Appendix 3 – UK-specific Implementation of the RESOLVE Protocol

The RESOLVE study will be conducted in the UK in accordance with the global RESOLVE protocol. Appendix 3 outlines specific aspects of implementation of the RESOLVE protocol in the UK for some parameters. For all aspects of the RESOLVE study not mentioned in this appendix, the main RESOLVE protocol will prevail.

Sponsor:	University College London (UCL)
Region:	United Kingdom
Chief Investigator:	Professor David Wheeler
Chair of the Regional Coordinating Committee:	Professor Patrick Mark
Consent Model:	Opt-out Consent
Study Phase(s):	Phase IV
Endpoints:	*The primary and secondary endpoints are as outlined in the RESOLVE protocol.*
Additional secondary endpoints:	Cost-effectiveness of intervention.
Data Management: *(Outline methods of data collection to be used in the country e.g., dialysis registries/administrative datasets/paper & electronic CRF)*	UK Renal Registry NHS Digital REDCap database

The study, in the UK, will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the Human Tissue (Quality and Safety for Human Application) Regulations 2007, the UK Data Protection Act, and the National Health Service (NHS) UK Policy Framework for Health and Social Care. Agreements that include detailed roles and responsibilities will be in place between participating sites and the Comprehensive Clinical Trials Unit (CCTU).

Participating sites will inform CCTU as soon as they are aware of a possible serious breach of compliance, so that CCTU can fulfil its requirement to report the breach if necessary, within the timelines specified in the UK Clinical Trials Regulations (currently 7 days). For the purposes of this regulation a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the study, or
- The scientific value of the study.

2 Administrative Information

2.2 Funding

RESOLVE, in the UK, is fully funded by a National Institute for Health Research (NIHR) Health Technology Assessment (HTA) grant, reference number **NIHR134660**. It is not expected that any further external funding will be sought.

2.3.2 Study Sponsor

UCL will act as the study sponsor in the UK and has delegated responsibility for the overall management of the RESOLVE study to the CCTU. Queries relating to UCL sponsorship of this study should be addressed to the CCTU Director or via the Trial Team.

Indemnity

UCL holds insurance to cover participants for injury caused by their participation in the clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical study is being carried out in a hospital or private care unit, the hospital, or private care provider when applicable, continues to have a duty of care to the participant in the clinical

study. UCL does not accept liability for any breach in the hospitals, or private care providers, duty of care, or any negligence on the part of the employees. This applies whether the hospital is an NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

Participants may also be able to claim compensation for injury caused by participation in this clinical study without the need to prove negligence on the part of UCL or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to UCL's insurers, via the Sponsor's office.

Units selected to participate in this clinical study shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to UCL, upon request.

2.3.4 Regional Coordinating Committees and Centres

The UK Steering Committee is an independent group responsible for oversight of the study, in the UK, in order to safeguard the interests of the study participants. The Steering Committee provide advice to the CI, the CCTU, the funder and the sponsor on all aspects of the study through its independent Chair. The membership, frequency of meetings, activity (including study conduct and data review) and authority will be covered in the CCTU TSC terms of reference.

