Personalising renal function monitoring and interventions in people living with heart failure: RENAL-HF

Work Package 2 Stages 1-6
RENAL-HF: Care pathway co-design

Study Title	**Co-creation of a care pathway for implementing personalised renal function monitoring & interventions for people with heart failure**
Short Title or Acronym	RENAL-HF: Care pathway co-design (WP2 Stages 1-6)
Sponsor Reference Number:	**UoL001712**
Funder reference number:	NIHR202349
IRAS Number:	316009

LIST OF CONTENTS

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirements.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest, accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature:

Signed by:
Karen Jennings-Wilding
Signer Name: Karen Jennings-Wilding
Signing Reason: I approve this document
Signing Time: 03 December 2024 | 12:33:30 PM GMT
E0AD3C9FD9A84DEAA9365BA11703D062

Date: 03 December 2024

Name (please print):
Mrs Karen Jennings-Wilding

Position:
Senior Clinical Research Governance Manager

Chief Investigator:

Signature:

Signed by:
Professor Sir Munir Pirmohamed
Signer Name: Professor Sir Munir Pirmohamed
Signing Reason: I approve this document
Signing Time: 11 December 2024 | 9:28:47 AM GMT
621714BDEC4742089DF2E53235263BAC

Date: 11 December 2024

Name: (please print):
Professor Sir Munir Pirmohamed

GENERAL INFORMATION:

This protocol describes work carried out during **Work Package 2 (Stages 1-6)** of an NIHR funded Programme Grant for Applied Research (PGfAR): *Personalising renal function monitoring and interventions in people living with heart failure* (RENAL-HF). The protocol is based on the NIHR grant proposal developed by the lead applicant, named co-investigators and the WP2 study team.

KEY CONTACTS

Chief Investigator	Professor Sir Munir Pirmohamed University of Liverpool T: +44 (0) 151 794 5549 F: +44 (0) 151 794 5059 E: munirp@liverpool.ac.uk
RENAL-HF Project Manager	Alison Gummery University of Liverpool T: +44 (0) 151 795 9679 E: ali01@liverpool.ac.uk
Postdoctoral Research Associate (PDRA)	Dr Emma Sowden (01/04/2022- 31/10/2023) University of Liverpool T:+44(0) 151 794 0241 E: E.Sowden@liverpool.ac.uk Dr Naila Khan (01/11/2023-30/06/2024) University of Liverpool nak@liverpool.ac.uk Dr Mark Goodall (current from 17/06/2024 – present) University of Liverpool mgoodall@liverpool.ac.uk Dr Suzy Hargreaves (current from 01/07/2024 – present) University of Liverpool
Research Fellow	Dr Sudeh Cheraghi-Sohi University of Manchester T: + 44 (0) 161 275 7665 E:sudeh.cheraghi-sohi@manchester.ac.uk
Sponsor	The University of Liverpool is the research Sponsor for this Study. As an employee of the University, it is recognised that the Chief Investigator has been delegated specific duties, as detailed in the Sponsorship Approval letter. For further information regarding the sponsorship conditions, please contact: Mrs Karen Jennings-Wilding Senior Clinical Research Governance Manager Sponsor@liverpool.ac.uk
Key Protocol Contributors	Prof Chris Armitage The University of Manchester T:+44 (0) 161 275 2556 E: chris.armitage@manchester.ac.uk
	Dr Ben Brown The University of Manchester E: benjamin.brown@manchester.ac.uk
	Dr Jenny Downing University of Liverpool T: +44(0)151 795 5390 E: J.Downing@liverpool.ac.uk

	Dr Carolyn Lees University of Liverpool T: +44 (0) 7833 435842 E: C.Lees4@liverpool.ac.uk
	Prof Bridget Young University of Liverpool T: +44 (0) 151 794 5525 E: Bridget.Young@liverpool.ac.uk
	Prof Nefyn Williams University of Liverpool E: Nefyn.Williams@liverpool.ac.uk

GLOSSARY OF ABBREVIATIONS

AHA	American Heart Association
AKI	Acute Kidney Injury
ARC	Applied Research Collaboration
CLAHRC	Collaborations for Leadership in Applied Health Research
CPRD	Clinical Practice Research Datalink
EMIS	Formerly known as the Egton Medical Information systems
ESC	European Society of Cardiology
HF	Heart Failure
GDPR	General Data protection Regulation
MRC	Medical Research Council
NIHR	National Institute for Health and Social Care Research
NICE	UK National Institute for Health and Care Excellence
PDRA	Post-Doctoral Research Associate
PGfAR	Programme for Applied Research
PPIE	Patient and Public Involvement and Engagement
PMG	Programme Management Group
PSC	Programme Steering Committee
SIGN	Scottish Intercollegiate Guidelines Network
SOP	Standard Operating Procedure
WP	Work Package

STUDY SUMMARY

Work Package 2 (WP2)	Co-creation of a care pathway for implementing personalised renal function monitoring and interventions for people with heart failure (RENAL-HF WP2)
Short Title	RENAL-HF Care pathway co-design (WP2 Stage 1-6)
Study Design	A mixed-method work package comprises six iterative stages **WP2 Stage 1: Understanding Current Practice** a) Healthcare professional survey: delivered by YouGov b) Focused qualitative interviews **WP2 Stage 2: Co-designing the pathway (clinical guidelines)** a)Evidence Synthesis**:** learning from WP1 & WP2 stage 1 to generate a set of proposals for the b) Stakeholder consensus workshops*:* Five parallels panel meetings (patients, GPs, nurses, pharmacists, key informants) RAND/UCLA Appropriateness Method to establish consensus on the design of the care pathway **WP2 Stage 3: Decision-making** Identification of intervention functions and behaviour change techniques informed by the APEASE criteria (acceptability, practicality, effectiveness, affordability, safety & equity) **WP2 stage 4: Training material** Up to 3 multi-disciplinary co-creation workshops with the research team **WP2 Stage 5: Beta Testing** Think aloud interviews during beta-testing of the care pathway **WP2 Stage 6: RENAL-HF Care pathway feasibility and acceptability sub-study** a) In-depth qualitative interviews with 34 providers who did engage and those that did not engage with the system. Observational data on how the system is used b) In-depth qualitative interview with 25 patient/carer dyads
Study Participants	**WP2 Stage 1** a) Data will be sent from YouGov to research team for analysis b) Healthcare practitioners **WP2 Stage 2** Healthcare practitioners,((GPs, pharmacists, nurses, key informants, patients) **WP2 Stage 3:** *No participants; research team only* **WP2 Stage 4:** *No participants; research team only* **WP2 Stage 5:** Healthcare practitioners (GPs, pharmacists, nurses, care navigators). **WP2 Stage 6: RENAL-HF Care pathway feasibility and acceptability sub-study** a) Healthcare practitioners (GPs, pharmacists, nurses, care navigators) b) Patients and carers.
Planned Size of sample	**WP2 Stage 1:** a) 600 participants; b) three groups, each with 17 participants. **WP2 Stage 2**: five groups, each with nine participants. **WP2 Stage 5**: four groups, each with nine participants. **WP2: Stage 6: RENAL-HF Care pathway feasibility and acceptability sub-study** a) two groups, each with 17 participants; b) 25 participants.

Planned Study Period	WP2 overall will span 36 months. Funding for the RENAL-HF programme commenced 01/02/2022 WP2 Stages 1-5 will span approximately 24 months
Follow-up duration	No follow-up required
Aim	Co-create with patients, primary care practitioners and specialists the clinical pathway for implementing personalised renal function monitoring and optimal interventions if renal function declines in primary care.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT

Project management

The Project Management Group will comprise the named co-investigators and researchers included in the NIHR proposal and chaired by the Chief investigator. The programme will be delivered by a study team for each WP, collaborating with relevant members of other WPs as needed to ensure a fully integrated project. The Project Management Group will also maintain integration across this large and diverse research group. The Project Management Group will convene once every two months to discuss each WP and review and implement actions recommended by the Programme Steering Committee and the Patient and Public Involvement and Engagement Group.

WP2 Study Team: roles & responsibilities

Study Team	Role	Responsibilities
Professor Sir Munir Pirmohamed	Lead applicant (CI)	Chief Investigator (CI) leadership and programme management; input into all WPs. As an employee of the University, the CI has been delegated specific duties, as detailed in the Sponsorship Approval letter.
Alison Gummery	Project Manager	Project Management across all WPs and partners; ensure that Sponsor and ethics requirements are satisfied; monitor expenditure; manage and administer PPI activities; co-ordinate reporting to NIHR; facilitate communication via social media.
Prof Chris Armitage	Co-applicant	Lead survey of current healthcare practice; lead co-design workshops for implementation; process evaluation; line-manage PDRA5 at the University of Manchester
Dr Ben Brown	Co-applicant	Develop training programme; co-create implementation pathway; co-lead feasibility study in GP surgeries.
Prof Dawn Dowding	Co-applicant	Specialist input into developing technological interventions - focus on usability, including by nurses.
Dr Jenny Downing	Co-applicant	PPIE co-lead; co-chair PPIE group and lead academic input into PPIE activities. Will inform implementation design, with particular emphasis on avoiding inequality.
Mrs Lynn Hedgecoe	Co-applicant	PPIE co-lead with Dr Downing. Will co-chair PPIE meetings & provide a patient voice at Programme Steering Committee (PSC) and Programme Management Group (PMG). Will lead the communication between the PSC, PMG, and the PPIE group. Will play a key role in selecting, mentoring & assigning roles to a diverse PPIE group and overseeing PPIE expenditure with the Project Manager (Alison Gummery)
Dr Carolyn Lees	Co-applicant	Preparation of training package, recruiting community nurses, ensuring nursing voice represented, and our intervention is tailored to their needs.
Prof Bridget Young	Co-applicant	Qualitative methodology with emphasis on understanding the patient perspective.
Prof Nefyn Williams	Co-applicant	Provide general practitioner perspective; lead the development of online training for intervention and an effective GP alert. Will line manage PDRA2 at the University of Liverpool

Dr Emma Sowden	PDRA 2 (01/04/2022-31/10/2023	Co-design implementation pathway; structured interviews with patients and practitioners; facilitate workshops; develop training materials, support PPIE.
Dr Naila Khan	PDRA 2 from 01/11/2023-30/06/2024	
Dr Mark Goodall	PDRA 2	
DR Suzy Hargreaves	PDRA 2	
Dr Sudeh Cheraghi-Sohi	PDRA 5	Surveying current UK practice, co-design workshops for implementation, and process evaluation.

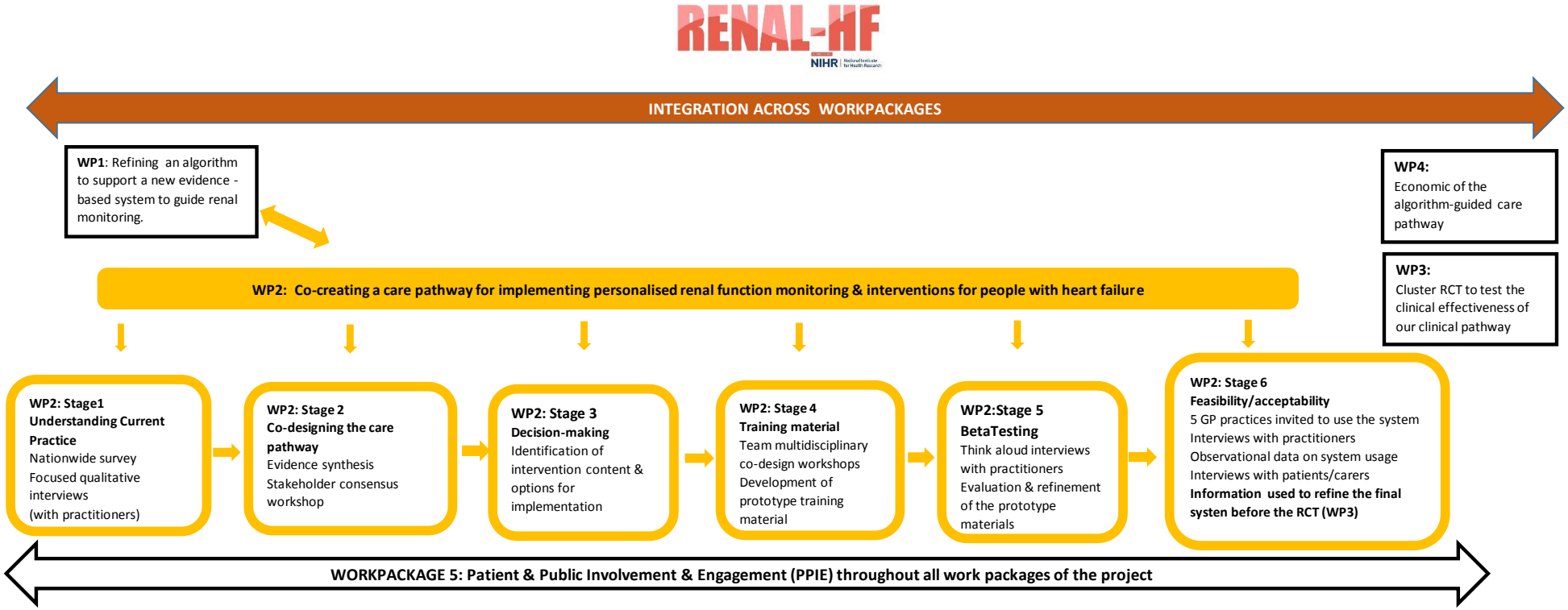
Study Steering Committee

An independent Programme Steering Committee will be appointed to advise the Chief Investigator and co-investigators on the work's quality, scientific and ethical aspects and review progress. The Programme Steering Committee will meet within the first three months of programme commencement and thereafter once per year.

