PROTOCOL FULL TITLE

A randomised controlled trial to assess the clinical-, technical- and cost-effectiveness of a cloud-based, **AR**tificially **I**ntelligent image fusion system in comparison to standard treatment to guide endovascular **A**ortic aneurysm repair (ARIA)

Protocol Short Title/

AI image guidance for endovascular surgery

ARIA

Trial Identifiers

ISRCTN:	13832085		
REC Number:	22/LO/0081		
IRAS Number:	280257		
Protocol Version Number:	1.2	Date:	10.10.2022

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1. STUDY SYNOPSIS

TITLE OF CLINICAL TRIAL:	A randomised controlled trial to assess the clinical, technical and cost-effectiveness of a cloud-based, **AR**tificially **I**ntelligent image fusion system in comparison to standard treatment to guide endovascular **A**ortic aneurysm repair (**ARIA**)
Protocol Short Title/ Acronym:	AI image guidance for endovascular surgery /ARIA
Study Phase:	III
Sponsor Name(s):	King's College London and Cydar Medical Ltd
Chief Investigator(s):	Dr Rachel Clough
IRAS Number:	280257
REC Number:	22/LO/0081
Medical Condition Or Disease Under Investigation:	Abdominal and Thoraco-abdominal Aortic Aneurysm
Purpose Of Clinical Trial:	To evaluate the clinical, technical and cost-effectiveness of a novel type of CE-marked medical device comprised of real-time cloud computing, AI and computer vision (Cydar EV) compared to standard treatment in endovascular aortic aneurysm repair. The device is used within its intended purpose and it not itself being investigated in this trial.
Primary Objective:	To assess the effect of Cydar EV on procedure time in comparison to standard treatment in endovascular aortic aneurysm repair

Secondary Objectives:	**1. Procedural efficiency**, as assessed by: Anaesthetic duration X-ray dose per procedure Contrast dose per procedure Consumable use per procedure **2. Technical effectiveness**, as assessed by: Proximal and distal seal zone at least 10mm and no evidence of endoleak **3. Patient outcomes**, as assessed by: Length of HDU admission Length of ITU admission Post-operative total length of hospital stay 30-day mortality Re-intervention – primary hospital visit / further admission (HRG/procedure code) Adverse events (category, LoS, HDU, ITU, general ward) Quality of life 4. **Cost effectiveness**, as assessed by: Total resource use and costs Quality-Adjusted Life Years (QALYs) Incremental cost per QALY
Trial Design:	Multi-centre, open-label, two-armed, randomised controlled clinical trial
Sample Size:	340 patients (allocation ratio 1:1; 170 intervention:170 control)
Summary Of Eligibility Criteria:	Inclusion criteria 1. Clinical diagnosis of AAA or TAAA suitable for endovascular treatment, as determined by CT imaging and multidisciplinary review by the treating team 2. Fit for endovascular repair as determined by the operating team 3. CT imaging must be in accordance with 'Cydar EV: Instructions for Use' i.e. scans should have the same slice thickness and intervals as the original scan acquisition, must not have any missing slices or discontinuities, must include the pelvis and whole vertebrae including the spinous processes and must not use gantry tilt (this will be done post-consent) 4. Written informed consent (patients lacking capacity will not be enrolled) 5. Age 18 years and above at the time of consent Exclusion criteria 1. Patients unable to provide written informed consent
Intervention (Description, frequency, details of delivery)	Patients will undergo endovascular aortic aneurysm repair using Cydar EV for planning and surgical guidance, as per instructions for use

Comparator Intervention:	Patients will be treated by standard techniques for planning and surgical guidance during endovascular aortic repair as determined by the treating physician.
Maximum Duration Of Treatment Of A Participant:	Followed up for 52 weeks post-operatively
Version And Date Of Final Protocol:	V1.2 dated 10.10.2022
Version And Date Of Protocol Amendments:	

1.1 PROTOCOL AUTHORISATION

Chief Investigator: Dr Rachel Clough

Signature  Date: 28/10/2022

Statistician: Dr Yanzhong Wang

Signature:  Date: 28/10/2022

1.2 REVISION HISTORY

Document ID - (Document Title) revision X.Y	Description of changes from previous revision	Effective Date

1.3 GLOSSARY OF TERMS

AAA	Abdominal Aortic Aneurysm
AE/AR	Adverse event/Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CT	Computerised Tomography
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EDC	Electronic Data Capture system
GP	General Practitioner
GCP	Good Clinical Practice
HDU	High Dependency Unit
ICF	Informed Consent Form
ITU	Intensive Treatment Unit
ITT	Intention to Treat
KCTU	King's Clinical Trials Unit
mgI/ml	Milligrams of Iodine per millilitre
MHRA	Medicines and Healthcare products Regulatory Agency
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator at each recruiting site
PIN	Participant Identification Number
PIS	Participant Information Sheet
PP	Per Protocol
REC	Research Ethics Committee
RN	Research Nurse
SAE/SAR	Serious Adverse Event/Serious Adverse Reaction
SDW	Source Data Worksheets
SS	Senior Statistician
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAAA	Thorco-Abdominal Aortic Aneurysm
TM	Trial Manager
TMG	Trial Management Group
TS	Trial Statistician
TSC	Trial Steering Committee