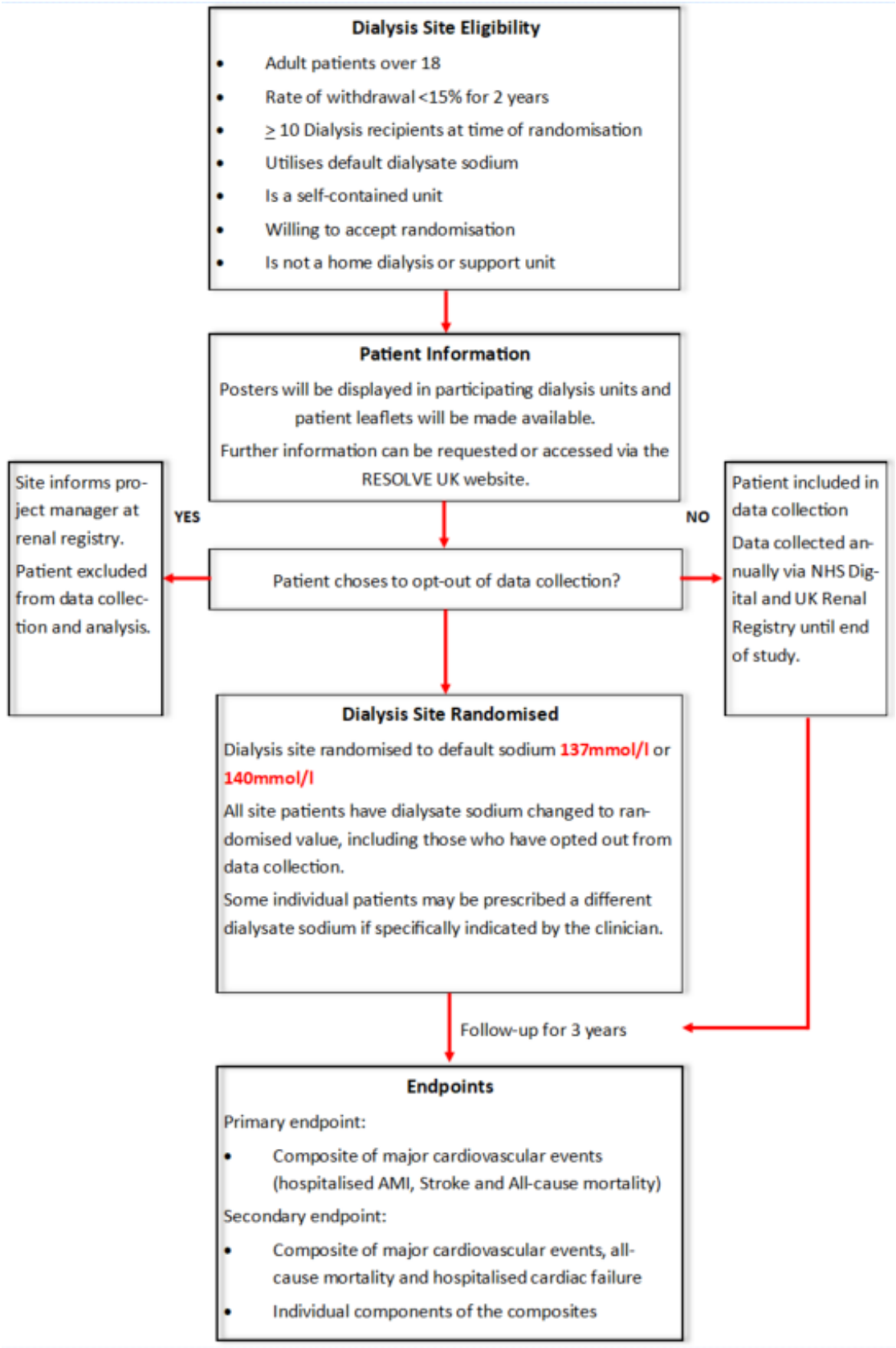
The UK Steering Committee is comprised as follows:

Name	Affiliation	Role and responsibilities
Prof. Patrick Mark	University of Glasgow	Chair
Prof. John Townend	University of Birmingham NHS Foundation Trust	Non-Independent Member
Prof. Jonathan Emberson	University of Oxford	Independent Statistician
TBC	TBC	Patient Representative
Prof. Joseph Eustace	Cork District General (Ireland)	Independent Nephrologist

The UK Trial Management Group is comprised as follows:

Name	Affiliation	Role and responsibilities
Professor David Wheeler	Professor of Kidney Medicine at University College London	Chief Investigator and Chair of TMG
Dr Fergus Caskey	University of Bristol	Co-applicant
Ms Gurpreet Badhan	Royal Free Hospital and UCL	Co-applicant
Ms Monica Panca	CCTU UCL	Senior Health Economist
Professor Simon Davies	Professor of Nephrology and Dialysis Medicine at Keele University	Co-applicant
Professor Sandip Mitra	Consultant Nephrologist at Manchester Royal Infirmary	Principal Investigator and Co-applicant
Professor Andrew Davenport	Consultant Nephrologist, Honorary Senior Lecturer at the Royal Free Hospital UCL	Principal Investigator and Co-applicant
Ms Grace Auld	CCTU UCL	Clinical Project Manager, Deputy Chair of TMG
Ms Rumana Jalil	CCTU UCL	Clinical Trial Manager, Facilitator of TMG
Ms Krishneya Anojan	CCTU UCL	Trial Data Manager
Ms Kashfia Chowdhury	CCTU UCL	Senior Trial Statistician
Mr Saiam Ahmed	CCTU UCL	Trial Statistician

3.1 Study Flow Diagram – UK



5 Methods: Participants, Interventions and Outcomes

5.6 Site and Participant Timeline

In the UK, before a site is randomised, the trial manager or delegate will notify the PI in writing about the plans for site activation. Sites will not be permitted to advertise the study, until a letter for activation has been issued.