External Steering Committee Members

- Dr Laurie Tomlinson – Chair (Laurie Tomlinson | LSHTM)
- Prof Theresa McDonagh (Professor Theresa McDonagh (KCL.ac.uk))
- Prof Amanda Farrin (Professor Amanda Farrin | School of Medicine | University of Leeds) (– PA Abigail Ledder - A.V.E.Ledder@leeds.ac.uk
- Andy Smith (andyjsmith3@gmail.com)

Figure 2
Study schema: Foregrounding Work package 2



1. PLAIN ENGLISH SUMMARY

Background

Almost a million people in the UK live with heart failure (HF), most of whom have kidney problems. Modern treatments help people with heart failure live longer, healthier lives, but the amount and type of medication need to be checked regularly. Too low a dose of heart medication makes heart failure symptoms worse. Higher doses of heart medication can cause kidney function to worsen. Either can lead to hospitalization and increase the risk of death. At present, there is wide variability in how kidney health in people with heart failure is managed in GP practices, and there are no agreed guidelines.

Overview of the wider project (RENAL-HF)

This work package forms part of a large programme of research called the RENAL-HF Project, which involves various integrated studies to develop better processes in GP practices to manage kidney health in people with heart failure. Medical records will be used to i) develop technology to predict how often each person with heart failure needs a kidney blood test and ii) inform the development of expert advice for GPs and nurses on how best to adjust medication. Working with patients, primary care practitioners and specialists, we will find the best way of implementing this personalised approach to kidney monitoring and interventions through the co-design of an improved care pathway. We will then determine if this approach is more effective or better value for money than the current standard of care. We will ensure that the patient voice is integrated throughout the studies and outputs.

RENAL-HF: Care pathway co design (WP2 Stages 1-6)

Work Package 2 (stages 1-6) will involve gathering the views of healthcare professionals, patients, and carers to ensure that the care pathway we develop is acceptable for patients and professionals and complements existing systems in GP practices. Without this work package, we cannot design a useful tool for patient benefit. To ensure that we achieve this objective, we will

- Conduct surveys and interviews with nurses, GPs and pharmacists who work in GP practices to understand current care
- We will combine all our learning to create a list of proposals to help improve guidelines for monitoring kidney health for people with heart failure
- Key groups (including patients, GPs, pharmacists, nurses, specialists, and commissioners) will discuss and vote on these proposals to decide which ones are the most important
- The RENAL-HF team, including members of the public, will work out what training would be most helpful to support professionals to use these new proposals in practice
- We will then invite a group of professionals to test the new system for monitoring kidney health to make sure they are happy with how it works and that the instructions are clear and easy to use
- This information will be used to help improve the system, so we are ready to test the feasibility and acceptability of the new care pathway in 5 GP practices during WP2 Stage 6 - RENAL-HF Care pathway feasibility/acceptability study

2. INTRODUCTION

This protocol describes patient and practitioner facing work carried out during WP2 Stages 1-6 of an NIHR funded Programme Grant for Applied Research (PGfAR): *Personalising renal function monitoring and interventions in people living with heart failure* (RENAL-HF). This wider research programme comprises of six highly interconnected work packages (Figure 1) that aim to develop an evidence-based system for generating guidelines for personalised renal function monitoring and treatment embedded within standard software used by primary care practitioners.
We hypothesise that implementing an algorithm-guided care pathway that includes personalised monitoring schedules for renal function, combined with guided intervention, can improve the quality of life and reduce the number of hospitalisations due to drug-induced renal injury in people living with heart failure.

WP1 will use advanced analytical methods and electronic health care records held by the Clinical Practice Research Datalink (CPRD) to refine the accuracy of an algorithm that predicts the change in renal function in patients with heart failure. The protocol here comprises Work Package 2 (WP2), Stages 1-6 RENAL-HF: Care Pathway co-design which will involve the *Co-creation of a care pathway for implementing personalised renal function monitoring and interventions for people with HF* (RENAL-HF Care pathway). During this phase, we will work with patients, primary care practitioners, and specialists to co-design an improved care pathway to implement a personalised approach to kidney monitoring and interventions which will be feasibility tested during Stage 6 of Work Package 2.

The success of the Renal-HF care pathway depends on its feasibility and acceptability for the primary care practitioners implementing it, and for the patients whose lives it will affect. Before full-scale roll out of the care pathway in the COMPUTATIONAL trial, it is therefore important to assess and refine the pathway based on evidence from primary care practices, practitioners and patients. Thus, we will implement the care pathway and tools in a small sub-set of primary care practices and use the findings of this mixed-methods feasibility and acceptability study to optimise the intervention before it is finalised for the clinical trial. ***Therefore, this sub-study will precede the main trial.***

By the end of the feasibility and acceptability study we will have produced an intervention, specified according to TIDieR guidelines[19], designed to change primary care practice and maximise future uptake and engagement with the new renal care pathway.

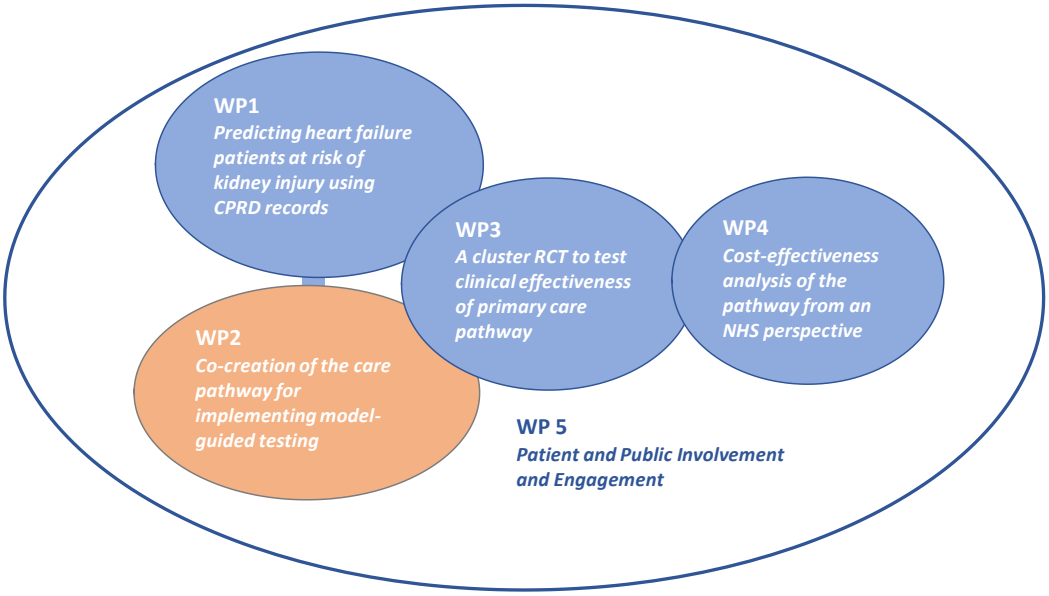
Work Package 2 is essential for informing the design of a cluster randomised controlled trial (WP3) which will assess the clinical effectiveness of our algorithm-guided care pathway compared with the current standard of care. This trial will be accompanied by a health economic analysis (WP4). In addition, Patient and Public Involvement and Engagement (PPIE) will be integrated throughout the project (WP5) with PPIE involvement in the design, data collection, analysis, outputs, and dissemination across work packages. Sponsorship for the trial (WP3) will be sought later, with the commencement of WP3 and WP4 dependent on the completion of WP1 and WP2. It is helpful to understand Work Package 2 in the context of the wider programme, so this protocol will outline the background and rationale for the wider NIHR Programme before focusing on the design and procedures for Work Package 2 Stages 1-6.

Work Package 2 involves an iterative approach, comprises six stages (Figure 2), and complements colleagues' Work in WP1, with whom we will work closely. This protocol describes stages 1-6 of Work Package 2, providing information about procedures for entering participants, study procedures, and governance requirements for these stages. Stage 6 will be informed by earlier stages of WP1 and WP2. Requirements according to the Medical Devices Directive (MDD)(1) and implementation of the software into GP practices will be covered in Work Package 1 and stage 6 of WP2

Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study following required approvals. This study will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act 2018 and the UK GDPR as amended from time to time and any successor legislation in the UK and any other directly applicable regulation relating to data protection and privacy and any other regulatory requirements as appropriate.

Queries relating to this Study should be referred, in the first instance, to the Project Manager Alison Gummery Gummery, ali01@liverpool.ac.uk or Project Researchers Suzannah Hargreaves (s.c.hargreaves@liverpool.ac.uk) and Dr Mark Goodall (m.goodall@liverpool.ac.uk).

Figure 2: RENAL-HF Programme



3. BACKGROUND

Heart Failure is a complex, clinical syndrome (2) affecting almost one million people in the UK and approximately 26 million people worldwide, and its prevalence is increasing (3, 4). Despite modern

treatment reducing morbidity and improving survival for this population, heart failure is a common contributing factor to acute and chronic kidney disease. Unfortunately, many drugs used to treat heart failure can impair renal function. Renal impairment associated with heart failure drugs is the second most common adverse drug reaction resulting in hospitalisation (5). It is a significant clinical issue with an unmet national and global need (6-9). These adverse drug reactions are potentially preventable through regular renal function monitoring and optimisation of drug dose and choice to prevent deterioration to acute kidney injury. However, optimising drug dose and choice is challenging because the clinician has to attempt to balance the competing factors of benefit to cardiac function and the risk of renal injury. Furthermore, heart failure and renal function decline are closely linked; approximately 50% of those with heart failure have chronic kidney disease (10). Even a small decline in renal function may precipitate hospital admission.

There is a delicate balance between maintaining cardiac function and preventing renal injury in people living with heart failure. For example, increased fluid load due to poor renal function can exacerbate heart failure; conversely, fluid overload primarily caused by heart failure can cause or aggravate renal impairment. This leads to the possibility of a vicious cycle with progressive deterioration of both heart and renal function. Furthermore, introducing or increasing doses of drugs used to treat heart failure (particularly diuretics and cardioprotective drugs such as ACE inhibitors, angiotensin receptor blockers and aldosterone antagonists) can cause or contribute to renal failure impairment or associated renal-related problems.

Nephrologists and cardiologists are well aware of the need for frequent reviews in patients with worsening cardiorenal or reno-cardiac syndrome. Still, clear guidance on the timing and frequency of reviews is lacking (11, 12). Existing guidelines are not tailored to this challenging cohort and lack consensus. For example, the UK National Institute for Health and Care Excellence (NICE) recommends 6-monthly renal function monitoring in stable patients with chronic heart failure. At the same time, the Scottish Intercollegiate Guidelines Network (SIGN), European Society of Cardiology (ESC) and American Heart Association (AHA) does not have any recommendation. There is some guidance on monitoring renal function in people with heart failure following changes in medication, but this also lacks consensus. For example, NICE recommends that renal function be measured within two weeks after a change in treatment, while SIGN suggests one to two weeks after, and ESC and AHA do not specify the appropriate intervals (13). Such non-specific and variable guidance leads to variable clinical practice largely due to the lack of evidence on the most beneficial testing frequency. This inevitably results in renal function deterioration in some people, ultimately leading to hospital admission and sometimes death. There is a pressing need to standardise care processes for this population to reduce the variability in clinical practice and improve outcomes by developing an improved care pathway within primary care.