1.4 PROTOCOL CONTENTS

2. INTRODUCTION

2.1 BACKGROUND AND RATIONALE

Minimally-invasive surgery, enabled by new medical device technologies, is revolutionising specialties such as cardiac and vascular surgery that have previously been dominated by open surgery. Endovascular surgery is an exemplar of this minimally-invasive surgical revolution: endovascular aneurysm repair (EVAR) has rapidly replaced open aortic surgery due to perceived advantages in patient survival, reduced postoperative complications, and shorter hospital lengths of stay (1).

Endovascular surgery is planned using 3D reconstructions of pre-operative computed tomography (CT) scans to assess access and determine the optimal type, configuration and sizing of the implantable medical device. The surgery itself is 'image-guided' using 2D X-ray fluoroscopy and injection of nephrotoxic contrast material to visualise blood vessels [Figure 1].

Figure 1. The loss of 3D information and reliance on intra-operative 2D fluoroscopy are important limitations in endovascular surgery

Despite the potential advantages of EVAR over open surgery, there are significant concerns related to the variability in planning and sizing, imprecise visualisation and positioning, unpredictability of individual patient outcomes and inconsistent outcomes between hospitals and regions leading to controversy over cost effectiveness (2, 3). Device positioning error can require secondary interventions and cause serious and even fatal complications (4). As patients with ever more challenging anatomy are undergoing endovascular procedures with more complex devices, these limitations are becoming increasingly more relevant.

Our central hypothesis is that digital technology - specifically cloud-computing, big-data and artificial intelligence (AI) - has the potential to improve the predictability of individual outcomes and the consistency of outcomes of image guided surgery in the NHS. The first test case for this hypothesis addresses the specific problem of poor visualisation of blood vessels in EVAR as a significant contributor to poor outcomes: long and inconsistent procedural times, device positioning errors and use of high doses of ionising radiation and nephrotoxic contrast material.

Previous solutions to improve visualisation during EVAR have included manually-aligned, operating table-tracked 3D-2D image overlay. This technology is available in hybrid operating rooms supplied by GE, Siemens and Philips but is widely considered too costly, complex, inaccurate, and unreliable. In a survey of actual use in 10 US centres, clinicians from several centres confirmed that although they have the facility for 3D overlay, they do not use it (5). This is mostly due to disruption of clinical work flow and clinically significant image positioning errors (median error distance 8.64mm, IQR 6.1-16.8, max. 24.5mm) in a range similar to the diameter of important aortic branches that cannot be covered (6-8mm) and the all-important seal zone length (10-15mm) (6).

Cydar-EV image fusion is a CE-marked medical device, which instead of a table-tracked overlay uses computer vision to fuse pre-procedural 3D images with intra-operative 2D fluoroscopy automatically and in real-time [Figure 2]. The key advantage of this type of image fusion is that it gives the surgeon real-time fully integrated 3D visualisation throughout the EVAR procedure with much greater spatial accuracy than achieved by previous technology. The computer vision is a form of artificial intelligence using NHS Digital-approved, GDPR compliant high-performance cloud computing [Figure 3]. Cydar-EV uses only existing patient data (i.e. no new imaging) and is designed not to change clinical workflows. There is no requirement for user interaction, no additional ionising radiation or iodinated contrast. It is agnostic to existing X-ray imaging equipment and can be used on fixed or mobile X-ray systems.