Each unit will participate in the study for up to 3 years, depending on the date of randomisation.

7 Methods: Data Collection, Management and Analysis

7.1 Data Collection Methods

Each UK participant, who has not opted out, will be assigned a unique study Participant Identification Number (PIN).

In the UK, after the close of the study, investigators agree to archive and/or arrange for secure storage of RESOLVE study materials and records for a minimum of 5 years, unless otherwise advised by the CCTU.

7.1.1.1 Data Collection via registry systems

In the UK collection of biochemical data will occur through the UK Renal Registry.

7.1.1.2 Data Collection via Data Linkage of Administrative Datasets

The UK will also use data linkage derived from NHS Digital using Hospital Episode Statistics including Admitted Patient Care (APC) and Emergency Care Data Sets (ECDS) in order to ascertain study endpoints. Office of National Statistics (ONS)-Hospital Episode Statistics (HES) civil registration of deaths will be used to collect data on all-cause mortality.

7.1.1.3 Data Collection via Electronic or Paper CRF

UK sites will be expected to complete a baseline registration form for all participants, who have not opted out of data collection. This includes new patients starting at the dialysis unit (whether with new kidney failure, transfers from another site, or transfers from another modality of kidney replacement therapy) for the duration of the study. This data will be entered into a database by a delegated member at site. The secure database, hosted by UCL, will be password protected and only accessible to delegated members of the site teams and the Trial Team at UCL CCTU.

The database will be developed by CCTU. The database software provides a number of features to help maintain data quality, including maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/missing data.

7.1.2 Data Management

The Central Coordinating Centre, in Sydney, will not be sent any UK full individual participant data (IPD). They will instead be sent aggregate UK data that has been de-identified.

In the UK, the CCTU study statistician will perform sub-analyses on the UK IPD.

7.1.2.1 Minimum Data Collection

Baseline Data – UK

- PIN
- Site number
- NHS Number
- Date of birth
- Age
- Gender
- Dry weight (kg)
- Primary renal disease
- History of acute myocardial infarction (AMI)
- History of stroke
- History of heart failure
- History of diabetes
- Pre-dialysis serum sodium (mmol/L)
- Pre-dialysis serum albumin (g/L or g/dL)
- Dialysate sodium (pre-study) (mmol/L)
- Haemodiafiltration (HDF) / Haemodialyis (HD)
- Weekly dialysis hours
- Ultrafiltration volume (L)

Annual collection – UK

- Pre-dialysis serum sodium (mmol/L)
- Pre-dialysis serum albumin (g/L or g/dL)
- Dry weight (kg)
- Hospitalised AMI

- Hospitalised stoke
- Hospitalised heart failure
- Diabetes
- HDF / HD
- Weekly dialysis hours
- All-cause mortality
- Transplantation
- Transfer to peritoneal dialysis

7.2 Statistical Methods

Statistical Analysis – UK

The primary and secondary analysis methods are as outlined in the RESOLVE protocol in section 7.2.

The UK-specific plan includes the examination of the effect of blood sodium on modifying the relationship between dialysate sodium and the outcomes.

Health Economics - UK

A health economic evaluation will be conducted to quantify the potential costs and health-related outcomes in patients undergoing dialysis with sodium concentration of 137 mmol/l vs. sodium concentration of 140 mmol/l over the duration of the study.

A health economics analysis plan (HEAP) will be developed for the within-study analysis and will be subject to approval by the Trial Steering Committee. Resource use data will be obtained from CRFs, UK Renal Registry (UKRR) and NHS Digital. These will be valued using relevant tariffs (e.g., NHS Reference Costs) and total costs per patient calculated from the perspective of UK's NHS and personal social services perspective. As the intervention cost is zero, we will examine the incremental differences in different cost categories across study arms, including ongoing dialysis costs, and the costs associated with major cardiovascular events and hospitalisations. Descriptive statistics will be reported to provide a clearer understanding of the future resource use implications. The cost saving is expected to result from reductions in hospitalisation and additional dialysis sessions for fluid overload and heart failure (expected with the lower dialysis sodium concentration (137 mmol/l).