Care pathways[1],also known as clinical pathways, care paths, critical pathways, integrated care pathways or care maps, have been implemented internationally since the 1980s (14) and are associated with improved patient outcomes (15). While a universally agreed definition and consistent terminology remain challenging (14), it is widely accepted that this tool to guide evidence-based healthcare aims to improve the quality of care through the creation of a consistent workflow for care delivery (16-18). Care pathways are generally agreed to comprise a complex intervention for

[1] For consistency throughout this protocol we have adopted the term ‘care pathway’

the mutual decision-making and organisation of care for a well-defined group of patients during a well-defined period (19).

Given that this group of patients will have individual co-morbidities and rates of renal decline, an optimal care pathway for this population would require renal monitoring to be personalised case-by-case (12, 20). Owing to the lack of evidence on the frequency of renal monitoring in people living with heart failure, we completed a series of earlier studies within the PERMIT project (Personalised Renal Monitoring via Information Technology) funded by NIHR ARC North West Coast (formerly CLAHRC). This project aimed to work toward much needed 'patient-based' guidelines for renal monitoring in heart failure. This involved using electronic health records to create a prediction model or algorithm that could highlight which patients with heart failure were most at risk of renal decline to intervene before requiring hospital admission (12, 20). This project forms the foundation for the RENAL-HF project to develop an algorithm-guided care pathway. Key findings from this programme of work are detailed below.

3.1 Developing an algorithm to predict the risk of kidney injury

Serum creatinine is the most widely used assay for measuring renal function (11), and the PERMIT study showed that in 112,676 people with newly diagnosed heart failure from 865 GP practices participating in the Clinical Practice Research Datalink (CPRD) between 2008 and 2020, (88%) had a record of blood creatinine level measurement. On average, GP practices measured 2.8 (95% confidence interval: 1.32-5.93) creatinine values per person with heart failure per year, with an approximately 5-fold variability in the frequency of renal function monitoring. Therefore, it is likely that some patients in this analysis had too many renal function tests while others did not have enough.

Data from 3800 heart failure patients (2008-2016) in the Salford Integrated Care Record (SIR) were used to identify up to 203 clinical variables that predicted how blood creatinine levels change over time (median follow up 2.3 years), with time modelled as a variable longitudinally. The clinical variables included demographics (age, gender, BMI, deprivation index and ethnicity), cardiovascular factors (such as hypertension, diabetes, smoking, atrial fibrillation, ischaemic heart disease), renal factors (including CKD status, renovascular disease, dialysis, nephrectomy, anaemia) and medications (such as diuretics, NSAIDs, drugs acting on the angiotensin system, antibiotics). Modelling each patient individually (via linear mixed models) using a statistical method termed FlexMix (21, 22) enabled the clustering of patients into different groups based on their trajectories. Seven distinct patient groups were identified with similar trajectories of variation in their kidney function over time: in two groups, kidney function declined rapidly (18.6% of patients), three groups showed a slow decline (57.7%), and two groups had stable kidney function (23.8%). However, the error in assigning individuals to different groups was up to 30%. Using each patient's baseline renal function to offset the clustering group prediction during proof-of-concept experiments showed that personalized prediction of creatinine in this way was superior to group-based predictions. Although this is a promising result and of the same order of magnitude as was recently published for predicting AKI in hospital inpatients (23), this analysis only used 300 records. Analysis of a much larger dataset (in WP1) is needed to ensure that we have not introduced selection bias.

3.2 Understanding patient and practitioner needs

Successful development of a care pathway involves the contribution of patients and practitioners to ensure all stakeholder's needs and preferences are considered (24-26). The PERMIT work systematically reviewed factors that have determined success in implementing community-based technological interventions in people with heart failure (27). These included telemonitoring services, remote consultations, and mobile apps tracking health status to patient-directed online education programs. This work involved co-production research methods with the PPIE group and health professionals interpreting the review findings. Five key themes were identified as impacting the engagement of patients, carers, and healthcare professionals with these technologies: 'convenience', 'ease of use', 'education', 'clinical care' and 'communication between patients, carers, and healthcare professionals. Findings from the review were then used in a discrete choice experiment (DCE) involving 93 people living with heart failure. The design involved placing the themes identified from the review in a questionnaire format to enable patients to 'trade' each of them against each other which showed that experiences relating to the clinical care theme were the most valuable of the five attributes for people living with heart failure.

A survey design was used to gather practitioners' (n=122) views on existing care pathways for renal function monitoring and on using a personalized algorithm for monitoring. Of those who responded to the question, 79% (72 respondents) wanted an integrated decision support tool, and 89% (81 individuals) wanted to receive alerts when a patient's renal function results were abnormal. In addition to monitoring alerts for abnormal renal function test results, 91% of respondents (83 individuals) wanted to receive alerts suggesting that they review a patient's medication and doses where appropriate. Survey respondents highlighted additional information in their free responses that are particularly pertinent to designing and implementing a future care pathway which incorporates a renal function monitoring solution. Some key points were:

- To ensure successful implementation, it will be necessary to provide evidence to healthcare practitioners regarding the difference between the personalized monitoring system and the existing system available via EMIS and the potential value compared to the current practice.
- It was suggested that the personalized monitoring system would need to differentiate between what is 'normal' and 'abnormal' for each patient in relation to renal test results. Suggestions from respondents also stated that any proposed new system needs to be fully integrated into the existing system and not sit on top of it. Additionally, it would be useful if the system allowed all relevant healthcare providers to see the results.

Comments also stated that any intervention must be capable of forwarding alerts to supporting professionals when the lead practitioner is unavailable due to annual leave or illness.

4. RATIONALE

Our project aims to build on the work from the PERMIT studies to develop an *improved care pathway for renal care in people living with heart failure*. The care pathway will include an algorithm that will predict the risk of renal injury and disease progression based on previous renal function measurements. In addition, the algorithm will be used to guide optimal renal test frequency in individual people with heart failure. This will address the need for evidence-based guidelines on the frequency of renal testing function tailored for this specific cohort. Importantly, recommendations on renal testing frequency will be linked with evidence-based, consensus guidelines on appropriate interventions in cases with renal function decline, created with input from a panel of cardiologists,

nephrologists and primary care practitioners, and our research team (including PPIE representatives).

These guidelines will be developed by the clinical experts panel the RENAL HF project. Potential interventions include adjustment of dose and type of medication and advice on fluid intake. These are all currently used to manage heart failure but without evidence-based guidance. This guidance is sorely needed due to the wide range of potential interventions: diuretic doses might be titrated up or down or discontinued temporarily; doses of ACEIs, ARBs, aldosterone antagonists or newer cardioprotective agents might be adjusted, commenced, or discontinued; important but non-pharmacological interventions might include increasing or decreasing 24-hour fluid restriction, increasing or decreasing recommended dietary potassium or salt intake.
Research to inform the development of an algorithm-guided care pathway has the potential to promote patient safety, enhance patient outcomes, and optimise available resources. This work will provide better access to decision support for clinicians. Using AI and predictive techniques will enable a care pathway to improve patient outcomes aligning with current NHS priorities (12, 28). We estimate that 27,500 people with heart failure are admitted to the hospital due to renal impairment caused by medication per year in England (5). The median hospital stay for heart failure patients is nine days (29), and recovery after hospitalisation is typically slow, with frequent readmissions. The annual cost of AKI-related inpatient care in England (2011) was estimated at £1.02 billion, just over 1% of the NHS budget. Therefore, even a small reduction in admission rate would significantly save overall costs(30).

We shall focus on heart failure, a condition increasing in prevalence and most common in older adults with multimorbidity. Our multi-disciplinary team will turn data into information, creating a patient and practitioner-informed intervention. The knowledge we create will lead to a step-change in clinical practice. Our care pathway may increase the frequency of renal function monitoring for some patients. Conversely, monitoring could occur at a lower frequency for those at low risk of renal injury, reducing the burden to both the individual and the healthcare systems and contributing to optimal disease management. If a modest 5% decrease in hospital admissions could be achieved in this patient population, we estimate this would correspond to 1,375 admissions avoided per year across England. Although our intervention focuses on primary care, this will also benefit secondary care clinicians through shared care guidelines, improving the overall cross-speciality coordination of renal function assessment in people living with heart failure. Taken together, this will improve patient outcomes and satisfaction and reduce hospital admissions, aligning with the NHS Long Term Plan (28) goal of reducing the morbidity associated with cardiovascular disease.

5. RESEARCH AIMS

5.1 Programme aims

This NIHR Programme Grant for Applied Research-RENAL-HF comprises six highly interconnected work packages (Figure 1), which aim to extend and refine our model to underpin an evidence-based system for generating guidelines for (i) personalised renal function monitoring and (ii) optimal interventions if renal function is declining.
Our aims for the full programme are shown below; WP 2 (Stages 1-6) objective 2 is considered in this protocol.

1. Use advanced analytic methods and electronic health record data held by CPRD to advance the work from the PERMIT to refine the algorithm's accuracy that predicts the change in renal function in patients with heart failure. This work will involve the comparison of 2 different methodologies, linear regression and machine learning (WP1) linear regression and machine learning in WP1
2. **Co-create with patients, primary care practitioners and specialists the care pathway for implementing personalised renal function monitoring and optimal interventions if renal function is declining in primary care (WP2).**
3. Assess the clinical effectiveness of our algorithm-guided clinical pathway, compared with the current standard-of-care, in a cluster randomised controlled trial (RCT) embedded within CPRD (WP3).
4. Perform health economic analyses to determine the cost-effectiveness of our algorithm-guided clinical pathway, which comprises personalised renal function monitoring and appropriate interventions (WP4).
5. Ensure that the patient voice is integrated throughout our studies, our findings and the subsequent guidance for people living with heart failure (WP5).

5.2 Work Package 2 Objectives and Outcomes

By the end of the work described in this protocol we will refine the prototype training materials designed to enable primary care staff to preserve renal function in patient with heart failure, considering the views of key stakeholders including primary care staff and patients. During WP2 Stage 6 the care pathway (including renal function monitoring tool, user interface, alert system guidelines, and training materials) will be tested through a feasibility study before testing its utility in a trial during WP3. By the end of WP2 we will have created an intervention, specified according to TIDieR guidelines(31), designed to change primary care practice and maximise future uptake and engagement of the new renal care pathway.

Study Stage	Objective	Outcomes
Stage 1a: Survey Stage 1b: Interview	To understand current practice To identify barriers and facilitators to optimising the treatment of patients with heart failure while preserving renal function	Refined early logic model to inform stage 2 Improved knowledge base to increase uptake of the future care pathway
Stage 2:	To work closely with critical stakeholders WP1 team and the expert clinical panel to develop prototype training material to ensure optimal design and uptake of the RENAL-HF care pathway (which we anticipate will include personalised renal function monitoring, thresholds for intervention and.clinical guidelines	Co-created prototype training materials for optimal implementation of the evidence based system
Stage 3	To consider the elements that will support optimal implementation of the evidence-based systemin relation to the APEASE criteria	Intervention content and options for implementation for selected elements of the pathway
Stage 4	To develop online training materials that will support optimal implementation of the evidence-based system	Online training materials to support the care pathway
Stage 5	Beta testing	Refined prototype training material for the primary care teams

Stage 6	Evaluation work to ensure acceptability of the pathway for practitioners and patients Refine the prototype training material for the primary care teams	Co-created an intervention, which will be specified according to TIDieR guidelines(31)

6. STUDY DESIGN

RENAL-HF Care pathway co-design (WP2 Stages 1-6) (months 1 – 24)

6.1 Overview

The design of the RENAL-HF programme is informed by the MRC Framework and related guidance for developing and evaluating complex interventions (32-35). In addition to designing components of the intervention, attention will be given to understanding how and under what circumstance the intervention will bring about change and any potential barriers and enablers when implementing the care pathway. In addition, we will consider a broader range of questions relating to the context in which the intervention will be developed, implemented, and evaluated. To ensure practitioner (particularly primary care) and patient acceptability of this new care pathway, we will integrate co-production research methods (36, 37) involving the expertise of key stakeholder groups (including patients, primary care practitioners, specialists, and other key informants). Co-production research methods will ensure researchers, clinicians, and the public will work together throughout the research process, sharing responsibility from the start to the end of the project (38). This work will be informed by frameworks relevant to technology-based intervention development and implementation science, including the behaviour change wheel (39) and the non-adoption, abandonment, scale-up, spread, sustainability (NASSS) Framework(40, 41) and Toolkit (42) to support the design and implementation of the pathway in primary care practices.