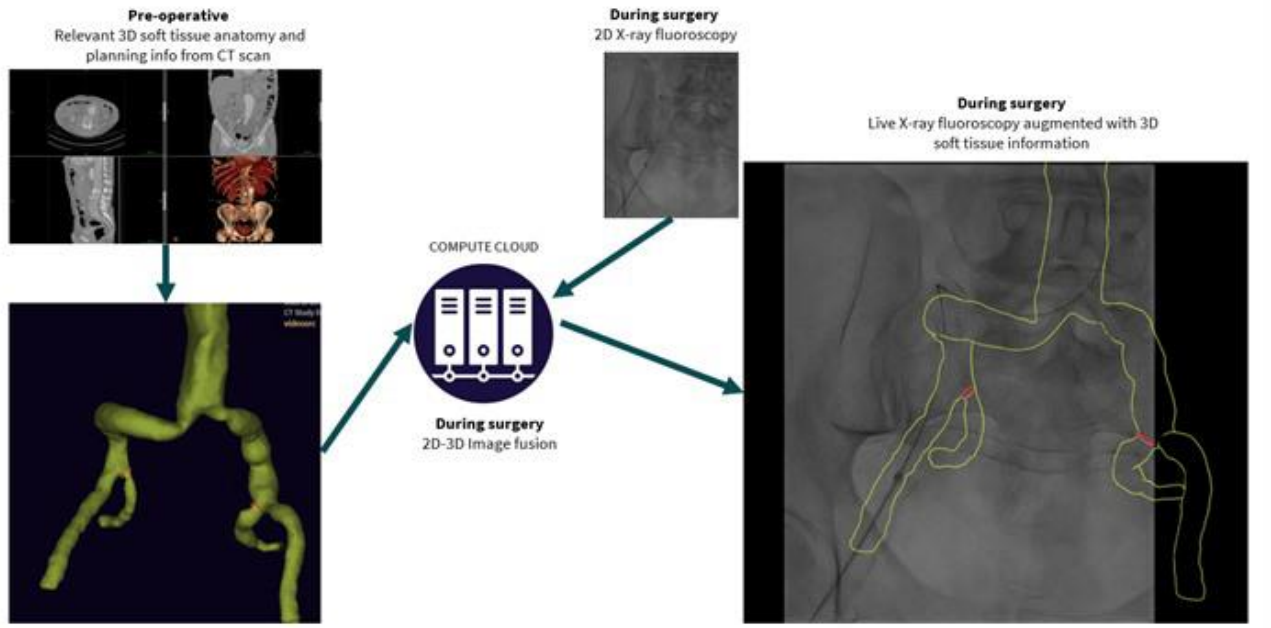

Figure 2. Cydar EV image fusion, pre-procedural 3D images are fused with intra-operative 2D fluoroscopy automatically, in real-time.

Importance of the research in terms of improving the health and/or wellbeing of the public and/or patients and health and care services

Image-guided, minimally-invasive surgery is growing rapidly: The global market for EVAR is £1.8bn (2016), with a compound annual growth rate (CAGR) of 6.8%; Transcatheter Aortic Valve Replacement (TAVR) £2.0bn (CAGR 14.9%) and is an increasing burden on health spending. Approximately 5,000 EVAR procedures are performed each year in the UK, with an average cost of £19k (5k*19k=£95M) (7, 8). EVAR is under an existing NHS care pathway (9) and reduces mortality from 4.7% to 1.7% compared to open surgery, with faster return to normal activities on discharge (1). There is a pressing need to improve the precision, consistency and transparency of outcomes in these procedures.

Establishing computer vision-powered image fusion as the standard of care in endovascular surgery would directly benefit patients and health and care services by:

1. Reducing procedure times compared to standard procedures and thus improve efficiency of resource use in the NHS.
2. Reducing patient exposure to anaesthesia and ionising radiation, lowering surgical site infection and reducing adverse events.
3. Improving procedural success with more precise device positioning compared to current practice.
4. Reducing x-ray exposure to patients and staff and reducing the use of nephrotoxic contrast agent, improving renal function.
5. Reducing capital expenditure- Cydar-EV can be easily implemented without the need for linked capital expenditure on new fixed imaging or hybrid operating room (cost to NHS ~£2-5m).

Review of existing evidence

A multi-centre observational study (109 patients) examining safety, performance, usability and efficacy of Cydar-EV was performed 2014-5. These data were used in the successful application for CE marking. The primary outcomes were:

1. Robustness: 2802 images were analysed, yielding a positive predictive value of 1, with a lower 95% CI of 0.998.
2. Accuracy: tested against the gold-standard data (Tomazevic 2002) the root-mean-square-error was 0.21mm (max 0.62mm) (10).
3. Speed: The mean time taken to return and display an updated 3D overlay in response to patient/table/ X-ray set movement was 8.395seconds (7.232s excluding network latency); this has since been significantly reduced to <4 seconds.
4. Usability: External usability testing in accordance with IEC 62366 validated the display of the 3D overlay information.

Patient benefit was observed by a significant reduction in the amount of X-rays used, with a mean reduction in X-ray fluoroscopy screening time of 35% (p=0.013), a 41% reduction in the amount of iodinated contrast used (p=0.008), and a nearly one hour reduction in mean operating time (17%, p=0.06). Superiority to the 3D cone-beam-aligned, robotically tracked Siemens Artis Zeego was demonstrated with a significant reduction in radiation exposure (11).

