be compared.

The value of further publically funded research into diagnostic tests at specific decision points will be determined and compared using value of information analysis. Value of information analysis is a method based on Bayesian decision theory that can be used to characterise the burden of uncertainty on an NHS reimbursement decision maker or commissioner (Claxton, 1999; Hall et al., 2013).

Commercial interests will be considered by considering cost-effectiveness conditional on alternative test prices and by proposing a value based price (with confidence intervals). The terms of reference for value-based pricing remain in development and a contemporary framework will be adopted at the time of analysis. Commercial headroom for further research and development will be proposed where requested by manufacturers by considering the net present value of a decision and of further research.

A value of information analysis will be conducted to assist with prioritisation and further research design, specifically to:

1. Capture important aspects of the care pathway and standard care that require more evidence or descriptive information.
2. Prioritise between each decision point in the care pathway in terms of priority for test development.
3. Recommend candidate tests for further development (for priority decision points).
4. Recommend an optimal research design strategy (for each priority test).

A note on scope

Although AKI is a problem across most care settings, this project focuses on critical care to provide an adequately focussed population with manageable heterogeneity and a high burden of AKI. Following the successful completion of this project the scope can be broadened to consider other patient populations with unmet need. Many of the finding of this study will also be generalizable to other settings.

PROJECT TEAM

RESEARCH TEAM	SPECIALIST ADVISORY GROUP (SAG)
Andrew Lewington, Co-Chief Investigator (Clinical)	CHAIR: Linda Sharples (Statistical Methods for Decision Models)
Peter Hall, Co-Chief Investigator (Methods)	Chris McCabe (Health Economics)
Liz Mitchell (Review Lead & Project Management)	Douglas Thompson (Clinical Biochemist)
Karen Vinall (Review & Project Co-ordination)	Walter Gregory (Statistics & Clinical Trials Research)
Judy Wright (Information Specialist)	Nick Selby (Renal Physician)
David Meads (Health Economics & Modelling)	Marlies Ostermann (Renal Physician & Intensivist)
Claire Corps (Patient representative)	Lui Forni (Renal Physician & Intensivist)
David Cairns (Statistics)	Patrick Hamilton (SpR in Renal Medicine, NHS Pennine)
Michelle Hutchinson (Statistics)	Duncan Young (Critical Care Specialist)
Michael Messenger (Healthcare Scientist)	Mark Bellamy (Critical Care Specialist)
Ashley Garner (Clinical Biochemist)	Marion Kerr (Health Economics of renal disease)
	Chris Smith (Data Scientist)

PROJECT GOVERNANCE

PROJECT DELIVERY BOARD

CHAIR: Professor Peter Selby (Leeds; Clinical Director of the NIHR DEC Leeds)
Professor Doug Altman (Methodology for the NIHR Diagnostics Evidence Co-operative Leeds, Oxford)
Dr David Kluth (Nephrologist, Edinburgh)
Nominated representative from Kidney Research UK (recruited nationally)
Representation in the board will also be sought from a manufacturer (BIVDA).

The Board's brief will be to ensure that the project remains true to its objectives.

FLOW DIAGRAM OF TIMELINES

Month	1	2	3	4	5	6	7	8	9	11	12	13	14	15
Phase 1: Literature Review														
S1: diagnostics identification														
S2: diagnostic properties for identified tests														
S3: care pathway and economic parameters														
Phase 2: Evidence synthesis														
Phase 3: Care Pathway analysis														
Phase 4: Decision analysis														
Phase 5: Research prioritisation														
Phase 6: Dissemination														

ETHICAL ARRANGEMENTS AND INFORMATION GOVERNANCE

The project does not use patient identifiable information or primary datasets, therefore there are no ethical or information governance issues. If a patient focus group recruits from outside the immediate research team then ethical approval will be sought from the University of Leeds ethics committee. In the event that patient-level data is obtained from previous research to inform the care pathway model, such data will be used only within the confines of existing permissions.

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