6.2 Methods

Within WP2, we will adopt a mixed methodology involving six iterative stages necessary to inform the development of a renal care pathway for people living with heart failure. To optimise recruitment during the uncertainty of the ongoing pandemic and the success of remote data collection in previous projects, we have included the option of remote data collection (video or telephone) in addition to face-to-face interviews.

6.3 Stage 1: Understanding current practice

We will examine current practice through surveys and interviews with primary care practitioners involved in delivering the intervention to inform the optimal design and implementation process. The results from this stage will be used to refine the logic model (Appendix 3), illustrating how our intervention will enable primary care staff to take steps to preserve renal function in patients.

6.3.1 Stage 1a) Healthcare Professional Survey

We will conduct a survey of healthcare professionals in England, including GPs, pharmacists, and nurses (n=115 GPs, n=115 Pharmacists and n=370 Nurses), to establish patient and practitioner views on the current standard of care and to identify barriers and facilitators to optimising the treatment of patients with heart failure while preserving renal function. The survey is being co-developed by our research team and public advisors and will be delivered through YouGov https://yougov.co.uk/, who have access to a representative healthcare workforce sample. The

survey will first be piloted with clinical colleagues and then within YouGov with 50 members of their panel of healthcare professionals. Final refinements will be made, and then the survey will be delivered.

YouGov will be responsible for the recruitment of the required sample, secure data collection and sending the data to the research team for quantitative data analysis. Free text data will be analysed thematically using inductive thematic coding with mapping onto the theoretical domains framework (43). We will work closely with the University approved Client Engagement Manager for YouGov on the design, implementation, and analysis of this practitioner survey.

6.3.2 Stage 1b) Qualitative interviews

Two PDRAs, experienced in qualitative research methods, will conduct brief focused qualitative interviews with GPs, nurses and pharmacists recruited from Liverpool and Manchester primary care practices to generate options for intervention functions. We anticipate interviewing 17 participants per group; however, this number will be reduced if saturation is reached earlier. Early data collection has indicated the importance of including the views of some Heart Failure Specialist Nurses (HFSNs) in addition to primary care-based nurses during Stage 1b.

Informed by the behaviour change wheel (39), we shall use the capabilities, opportunities and motivations model of behaviour change(39) to structure the interviews and understand the drivers of optimising the treatment of patients with heart failure while preserving renal function. The topic guide is being co-developed by our research team and public advisors and will be piloted with clinical colleagues, following which final refinements will be made before data collection. According to individual preference, interviews will take place in person or remotely via video conferencing or telephone. Interviews will be audio-recorded, transcribed, checked and pseudo-anonymised before analysis. Data will be analysed using inductive thematic coding followed by mapping onto the theoretical domains framework (43).

6.4 Stage 2: Co-designing the care pathway-

6.4.1 Evidence synthesis

The research team will synthesise the material generated in WP1 and the outputs from WP2 Stage 1 during a series of meetings to generate possible elements of the care pathway. These proposals will be rated during stakeholder workshops.

We anticipate that the evidence-based system developed by WP1, and the clinical expert panel will comprise three key outputs.

- 1 Personalised renal function monitoring schedules
- 2 Trigger points (thresholds) for intervention
- 3 Clinical guidelines to prevent renal decline.

The clinical expert panel comprised of cardiologists, nephrologists, clinical pharmacologists, and GPs will identify the best algorithm and clinical parameters for the key outputs. WP2 will generate intervention components that will enable the optimal design and uptake of this evidence-based system.

6.4.2 Stakeholder consensus workshops

We will use the RAND/UCLA Appropriateness Method (RAM) (44) involving diverse groups (including patients, specialists, primary care practitioners and other key informants) to ensure the views of key stakeholders are included in the design of the intervention. Typically, RAM involves only a single group of experts (e.g., nephrologists), but as the complexity of health care delivery increases, it is beneficial to adapt the RAM and similar methods of defining standardised quality care to include diverse healthcare professionals (45). Furthermore, there is a growing need to have patients, families, and caregivers in healthcare decision-making (24, 25). Therefore, our workshop design will comprise five stakeholder groups, including (patients, pharmacists, nurses, GPs, and key informants) each containing 9 participants.

Each group will engage in three rounds, rating the proposals created from the synthesis of WP1 and Stage 1 of WP2. The rounds will require: (i) independent individual ratings of appropriateness, (ii) moderated group ratings of appropriateness, and (iii) independent individual ratings of necessity. We will set *a priori* criteria, informed by the RAND/UCLA Appropriateness Method (46) for group consensus, and undertake anonymised electronic voting, recording if and when consensus is reached. Consistent with the RAND/UCLA approach, the criteria for agreement for a 9-member panel will be a median of >7 on a 9-point Likert scale and no more than two members rating outside the 3-point region containing the median (i.e., 7–9 on a 9-point Likert scale). We anticipate that the workshop will comprise five parallel groups. The PPIE group will inform the format of the workshops and the patient group will be offered the opportunity of holding all of their meetings face-to-face, but the remaining groups will be conducted online. The postdoctoral researchers will manage the consensus workshops.

6.5 Stage 3: Decision-making

Based on data generated by WP2 Stages 1 and 2, the research team will use the behaviour change wheel to identify intervention functions and behaviour change techniques that will be most likely to achieve the change required (47). We will evaluate the interventions according to acceptability, practicability, effectiveness/cost-effectiveness, affordability, and safety/side-effects (APEASE) defined in the Behaviour Change Wheel (47).

6.6 Stage 4: Training material

We will develop prototype training material for the primary care teams (GPs, pharmacists, nurses, care navigators) and refine these through the beta testing (Stage 5 below) and feasibility study (Stage 6 below), ready for the cluster RCT in WP3. We will work with RENAL-HF team members across work packages, including the PPIE group, primary care staff and specialists, to co-design the proposed behaviour change interventions in a series of up to three workshops in preparation for WP2 stage 5. The findings from WP1 and stages 1-3 of WP2 will be important in determining the type of content to be included in the training material. We will cover the rationale for the study, how the algorithm and interventions have been developed (including the input from patients), the evidence bases for undertaking interventions (increased renal function monitoring, changing drugs or doses etc.), how to use the tool, and how the utility of the tool is being assessed. We will explore the possibility of accrediting the training material for continuing professional development.

The materials will be developed by WP2 postdoctoral researchers under the direction of GP leads (Williams and Brown) and nursing leads (Lees and Dowding) with input from other co-investigators

and software specialists. The format for training materials will be informed by stakeholders, but may include videos on platforms such as YouTube, simple animations and integrated self-guided learning materials. The NIHR Applied Research Collaboration (ARC) North West Coast (NWC) have extensive experience developing and delivering training programmes. We will draw on their resources to create effective materials. These materials are likely to include environmental restructuring (e.g., adjustments to the GP dashboard), education, training, and enablement that will be deliverable remotely.

6.7 Stage 5: Beta testing

We will evaluate the usability of the prototype materials developed in WP2 Stage 3 through a series of rapid rounds of beta testing. This evaluation will use 'think aloud' interviews with 36 primary care staff (nine GPs, nine pharmacists, and nine nurses, nine care navigators). This technique will provide insight into how primary care staff interact with the system, and we will make refinements where appropriate(48). During think-aloud interviews, participants will be instructed to verbalise their thoughts while conducting predefined tasks with the software/dashboard within a dummy environment. This approach will enable us to assess whether target users of the system interact with it as intended.

Data collection for this stage will be completed in person or by remote interview:

- In-person interview - researcher and participant will be physically present and will be audio-recorded using an encrypted digital recording device.
- Remote interview – participant and researchers will meet online using Microsoft Teams. Audio of the interview recorded on a separate encrypted digital recording device.

Participants' data will be analysed using thematic analysis. The prototype training materials will be refined according to the findings of this beta testing in preparation for feasibility/acceptability testing of the device as part of the 'real-world' during stage 6.

6.8 Stage 6 Feasibility and acceptability sub-study

Stages 1-5 of this protocol will inform the pre-clinical development and usability testing of an algorithm-guided care pathway to improve the kidney health of people with heart failure. During stage 6 we plan to conduct a feasibility and acceptability study of the whole process in the 'real-world' environment (including the renal function monitoring tool and the user interface), which will inform our final refinements before the commencement of the cluster randomised controlled trial in WP3. In preparation for Stage 6 of WP2 it is planned that WP1, the interventional team of the Clinical Research Data link in collaboration with EMIS will install the algorithm in five GP practices using the EMIS system and contributing data to CPRD.

Quantitative evaluation

After installing the care pathway and implementing the training in the five practices, we will gather quantitative data on the number of patients with cardiac failure, the number of patients with cardiac failure who already have renal impairment, and those that develop renal impairment. We will confirm that these patients are identified by the RENAL-HF care pathway and utilise the analytics from EMIS to understand the number of times that the RENAL-HF care pathway is used and by whom (e.g. by

role), and in what circumstance(s). We will look at the number of alerts triggered and ignored, actions taken e.g. patient contacted for repeat blood test performed in accordance with, and/or contrary to the suggested schedule, and changes in treatment after using the pathway. We will also collect data on referrals to cardiology and renal services in secondary care and emergency hospital admissions. To assess the health inequalities impact of this intervention, we will collect information relating to gender, ethnicity, and age of patients, and postcodes of both the patients and general practice. This will contribute to a health inequalities impact assessment, informed by indices of multiple deprivation and distance travelled to services.

Qualitative evaluation: practitioners

In parallel with the above quantitative evaluation, experienced researchers will carry out in-depth semi-structured interviews with a purposive sample of primary care practitioners at each of the five participating practices. We anticipate interviewing up to 34 practitioners, sampling for diversity in terms of their role (GPs, nurses, pharmacists etc.) and including those who did not engage with the care pathway and well as those who did[20]. We will ask practice managers to forward invitation emails and further information about the interview study to relevant practice staff. Invitation emails will ask staff to indicate their interest in being interviewed by replying to the email. Initial invitations will be followed by up to two reminders as necessary; we will also liaise with practice staff and use snowball sampling to facilitate recruitment to the interviews.

Interview topic guides will be informed by implementation science theories, particularly the behaviour change wheel and the capabilities, opportunities and motivations model[21], to explore the drivers of uptake/rejection of the pathway. Draft topic guides will be reviewed by research team members who have experience of primary care and implementation of training, and by members of the PPIE group. To explore important but unanticipated issues, interviewing will run in parallel with data analysis. Interviews will usually occur after practices have acquired at least 6 weeks' experience of using the care pathways tools, be arranged at the convenience of practitioners and last between 30-60 minutes. These will be conducted by experienced qualitative researchers either remotely via a video-conferencing platform or telephone, or in-person in a private room at a suitable venue, according to the preferences of participants. Informed consent of practitioners will be obtained verbally to reduce paperwork for participants. This will be audio-recorded prior to conducting the interviews; audio-recordings of consent will be made separately to interview recordings. Data analysis will initially use inductive thematic coding followed by mapping onto the theoretical domains framework[16] and informed by the Health Inequalities Assessment Toolkit (HIAT).[22]

Qualitative evaluation: patients and carers

To examine the acceptability and health inequalities impact of the care pathway from the patient perspective, researchers will also conduct in-depth semi-structured interviews with a purposive sample of up to 25 patients with heart failure and their informal carers. The sample size for this component will be informed by the principles of information power.[23] In most other respects, data collection and analysis methods for patient interviews will be similar to those described above for the practitioner interviews. Eligible patients will have cardiac failure, with or without renal impairment, and managed entirely in primary care or also involving secondary care services. Purposive sampling

will be conducted across the five participating practices and aim for balanced coverage in terms of patient socio-demographics (gender, ethnicity and socio-economic status), those with normal renal function and those with chronic kidney disease stage 3 or higher. Potentially eligible patients will be identified via searches of electronic patient records and then screened by practice staff to confirm they meet the inclusion criteria. Patients/carers will be contacted by the practice either during face-to-face/telephone consultations, or via a letter/text message to briefly explain the study. Fliers briefly outlining the study will be made available to patients at this point together with a form for them to indicate whether they give permission for researchers to get in touch. Where patients do not return the form, a reminder will be sent by the practice via text or letter followed by a phone call from the practice. Patients who indicate an interest in being interviewed will be contacted by the research team to explain the study in more detail and sent the study information sheet via post or text. Posters outlining the study will be displayed in practice waiting rooms and on practice websites to further facilitate patient engagement with the study. All patients taking part will need to provide informed consent (a separate informed consent is available for this).