Within-study health-related outcomes will be measured in life years (LYs) gained estimated from all-cause mortality. Due to the constraints inherent in a large-scale pragmatic study of this nature, patients will not be approached in person except for the opt-out consent. Therefore, we are unable to gather direct information on HRQoL to construct quality-adjusted life years (QALYs).

The mean total costs over the study duration (including dialysis costs and costs of major cardiovascular events) and the mean health outcomes in each study arm will be used to estimate the incremental cost-effectiveness ratio (ICER). An incremental cost per additional patient avoiding major cardiovascular events, and incremental cost per life year gained in the superior intervention group, compared to the other group will be calculated. Bootstrapping will be used to estimate a distribution around costs and health outcomes, and to calculate the confidence intervals around the ICERs. One-way and multi-way sensitivity analysis will be conducted around key variables.

An exploratory analysis using the UKRR's EQ-5D-5L data collected from over 3,000 patients will be conducted. The EQ-5D-5L will be assessed for quality (including completeness), and relevance to the RESOLVE study population and could be used to value health states (or events) experienced by participants in the study. Subject of feasibility, utilities obtained from UKRR and relevant published sources existing at the time of data analysis could be combined with survival estimates from within the study to generate a model of the expected changes in HRQoL (and construct QALYs) likely to have resulted from the observed events and health outcomes of the study.

7.2.1 Power Calculations

The RESOLVE study will have 90% power (alpha=0.05) to detect a 10% reduction in the primary outcome with 414 sites. Accounting for clustering, a total of 26,910 primary endpoints are required. The study will run until the required number of endpoints has been observed globally allowing all countries to finish simultaneously, thus avoiding power being compromised by alterations in accrual times, which could potentially lead to lower than predicted event rates. The UK arm of the RESOLVE study will recruit 100 dialysis units (25 main sites each with an average of 4 satellites) and will contribute approximately 24% of total site recruitment globally with an estimated 10,000 participants over 3 years.

Further details are in section 7.2.1 of the RESOLVE protocol.

8 Methods: Monitoring

8.4 Safety Reporting

Safety events for participants will be collected from NHS Digital. However, SAEs will not be reported to the approving UK independent research ethics committee for two reasons. Firstly, the two sodium dialysate concentrations, 137mmol/l and 140mmol/l, are routinely used in UK clinical practice. As

such, we do not anticipate any SAE associated with the interventions. Secondly, there will be a delay between event occurrence and dataset receipt by the CCTU (6-, 12-, 24- and 36-months).

8.5 Ethics Approvals and Consent

8.5.2 Consent Model

To facilitate opt-out consent in the UK, a poster will be put up in each dialysis unit advising patients of the study and including a link to additional information. This poster will advise those who do not want their data to be included to inform the dialysis staff and/or local research team. The poster will be replicated in the form of a leaflet that can be provided to each patient during their dialysis session.

In addition, patients who request additional information will be provided with a 'Study Information Sheet'. If a patient decides they do not want their data to be included, they must inform the dialysis staff and/or local research team and health information will not be passed on to the UCL CCTU. Sites will keep track of patients who decide not to participate in the study.

8.7 Confidentiality

The baseline registration data for UK participants will be pseudonymised and stored in a database stored on servers at UCL. The primary identifier will be the PIN, with secondary identifiers of month and year of birth.

In order to access participant data from the UK Renal Registry and NHS Digital, UCL CCTU will also store identifiable participant data in the form of NHS number and full date of birth, along with gender. These will be linked to their PIN and stored securely in the UCL Data Safe Haven with access limited to members of the RESOLVE Trial Team.

The datasets received from the UK Renal Registry and NHS Digital will also be stored in the UCL Data Safe Haven and analysed by the CCTU study statistician.

No health data will be transferred to UCL CCTU for those patients who chose to opt-out.

10 Publication and Dissemination Policy

The publication of UK results will comply with the Global Protocol and with the UCL and CCTU Publication Policies.

The results of the study will be disseminated regardless of the direction of effect.

Declaration of Interests

The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the study.