Topic-guides for patient/carer interviews will be co-developed with the PPIE group and informed by the Theoretical Framework of Acceptability[24, 25] with questions to explore areas such as burden, intervention coherence, opportunity costs or gains and perceived safety and risk of the care pathway. Interviews will be conversational and responsive to participants and contextualised around their recent experiences of heart failure care such as monitoring visits; treatment decision-making; medicine-taking; information and support needs; and communication with healthcare professionals. Interviews will be arranged at the convenience of patients/carers and last between 30-60 minutes. These will be conducted either remotely via a secure video-conferencing platform or telephone, or if interviewees prefer, in-person at their home. Patients and carers will be offered the choice of being interviewed together or separately. Researchers will obtain the informed consent of patients/carers before conducting the interviews. For telephone/video-conference interviews to reduce the burden of paperwork for participants, consent will be verbal and audio-recorded separately to interview recordings. For in-person interviews written consent will be obtained. Data analysis will initially be inductive, drawing on reflexive thematic approaches,[26] and then deductive, informed by the Theoretical Framework of Acceptability[24, 25] and the HIAT.[22] Coding of transcripts will be assisted by QSR NVivo software.

Refining the care pathway and tools

The sub-study team will hold regular meetings with the wider Renal-HF team and the PPIE group to interpret and integrate the findings from the quantitative and qualitative studies. We will work iteratively to identify what improvements are necessary to ensure the care pathway tools are optimised prior to the COMPUTATIONAL trial. Alongside making any refinements to enhance the feasibility and acceptability of the tools, special consideration will be given to avoiding any exacerbation of health inequalities that might arise from introducing the care pathway and findings from the practitioner and patient/carer interviews will inform iterative use of the HIAT.

7 SETTING (stages 1-6)

Stage 1a) survey will use YouGov https://yougov.co.uk/, a public opinion data company, to run a survey targeting healthcare professionals working in the NHS or the wider care sector in England (including GPs, Pharmacists and Nurses). Using this setting will provide efficient access to a representative sample of practitioners. YouGov will be responsible for the identification and recruitment/informed consent of potential participants and the collection of data. YouGov will share anonymised patients' data for analysis. Participating GP practices will act as research sites for Stage 1b, 2 and 5. During these stages primary care staff and patients from participating GP practices will participate in the study and some professional interviews will take place at GP practices. Patient participants will be invited to attend a workshop event on University premises although the meeting may be conducted online according to personal preferences.

The study will be included in the primary care portfolio of the NIHR CRN North West Coat and Greater Manchester to support recruitment of primary care staff, and pharmacists and specialists in the North West. If necessary, we can recruit outside of these regions for Stage 1b (qualitative interviews) and professionals for Stage 2b (Stakeholder consensus workshop). We will recruit GP practices for Stage 5 (Beta Testing) in the NW Coast or Greater Manchester regions, with the support of the CRN. Participants for stage 2b will also be recruited through GM and NW coast CRN, professional, charity and PPIE networks via social media channels. No participants will be recruited for stage 2a and stage 3 and stage 4

8. SAMPLE AND RECRUITMENT PARTICIPANT ENTRY

8.1 Eligibility Criteria (Stages 1-6)

The study sample for Work Package 2 stages 1-6 will comprise: i) GPs ii) nurses; iii) pharmacists, iv) patients and other key informants (practice managers, clinical commissioners) cardiovascular, heart failure and renal specialists. To reduce the cost of travel, we will be recruiting GP practices (and practitioner/patient/carer participants) in the NW Coast and Greater Manchester for stages 5 and stage 2b (patient sample).

8.1.1 Inclusion Criteria

Stage 1a professionals

Nurses, GPs and pharmacists working in the NHS or wider care sector in England

Stage 1b and 5 professionals

Nurses, GPs, pharmacists, and care navigators (stage 5) working within GP practices in England. For Stage 5 we anticipate that recruitment will be supported via the NW Coast CRN and GM CRN.

Stage 2b and 6 professionals

Primary care practitioners (including nurses, GPs, pharmacists practice managers and clinical commissioners), secondary care specialists (renal and cardiovascular). To recruit practices for stage 6, we will work with CPRD; they will approach selected practices and obtain consent from the five practices.

Stage 2b and 6 patients

Adult patients with:

- Diagnosis of heart failure as identified by their practice or self-report if recruited via charity or PPIE networks. During stage 6 we will interview patients and carers.

8.1.2 Exclusion criteria

Professionals

- Professionals who work outside England

Patients

- Lack of mental capacity as identified by the practice
- Currently receiving inpatient treatment or admitted to hospital for an exacerbation of their heart failure in the previous six weeks
- Registered with a GP outside of England

8.2 RECRUITMENT

For stage 1a (Healthcare Professional Survey), YouGov will recruit a representative sample of GPs, Pharmacists and Nurses working in NHS settings or the wider care sector in England. Sampling will be purposive to ensure maximum variation for the remaining stages involving participants (Stage 1b, 2b,5). We will use the HIAT (49) iteratively to guide our purposive sampling to ensure that health inequalities are considered wherever possible and that our care pathway is designed to reduce health inequalities. We will recruit rural and urban practices, and to optimise recruitment, where possible we will target practices with HF registers of 50-100 patients.

8.2.1 Sample identification

GP Practices

Potential GP practices in the NW coast and Greater Manchester region will be initially approached by the relevant CRNs using the Research Information Sheet for Practice (RISP) template to determine the expression of interest. For Stage 1 and 2 we will also use additional CRN teams where necessary. Practices interested in participating in the research will be forwarded a copy of the protocol, approvals, and participant facing documentation. A site visit will be arranged with the practice manager and interested practitioners. For stage 1b, this sampling of practices can be extended outside these regions if required. For stages 5, we will recruit both rural and urban practices in the North West Coast and Greater Manchester. Alongside CRN activity to ensure that we achieve our recruitment target and that we capture a broad range of views, GP practices will also be identified through local and national research, professional and individual networks (including those of our PPI collaborators). We will seek to attend relevant community meetings e.g., Primary Care Network and local medical/pharmaceutical committee meetings and Patient Participation Groups (PPG) to increase awareness and interest in the research. Where appropriate we will also use snowball sampling to extend the study sample, with GP practices already recruited nominating colleagues at additional GP practices for the RENAL-HF team to approach. GP practices identified by these additional pathways will be invited in-person or email by a member of the RENAL-HF team.

Professionals

For Stage 1a) (Healthcare professional Survey), under the instruction of WP2 researchers, YouGov will be responsible for identifying eligible participants.

Once a practice has agreed to participate for stages (1b,2b,5), the named collaborator or 'research champions' or practice manager will send an email invitation and the participant information sheet to eligible staff members at the practice. Alongside CRN recruitment strategies GPs, nurses and pharmacists will also be identified through local and national research, professional and individual networks, (including those of our PPI collaborators). We will seek to attend relevant community meetings e.g. Primary Care Network and local medical/pharmaceutical committee meetings, to increase awareness and interest in the research. Where appropriate we will also use snowball sampling to extend the study sample, with healthcare professionals already recruited nominating colleagues at their respective or additional sites for the renal team to approach. Participants identified by these additional pathways will be invited in-person or email by a member of the RENAL-HF team. We will advertise the workshop and other participant stages via Study/University social media channels (website/Twitter account), professional and local networks for primary care practitioners (e.g., Royal College of General Practitioners, SAPC, Royal Pharmaceutical Society) and specialists (e.g., British Society for Heart Failure, British Heart Foundation, RCN Advanced Nurse Practitioner Forum). Co-investigator Carolyn Lees who has strong links with specialist nurses, will support the recruitment of Heart Failure Specialist Nurses (HFSN) to the workshop.

Patients
Patients will be recruited from GP practices identified through the NW Coast and GM CRN. Sampling will aim for balanced coverage in terms of patient socio-demographics (gender, ethnicity and socio-economic status) and renal function/monitoring profiles.

GPs will screen their caseloads for heart failure patients, confirm their eligibility against the inclusion/exclusion criteria and if they meet the criteria, then either:

- Discuss the study with the patient during face-to-face contact either in clinic or at home visits or during a remote consultation. Provide the Participant Information Sheet (PIS)
  OR
- Screen any registry they maintain for eligible patients, then send an invitation letter and PIS

Once the patient has received the study documentation, they will be able to 'opt-in' through the study web page or by contacting the project researcher by telephone or text -via study mobile, email. In addition, we will share a study advert with participating GP practices which can be displayed in waiting areas, on the practice website or via practice social media channels.
To ensure a wide range of patients have the opportunity to take part in the consensus workshop and to ensure that we recruit to target within our timeframe we will also advertise the workshop via third sector and PPIE channel. We will work with our PPIE advisors to identify opportunities to advertise the workshop. Patients who are interested in taking part in the workshop will 'opt-in' through the study web page or by contacting the project researcher by telephone or text -via study mobile, email.

Sampling and recruitment of primary care practices for the feasibility and acceptability sub-study stage 6

We will conduct the feasibility and acceptability study in five GP practices. Practices will be eligible for the study if they use EMIS software and contribute data to CPRD in series. Sampling of practices will aim for diversity in terms of practice size and the socio-demographic profile of its locality. Specifically,

CPRD will provide summary statistics for the practices in the Greater Manchester, West Yorkshire and North-West Coast CRN areas based on small area level data for the GP practice postcode. From these summaries, based on area level data on the rural-urban classification, the index of multiple deprivation and practice list size, we can indicate which practices we need and CPRD will aim to select these practices on this basis.

To recruit practices, we will work with CPRD; they will approach selected practices and obtain consent from the five practices. CPRD will then provide the practice contact details to the WP2 team and/or via the CRN who will then manage the process from this point. If needed we may also use a second route to recruit practices, whereby we will send invitation emails and further study information to practice managers of eligible practices (CPRD member practice and EMIS user), asking them to consult with colleagues and indicate their interest in participating in the study by replying to the email. Practices that do not respond will receive a reminder email followed by a telephone call. While we anticipate that practice managers will be our main point of contact for recruiting practices via this second route, we will also liaise with other members of the practice team who have a particular interest in the study. Alongside this we will use our existing networks and contacts to facilitate recruitment of practices and support their ongoing participation in the study.

8.2.2 Informed Consent

Fully informed consent will be required for all participants taking part in Stages 1b, 2b,5,6 except Stage 1a. In Stage 1a (Health professional survey), YouGov will be responsible for consent/data protection procedures and data collection. Research sites will be responsible for identifying and signposting potential participants to the RENAL-HF research team if they are interested in participating or finding out more about the study. The research team will be responsible for the recruitment of participants, including obtaining informed consent.

All potential participants will be provided with a RENAL-HF Information Sheet, which has been designed according to the different requirements of the various stages of the study. Stage 2b (Stakeholder consensus workshop) has the same Participant Information Sheet for both patient and professional participants. All participants will be given a minimum of 24 hours to consider the RENAL-HF relevant Participant Information Sheet and whether they would like to participate in the study. The RA will ensure that they are completely satisfied that the person fully understands the research and has had the opportunity to ask questions and have them answered before they can be asked to provide informed consent. Participants will be able to complete the consent form either digitally or as a paper document. Participants who prefer to receive a paper document will be sent a printed version with a stamped addressed envelope to return completed consent forms to the research team. Researchers will provide participants with guidance on how to provide a 'simple online signature' which includes a stylus or finger drawn signature, a typed name or a tick box declaration within secure University approved survey software. Information around how to provide a 'simple electronic signature' will be also included on the RENAL-HF website. We will follow University and NHS digital guidelines https://digital.nhs.uk/services/nhsmail/guidance-for-sending-secure-email to support the secure transfer of electronic consent forms. If the university email provider is unable to encrypt emails we will create the consent form within University approved

secure software to ensure to ensure the necessary standards of security are met. We have also included the option of verbal consent for patient/carer participants in Stage 2.

9. DATA ANALYSIS

9.1 Sampling

We will work with YouGov to use a representative sampling of healthcare professionals across the three subgroups GPs, nurses and pharmacists to help ensure the data is free of bias. As this survey forms a component of the overall work package, based on prior experience, a survey sample size of 600 will be adequate to achieve our research objective. For the qualitative components of the work package (Stage 1b,5,), the sample size will be guided by the principle of information power, and the number recruited for each qualitative stage will be reduced if the data is judged to have adequate power at an earlier point (50). The sample size for the sub-groups in the consensus workshops has been determined by the RAND/UCLA Appropriateness Method (RAM) (44).

9.1.2 Size of sample

We aim to recruit different participants for each stage; however, there may be some overlap

- Stage 1a: 600healthcare professionals: (n=115 GPs, n=115 pharmacists and n=370 nurses)
- Stage 1b:51 primary care providers (n=17 GP, n=17 pharmacists, n=17 nurses)
- Stage2b: 36 professionals (nurses, pharmacists, GPs, other key informants) & patients(n=9)
- Stage 5: 36 primary care providers (n=nine GPs, n=nine pharmacists, n=nine nurses, n=nine care navigators)
- Stage 6: 34 practitioners and 25 patients

9.2 Analysis

The analytical process will involve iteration between stages. It will be informed by the MRC Framework and related guidance for developing and evaluating complex interventions (32-35) and frameworks relevant to technology-based intervention development and implementation science, including the behaviour change wheel (39) and the non-adoption, abandonment, scale-up, spread, sustainability (NASSS) Framework(40, 41) and Toolkit (42). All research team members, including PPIE members, will be required to comply with the Data Protection Act 2018 and General Data Protection Regulation (GDPR) regarding the collection, storage, processing, and disclosure of personal information and will uphold the regulation's core principles. All personal data will be collected electronically and will be stored on password-protected secure University servers according to our Data Management Plan (reviewed by the University Information Governance Team). All data will be transferred to a secure University server as soon as is practically possible, and all other sources of data will be safely destroyed.

9.2.1 Health professional survey

Survey data will be sent from YouGov to the research team for quantitative analysis. Free text data will be analysed thematically using inductive thematic coding with mapping onto the theoretical domains framework (43).

9.2.2 Consensus workshops

We will set a priori criteria informed by the RAND/UCLA Appropriateness Method (46) for group consensus and undertake anonymised electronic voting, recording if and when agreement is reached. Data from the workshop will include anonymised rating scores for each round of voting and field notes and any design work produced during the workshop to inform our intervention development (including anonymised chat in video conferencing software). We will also audio-record the workshop to inform anonymised field notes. All workshop material will be anonymised, and any potentially identifying details will be removed from any design work produced during the workshop.

9.2.3 Qualitative data analysis

All interview data will be transcribed using a university-approved transcription company or via Microsoft Teams transcription software when conducting remote interviews. Anonymised transcribed interview data will be imported into the qualitative Data Analysis Software NVivo-QSR 12 on secure University servers to facilitate the analytical process. The analysis will take place on the anonymised data set only, and the analysis will involve members of the RENAL-HF research team across participating institutions, including our PPIE group. Qualitative analysis will be informed by thematic approaches involving inductive and deductive coding (51, 52).

All data (except for the participant consent form) will be coded and depersonalised. The participant's identifying information will be replaced with a unique ID number (comprised of an unrelated sequence of characters). The identification key enabling pseudonymisation of the data will be stored in a password protected Excel spreadsheet, separately from all other data. Only the CI, research associates and co-investigators will access this key.

9.2.5 Demographic data

All participants will be invited to answer some background questions (demographic details) using standard ONS measures. It will be explained to the participant that this information will help inform understanding of the data and will be anonymised and grouped with other participant data and will only be used individually to provide context to individual quotes, e.g., Pharmacist or GP. It will be made clear to the participant that they are free to decline any questions. A series of background questions have been designed, which will be collected verbally or digitally, either at the beginning or end of data collection, according to preferences.

10. PATIENT & PUBLIC INVOLEMENT AND ENGAGEMENT (PPIE)

Within the programme, there is a designated PPIE Work Package 5 to ensure that the patient voice is integrated at all stages, from design to evaluation, throughout all work packages in the programme. Our public co-applicant, Lynn Hedgecoe, has lived experience of heart failure and will co-lead our PPI group with Dr Jenny Downing. Up to twelve PPIE members will be recruited and trained to work closely with researchers across all work packages to ensure that changes to healthcare as a result of this project are supported by people living with heart failure. The PPIE group will be invited to take active roles (according to availability and experience), in all the iterative stages of Work Package 2, including input into co-developing surveys, interview schedules, co-facilitating interviews with PDRAs, acting as advocates/co-facilitators during the workshop (stage 2), developing training materials, data analysis and plain language summaries.
Given that men have a higher prevalence of heart failure and women have higher mortality rates for heart failure, we would like to ensure equal representation of both males and females in the group.

In addition, it is important that we capture varied voices who can contribute different experiences from both rural/urban, coastal/non-coastal, different ethnic groups and deprived areas which can show that they have relevant experience, a strong interest in the topic area and a commitment to be involved in a long-term project. Should sufficient diversity not be achievable at the start of the study, we will continue to recruit additional PPIE representatives during the Work Package.

11. HEALTH INEQUALITIES

Consideration of health inequalities underpins our work. The PERMIT study used the Health Inequalities Assessment Tool (HIAT) (49). We will continue to use this tool iteratively to ensure that health inequalities are considered wherever possible and that our care pathway is designed to reduce health inequalities. There is a strong relationship between socio-economic status and heart failure; those living in deprived areas are more likely to be diagnosed at a younger age and experience multimorbidity. (4) They are also more likely to experience an adverse drug reaction, experience poorer health outcomes and be admitted to hospital. (53, 54) People living in deprived areas may have a greater need for closer, more personalised management. More frequent and improved communication of test results has the potential to help ensure the most appropriate medication regimen and support patients in implementing and maintaining clinically advised lifestyle changes. In this programme, we will continue to evaluate what is practical and acceptable to both people living with heart failure and practitioners as a result of implementing personalised renal function monitoring.

12. ETHICAL AND REGULATORY ISSUES

12.1 Ethics approval

This study has been designed according to the UK Policy Framework for Health and Social Care (HRA, 2017). Ethical, HRA and MHRA approval will be sought where required. Using the current UK classification rules (UKMDR2002 Part Annex IX, and Part III, Annex IX, of the UK Medical Devices Regulations 2002 as modified by Part II of Schedule 2A to the UK Medical Devices Regulations 2002), we anticipate that the algorithm-guided pathway will be considered a *General Medical Device Class I.* However, we will not know the exact nature of the device until we have completed the pre-clinical device development and usability testing during Stages 1-5 of Work Package 2 (in parallel with interconnected work from Work Package 1). Therefore, MHRA approvals for Stage 6 (Feasibility/acceptability testing) will be sought later once we are clear about what the device will entail. Stages 1-5 of WP2 will involve pre-clinical device development work and usability beta testing in a 'dummy environment' so will not require MHRA approval. The study will be submitted to each proposed research site for Confirmation of Capacity and Capability. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964, and later revisions.

Substantial amendments that require review by the appropriate ethics committee (as advised by the HRA) will not be implemented until that review is in place and other mechanisms are in place to implement at sites. All correspondence with the relevant ethics committee will be retained, and the CI will notify the committee of the end of the study. An annual progress report (APR) will be submitted to the ethics committee within 30 days of the anniversary date on which the favourable opinion was given and annually until the study is declared ended. If the study is ended prematurely,

the Chief Investigator will notify the ethics committee including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the ethics committee.

12.2 Assessment and management of risk

A study risk assessment will be completed as part of the sponsor review process. It is important that people living with heart failure have the opportunity to take part in our consensus workshop which will inform the content of a new care pathway. However, it is possible that people living with heart failure may be facing a difficult time because of their condition. For such individuals, there is a risk that taking part in research relating to their condition could cause them to experience some distress. To minimise this, our consensus workshop has been developed with our PPIE advisors, who have lived experience in managing heart failure. Additionally, where PPIE advisors express an interest, they will be trained and supported by our PPIE leads in Work package 5 to act as advocates and/or co-facilitators during the workshop event under the supervision of the RENAL-HF researchers. Researchers facilitating the workshop will be guided by a distress protocol which will include referring back to their GP if necessary.

12.3 Peer review

To secure funding for this research programme, the application process involved two stages of scientific review conducted by the NIHR PGfAR.

12.4 Data protection/confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and will abide by the Data Protection Act 2018 and the UK GDPR as amended from time to time and any successor legislation in the UK and any other directly applicable regulation relating to data protection and privacy. The University of Liverpool is the data controller. Researchers at the University of Liverpool and the University of Manchester will collect all participants' names in the qualitative studies outlined above and a corresponding record of the informed consent process. Participants comprise some, or all, Secondary Care Specialists, General Practitioners, Nurses, Pharmacists, Care Navigators, Patients and Carers.

University of Liverpool: Consent forms will be physically separated from the participant's data. Where consent is taken as a hard copy, the form will be scanned and stored on secure University servers, with password protection. Once digitalised, hard copies will be shredded and disposed of through the University's confidential waste stream. Digitally completed consent forms or audio recorded consent forms will be directly stored on University servers. Consent forms will be accessible, for active research use, only by trained research team members (as outlined in the approved research plan).

University of Manchester: Consent forms will be scanned (if hard copies) and stored on secure University servers, which are password protected. Any paper documents, once digitalised, will be securely shredded. Any hard copy data that is not digitalised will be stored in a locked filing cabinet in a locked room at The University of Manchester, accessible only to trained research team members. Digitally completed consent forms will be directly stored on University servers.

Interviews will be audio-recorded using a University approved encrypted digital recording device or approved University video conferencing software (e.g. TEAMS; only audio files will be saved). Video conferencing software will only be used where required, and only audio files will be saved on secure

University servers. Associated video files, which are automatically created during the recording process (with videoconferencing software); will be saved to a university encrypted laptop C drive and will be permanently deleted immediately after the interview has ended. Only audio-recording will be transferred to a secure University server (once checked) and then deleted from the temporary storage as soon as possible. Audio-recordings will be encrypted and stored on a secure University server until the data has been transcribed, checked for accuracy, after which time audio-recordings will be safely destroyed.

Interview data will be transcribed as soon as possible either by an approved member of the research team using the transcription facility within a password protected version of Microsoft 365 or an approved Transcription Company (e.g., 1st Class Secretarial). During the transcribing phase or as quickly as possible on receiving the transcript, any identifiable information will be replaced with non-identifiable generic terms or pseudonyms. All audio files (and associated transcriptions) will be labelled with a unique ID number to ensure confidentiality at all times (pseudonymisation). The identification key enabling pseudonymisation of the data will be stored in a password protected Excel spreadsheet, separately from all other data. Only approved members of the research team will have access to this key. The identification key will be destroyed once the analysis is complete, and only the consent forms and anonymised data will be archived. Pseudo-anonymised encrypted data will be shared between WP2 researchers at the University of Manchester and members of the PPIE groups using university approved methods.

During this feasibility and acceptability study, data will be stored on the University of Liverpool Active Datastore or equivalent at the University of Manchester. Data containing identifiable information will be encrypted and stored separately to pseudonymised data. Only pseudonymised data will be shared with WP2 and PPIE members across institutions and sharing will be via secure platform with all files password protected. Any paper records (including consent forms) will be stored in a locked cabinet in a secure location, only available to the researchers and digitised as soon as possible. At the end of the feasibility and acceptability sub-study and in line with NIHR and University policy, pseudonymised data will be shared as safeguarded data via a suitable repository (such as UK Data Service Reshare), provided participants consent to sharing and there are no other barriers to doing so.

University of Liverpool: Consent forms will be retained for ten years beyond the study completion date, as per the University of Liverpool Records Retention Schedule to ensure that the data can inform follow-up studies. The forms will then be securely deleted. Consent forms will be stored electronically on the University Research Data Storage following the publication of our results in accordance with the University records retention schedule. At that point, any hard copies will be shredded, and digital versions securely deleted. A process will be in place for risk-based QC checks of certified copies, before destruction of the original paper-based copies. This will include the following quality features

- congruency of the information contained between original and certified copy
- accuracy of the metadata attributed to the document (when applicable)
- accuracy of file name; including that it is marked as an updated version of an already existing document
- quality of the image (suitable resolution to allow readability as per the original, legibility and reproduction of colour — when the colour gives meaning and legibility of wet-ink signatures or annotations and handwriting in general etc. (when applicable)

- the eTMF audit trail associated with the document (when applicable)
- approval of the certification process (when applicable)

12.5 Indemnity

The University of Liverpool holds Indemnity and insurance cover with Newline Insurance Company, which applies to this study.

12.6 Audits

The study may be subject to inspection and audit by the University of Liverpool under their remit as Sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Framework for Health and Social Care Research (v3.2 10th October 2017).

13. END OF STUDY

The Programme Grant for Applied Research (RENAL-HF) is 60 months duration with the funding start date 1st February 2022 and the end date 31st January 2027. Work Package 2 including all 6 stages is 36 months in duration. We have defined the end of the study for WP2 as the point at which the pathway informed by WP2 has been rolled out across all clinical trial practices. The end point for this protocol will be completion of the beta testing (stage 5) which will overlap with the set-up period for stage 6 (feasibility and acceptability study).

14. DISSEMINATION POLICY

We shall co-develop a multi-modal dissemination strategy with our PPIE group, which will be integrated across all work packages.

- We shall work with our PPIE group to co-design materials, such as posters, a newsletter, blogs, YouTube videos and lay summaries promoted via social media (including our study website), to share our results with patients and the public.
- Our PPIE group will share knowledge with their patient networks through informal Q&A engagement activities, signposting resources and, where appropriate, more formal presentations.
- To maximise dissemination and future implementation, we shall exploit our connections with: NIHR ARCs, Academic Health Science Networks, Specialist Societies and the Society for Academic Primary Care.
- Royal Colleges will be used to disseminate our results across multiple specialities and to medical and non-medical professionals (including nurses and pharmacists).
- In addition to university and GP practice social media channels, our project manager will develop online identities for this project (website, Twitter, Facebook).
- We shall publish papers in high impact journals and present our findings at various conferences (including medical, specialist society, pharmacy and nursing).
- We are also part of HDR UK (Pirmohamed acts as Director of HDR North) and will thus use the HDR infrastructure to engage with individuals and organisations involved in health data research. In addition, we will provide metadata via the HDR Innovation Gateway.

14.1 Data ownership

To comply with the terms of the contract between the Department of Health and Social Care contract with Liverpool University Hospitals NHS Foundation Trust, Foreground IP will vest in the University of Liverpool, 'Liverpool'. Liverpool shall manage and own Research Data. Arising Know How shall vest in the party or parties that generated it. Liverpool has granted other participating institutions an irrevocable, non-transferable, royalty-free right to use all foreground IP and research data generated in the course of the research for academic and non-commercial research purposes for patient benefit.

14.2 Study report

Upon completing the wider programme, the data will be analysed and tabulated within a Final Study Report and shared via the NIHR. We will also submit an interim report for this work package. This wider programme will also be registered with ISRCTN.

14.3 Publications

In accordance with normal academic practice, all employees, students, agents, or appointees of the participating institutions shall be permitted to publish results, jointly where applicable, obtained during the course of work undertaken as part of the research. Each party shall endeavour to submit material intended for publication to the others in writing not less than thirty days in advance of the submission for publication or, in the case of conference abstracts, not less than fifteen days before the date intended for publication. The publishing party may be required to delay submission for publication if, in the other party's reasonable opinion, such delay is necessary to protect Foreground IP. Such delay shall not last longer than is absolutely necessary and not last longer than three months, though the parties agree that they will not unreasonably refuse a request for an additional delay in the event that intellectual property rights would otherwise be lost. All publications must comply with "NIHR Research Outputs and Publications Guidance."

Any publication of or resulting from the research shall acknowledge the NIHRs financial support and carry a disclaimer in accordance with the contract between the Department of Health and Social Care and Liverpool University Hospitals NHS Foundation Trust.

14.4 Authorship eligibility guidelines and any intended use of professional writers

We will follow the International Committee of Medical Journal Editors' recommendation for that authorship. Any members of the research team who meet the following four criteria will be designated authors?

1 Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the Work; AND
2 Drafting the work or revising it critically for important intellectual content; AND
3 Final approval of the version to be published; AND
4 Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

15. ARCHIVING

Data and all appropriate documentation will be stored in the Liverpool Data Catalogue for a minimum of 10 years after completing the study. We intend to make study data available for open

access where possible, as per NIHR policy. Where there are no barriers to sharing or actions have been taken to overcome barriers, metadata and data will be assigned a digital object identifier (DOI) which will be used to enable discovery of the data archive. The DOI will be cited in all publications and data statements.

Potential barriers to sharing – and mitigations - include:

- Lack of consent to share – consent will be requested for data sharing; where consent is not given, the data will be archived securely at University of Liverpool, but access will not be granted to those outside the research team.
- Identification of individuals/disclosure of personal information - relevant data will be anonymised according to the guidance at the UK data archive.

16. POJECT MILESTONES (stage 1-6)

Month	Description
12	Completion of survey and interviews identifying barriers and facilitators to renal function monitoring (Stage 1)
18	Co-design of the care pathway/clinical guidelines (Stage 2)
20	Prototype materials designed to enable primary care staff to preserve renal function in patients developed. (Stage 3 & 4)
23	Beta testing of prototype materials with primary care staff (Stage 5)
30	Training materials refined (Stage 5 & Stage 6 set-up)
31	Establish acceptability of the intervention to primary care staff (stage 6)
31	Establish acceptability of the intervention to patients (stage 6)

17. REFERENCES

1. DIRECTIVE 2007/47/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL, (2007).
2. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, et al. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail. 2021.
3. Ponikowski P, Anker SD, AlHabib KF, Cowie MR, Force TL, Hu S, et al. Heart failure: preventing disease and death worldwide. ESC Heart Fail. 2014;1(1):4-25.
4. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. The Lancet. 2018;391(10120):572-80.
5. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ. 2004;329(7456):15.

6. Patel NS, Patel TK, Patel PB, Naik VN, Tripathi CB. Hospitalizations due to preventable adverse reactions—a systematic review. European Journal of Clinical Pharmacology. 2017;73(4):385-98.
7. Pierson-Marchandise M, Gras V, Moragny J, Micallef J, Gaboriau L, Picard S, et al. The drugs that mostly frequently induce acute kidney injury: a case - noncase study of a pharmacovigilance database. Br J Clin Pharmacol. 2017;83(6):1341-9.
8. Welch HK, Kellum JA, Kane-Gill SL. Drug-Associated Acute Kidney Injury Identified in the United States Food and Drug Administration Adverse Event Reporting System Database. Pharmacotherapy. 2018;38(8):785-93.
9. Hosohata K, Inada A, Oyama S, Furushima D, Yamada H, Iwanaga K. Surveillance of drugs that most frequently induce acute kidney injury: A pharmacovigilance approach. J Clin Pharm Ther. 2019;44(1):49-53.
10. Damman K, Valente MAE, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. European Heart Journal. 2013;35(7):455-69.
11. Al-Naher A, Wright D, Devonald MAJ, Pirmohamed M. Renal function monitoring in heart failure - what is the optimal frequency? A narrative review. Br J Clin Pharmacol. 2018;84(1):5-17.
12. Al-Naher A. The PERMIT Project: Personalised Renal Function Monitoring via Information Technology: University of Liverpool; 2020.
13. Al-Naher A, Wright D, Devonald MAJ, Pirmohamed M. Renal function monitoring in heart failure – what is the optimal frequency? A narrative review. Br J Clin Pharmacol. 2018;84(1):5-17.
14. Kinsman L, Rotter T, James E, Snow P, Willis J. What is a clinical pathway? Development of a definition to inform the debate. BMC Medicine. 2010;8(1):31.
15. Rotter T dJR, Lacko SE, et al. . Clinical pathways as a quality strategy. . In: Busse R KN, Panteli D, et al., editors, editor. Improving healthcare quality in Europe: Characteristics, effectiveness and implementation of different strategies: [Internet]. Copenhagen (Denmark): European Observatory on Health Systems and Policies; 2019. (Health Policy Series, No. 53.) 12. Available from: https://www.ncbi.nlm.nih.gov/books/NBK549262/

2019.
16. Schrijvers G, van Hoorn A, Huiskes N. The care pathway: concepts and theories: an introduction. Int J Integr Care. 2012;12(Spec Ed Integrated Care Pathways):e192-e.
17. Hipp R, Abel E, Weber RJ. A Primer on Clinical Pathways. Hosp Pharm. 2016;51(5):416-21.
18. Rotter T, de Jong RB, Lacko SE, Ronellenfitsch U, Kinsman L. Clinical pathways as a quality strategy. Improving healthcare quality in Europe. 2019:309.
19. (EPA) EPA. EPA Care Pathways [Available from: Available at: http://e-p-a.org/care-pathways/.
20. Pirmohamed M. Personalised Renal Monitoring via Information Technology.
21. Leisch F. FlexMix: A General Framework for Finite Mixture Models and Latent Class Regression in R. 2004. 2004;11(8):18.
22. Grün B, Leisch F. FlexMix Version 2: Finite Mixtures with Concomitant Variables and Varying and Constant Parameters. 2008. 2008;28(4):35.
23. Tomašev N, Glorot X, Rae JW, Zielinski M, Askham H, Saraiva A, et al. A clinically applicable approach to continuous prediction of future acute kidney injury. Nature. 2019;572(7767):116-9.
24. Wind A, van der Linden C, Hartman E, Siesling S, van Harten W. Patient involvement in clinical pathway development, implementation and evaluation – A scoping review of international literature. Patient Education and Counseling. 2021.
25. Ersek JL, Nadler E, Freeman-Daily J, Mazharuddin S, Kim ES. Clinical Pathways and the Patient Perspective in the Pursuit of Value-Based Oncology Care. Am Soc Clin Oncol Educ Book. 2017;37:597-606.

26. Chawla A, Westrich K, Matter S, Kaltenboeck A, Dubois R. Care pathways in US healthcare settings: current successes and limitations, and future challenges. Am J Manag Care. 2016;22(1):53-62.
27. Al-Naher A, Downing J, Scott KA, Pirmohamed M. Factors Affecting Patient and Physician Engagement in Remote Health Care for Heart Failure: Systematic Review. JMIR Cardio. 2022;6(1):e33366.
28. NHS. The NHS long term plan. 2019.
29. Research NIfCO. National Heart Failure Audit; 2019 Summary Report. 2019.
30. Kerr M, Bedford M, Matthews B, O'Donoghue D. The economic impact of acute kidney injury in England. Nephrol Dial Transplant. 2014;29(7):1362-8.
31. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ : British Medical Journal. 2014;348:g1687.
32. Skivington K, Matthews L, Simpson SA, Craig P, Baird J, Blazeby JM, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. BMJ. 2021;374:n2061.
33. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluation of complex interventions: Medical Research Council guidance. BMJ : British Medical Journal. 2015;350:h1258.
34. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. Int J Nurs Stud. 2008;50(5):587-92.
35. Cathain A, Croot L, Duncan E, Rousseau N, Sworn K, Turner KM, et al. Guidance on how to develop complex interventions to improve health and healthcare. BMJ Open. 2019;9(8):e029954.
36. Farr M, Davies P, Andrews H, Bagnall D, Brangan E, Davies R. Co-producing knowledge in health and social care research: reflections on the challenges and ways to enable more equal relationships. Humanities and Social Sciences Communications. 2021;8(1):105.
37. Farr M, Davies R, Davies P, Bagnall D, Brangan E, Andrews H. A map of resources for co-producing research in health and social care. National Institute for Health Research ARC West and People in Health West of England. 2020.
38. Coldham T, Group I. Guidance on co-producing a research project. National Institute for Health Research UK; 2018.
39. Michie S, van Stralen MM, West R. The behaviour change wheel: A new method for characterising and designing behaviour change interventions. Implementation Science. 2011;6(1):42.
40. Greenhalgh T, Wherton J, Papoutsi C, Lynch J, Hughes G, A'Court C, et al. Analysing the role of complexity in explaining the fortunes of technology programmes: empirical application of the NASSS framework. BMC Medicine. 2018;16(1):66.
41. Greenhalgh T, Abimbola S. The NASSS Framework - A Synthesis of Multiple Theories of Technology Implementation. Stud Health Technol Inform. 2019;263:193-204.
42. Greenhalgh T, Maylor H, Shaw S, Wherton J, Papoutsi C, Betton V, et al. The NASSS-CAT Tools for Understanding, Guiding, Monitoring, and Researching Technology Implementation Projects in Health and Social Care: Protocol for an Evaluation Study in Real-World Settings. JMIR Res Protoc. 2020;9(5):e16861-e.
43. Atkins L, Francis J, Islam R, O'Connor D, Patey A, Ivers N, et al. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. Implementation Science. 2017;12(1):77.
44. Fitch K, Bernstein SJ, Aguilar MD, Burnand B, LaCalle JR, Lazaro P, et al. The RAND/UCLA Appropriateness Method User's Manual. Santa Monica, CA: RAND Corporation; 2001.

45. Berian JR, Baker TL, Rosenthal RA, Coleman J, Finlayson E, Katlic MR, et al. Application of the RAND-UCLA Appropriateness Methodology to a Large Multidisciplinary Stakeholder Group Evaluating the Validity and Feasibility of Patient-Centered Standards in Geriatric Surgery. Health Serv Res. 2018;53(5):3350-72.
46. Fitch K, Bernstein SJ, Aguilar MD, Burnand B, LaCalle JR. The RAND/UCLA appropriateness method user's manual. Rand Corp Santa Monica CA; 2001.
47. Michie S, Atkins L, West R. The behaviour change wheel : a guide to designing Interventions: Silverback; 2014.
48. Kaklamanou D, Armitage CJ, Jones CR. A further look into compensatory health beliefs: A think aloud study. British Journal of Health Psychology. 2013;18(1):139-54.
49. Porroche-Escudero A, Popay J. The Health Inequalities Assessment Toolkit: supporting integration of equity into applied health research. Journal of Public Health. 2020.
50. Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. Qual Health Res. 2016;26(13):1753-60.
51. Braun V, Clarke V. Reflecting on reflexive thematic analysis. Qualitative Research in Sport, Exercise and Health. 2019;11(4):589-97.
52. Ritchie J, Lewis J, Nicholls CM, Ormston R. Qualitative research practice: A guide for social science students and researchers: sage; 2013.
53. Taylor CJ, Ordóñez-Mena JM, Roalfe AK, Lay-Flurrie S, Jones NR, Marshall T, et al. Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: population based cohort study. BMJ. 2019;364:l223.
54. Hawkins NM, Jhund PS, McMurray JJV, Capewell S. Heart failure and socioeconomic status: accumulating evidence of inequality. European Journal of Heart Failure. 2012;14(2):138-46.

18. APPENDICES

18.1 Appendix 1 -Required documentation

Document	Version (where applicable)	Date (where applicable)
Localised Organisation Information Document (Only primary care sites will liaise with CRN)		
REC Approval		
HRA and HRCW Initial Assessment Letter (or HRA and HCRW Approval letter if application is already approved by the HRA and HCRW)		
IRAS Form or StudyProjectInfromation.pdf document (for studies using combined review)		
Protocol and any amendments		
Participant information and consent documents (without local logos/ headers)		
Interview schedule		
Distress protocol		
Relevant model agreement		
Schedule of events or SoECAT		

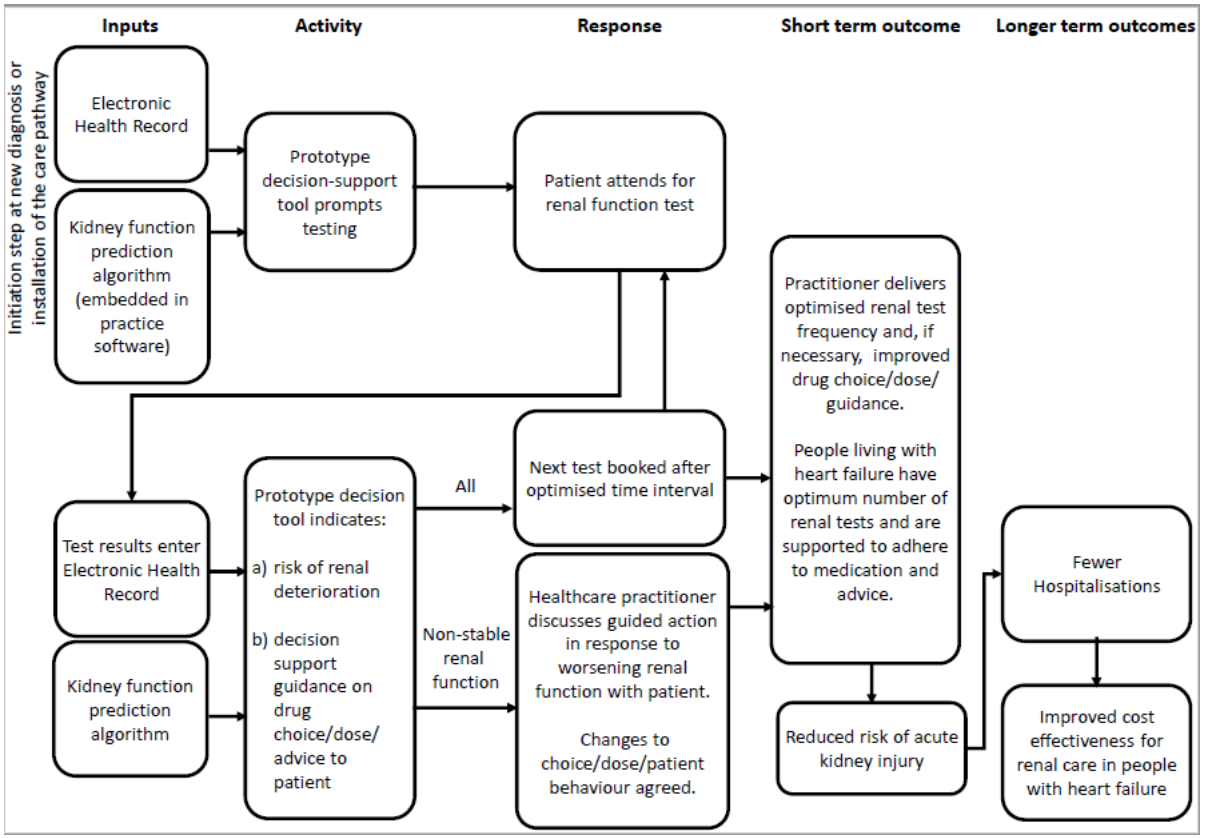
Any other documents that the Sponsor wishes to provide to the site to support the set up and delivery of the study		

18.2 Appendix 1: Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
SA01	V1.2	17/11/2022	E.Sowden	Survey and interview design finalised. Extension of recruitment pathway to include professional networks & snowball sampling. Refine aim to 'optimising the treatment of patients with heart failure while preserving their renal function'. Study advert for Stage 1b
Amendment 2(non-substantial)	V1.2		E.Sowden	Minor changes to invitation letter so changes are aligned to SA)1
Amendment 3(non-substantial)	V1.2	21/12/2022	E,Sowden	Minor changes to the Stage 1a Survey Script following further feedback from the RENAL-HF team, the YouGov team and clinical colleagues.
Amendment 4(non-substantial)	V1.2	02/02/2023	E.Sowden	Site addition
Amendment 5(non-substantial)	V1.2	10/03/2022	E.Sowden	Targeted professional advert
Amendment 6(non-substantial)	V1.2	24/04/2023	E.Sowden	Site addition
Amendment 7(non-substantial)	V1.3	19/06/2023	E.sowden	Extend sample 1b to include HFSNs
Amendment 8 (substantial)	V1.4	06/07/2023	E.Sowden	Clarification of boundaries between WP1 and WP2. Inclusion of verbal consent for patient participants in Stage 2.Inclusion of ethnicity for professional sample. Targeted adverts for workshops
Amendment 9 (substantial)	V1.4	26/07/2023	E.Sowden	Increase patient recompense to £50
Amendment 10 (non-substantial)	V1.5	27/10/2023	E.Sowden	Inclusion of new PDRA details in protocol and Stage 5 study documents.
Amendment 16 (substantial)	V1.6	09/06/2024	N.Khan	Inclusion of the feasibility and acceptability sub-study stage 6 and inclusion of new PDRA details.
Amendment 20 (substantial)	V1.7	28/10/2024	S Hargreaves	Inclusion of care navigators to the list of participants in stage 5. Update of PDRA details page 13. Update of version number to 1.7.

Figure 3. Logic model:

Illustrating how our intervention will enable primary care staff to take steps to preserve renal function in patients



Certificate Of Completion

Envelope Id: 6EBA049F-D7C8-467C-9F1D-FD3AAF516479
Status: Completed
Subject: Complete with Docusign: RENAL-HF WP2 (Stage 1-6) Protocol_V3 _28.10.2024 CLEAN.docx
Source Envelope:
Document Pages: 41
Signatures: 2
Envelope Originator:
Certificate Pages: 5
Initials: 0
Karen Jennings-Wilding
AutoNav: Enabled
kwilding@liverpool.ac.uk
EnvelopeId Stamping: Disabled
IP Address: 138.253.14.137
Time Zone: (UTC) Dublin, Edinburgh, Lisbon, London

Record Tracking

Status: Original
03 December 2024 | 12:31
Holder: Karen Jennings-Wilding
kwilding@liverpool.ac.uk
Location: DocuSign

Signer Events	Signature	Timestamp
Karen Jennings-Wilding kwilding@liverpool.ac.uk Senior Clinical Research Governance Manager University of Liverpool Security Level: Email, Account Authentication (Required)	Karen Jennings-Wilding Signature Adoption: Pre-selected Style Signature ID: E0AD3C9F-D9A8-4DEA-A936-5BA11703D062 Using IP Address: 138.253.14.137 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 03 December 2024 | 12:32 Viewed: 03 December 2024 | 12:33 Signed: 03 December 2024 | 12:33
Electronic Record and Signature Disclosure: Accepted: 01 September 2021 | 14:23 ID: 357ba546-1b5c-402b-87b7-541203fc3080		
Professor Sir Munir Pirmohamed munirp@liverpool.ac.uk Security Level: Email, Account Authentication (Required)	Professor Sir Munir Pirmohamed Signature Adoption: Pre-selected Style Signature ID: 621714BD-EC47-4208-9DF2-E53235263BAC Using IP Address: 138.253.52.154 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 03 December 2024 | 12:32 Viewed: 11 December 2024 | 09:28 Signed: 11 December 2024 | 09:29
Electronic Record and Signature Disclosure: Accepted: 11 December 2024 | 09:28 ID: 27893e15-a35d-4fc3-bf3e-ffaabeecdc4c		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	03 December 2024 | 12:32
Certified Delivered	Security Checked	11 December 2024 | 09:28
Signing Complete	Security Checked	11 December 2024 | 09:29
Completed	Security Checked	11 December 2024 | 09:29

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, UNIVERSITY OF LIVERPOOL - Clinical trials (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact UNIVERSITY OF LIVERPOOL - Clinical trials:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: victoria.shaw@liverpool.ac.uk

To advise UNIVERSITY OF LIVERPOOL - Clinical trials of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at victoria.shaw@liverpool.ac.uk and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from UNIVERSITY OF LIVERPOOL - Clinical trials

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to victoria.shaw@liverpool.ac.uk and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with UNIVERSITY OF LIVERPOOL - Clinical trials

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to victoria.shaw@liverpool.ac.uk and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify UNIVERSITY OF LIVERPOOL - Clinical trials as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by UNIVERSITY OF LIVERPOOL - Clinical trials during the course of your relationship with UNIVERSITY OF LIVERPOOL - Clinical trials.