Consistent with this previous report, a second recent prospective observational cohort study of 119 patients, conducted at Duke University Medical Centre, reported a mean reduction in procedure time of 18.2% (p=0.04), with Cydar-EV and a reduction in the number and duration of unexpectedly very long operations (12). There was also significantly better renal function after the procedure and at 30 days, an indirect metric of the effect of less nephrotoxic contrast agent and better device positioning.

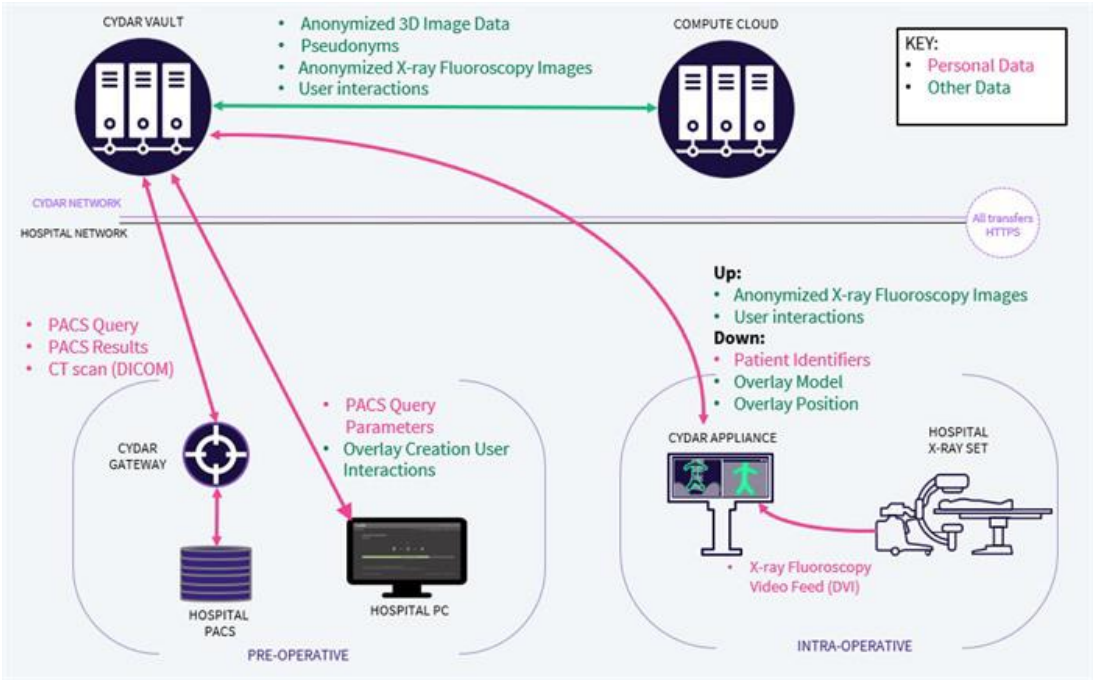

Figure 3. Cydar is a digital health technology using cloud-computing, big-data and AI

Demonstrating Cydar-EV improves the outcomes of endovascular surgery at a lower cost for the NHS would also be a key demonstration of the potential of digital technology (cloud-computing, big-data, AI) to improve precision and consistency of outcomes for image-guided surgery. It would establish a new concept of data guided surgery to deliver intelligent planning and outcome analysis, aggregating and learning from existing data to improve the precision, consistency and transparency of patient outcomes for stakeholders across the NHS: patients, commissioners, hospitals, and clinical teams.

2.2 SUMMARY OF KNOWN AND POTENTIAL RISKS OF INTERVENTION

The potential complications of endovascular stent grafting include:

- Leaking of blood around the stent graft (endoleak)
- Movement of the graft away from the desired location (migration) (uncommon, can occur many years after placement of stent-graft)
- Blockage of the blood flow through the graft (uncommon)
- Heart problems, respiratory problems
- Vessel problems: rupture, dissection
- Reduced blood flow to bowel or kidneys
- Deterioration in kidney function from the X-ray dye (common although usually transient)
- Other complications that are rare but serious include a ruptured artery, injury to the kidneys (may be permanent requiring dialysis), paralysis, stroke, infection of the graft and delayed rupture of the aortic aneurysm and death

There are no known additional risks of using Cydar EV in comparison to standard treatment. Interruption of the internet connection during the procedure is possible but rare (<0.001%).

2.3 OBJECTIVES

The overarching aim of this trial is to evaluate the clinical, technical and cost-effectiveness of a novel type of medical device comprised real-time cloud computing, AI and computer vision (Cydar EV) compared to standard treatment in endovascular aortic aneurysm repair.

2.3.1 PRIMARY OBJECTIVE

To assess the effect of Cydar EV on procedure time in comparison to standard treatment in endovascular aortic aneurysm repair

2.3.2 SECONDARY OBJECTIVES

The secondary objectives of this study are to evaluate:

1. **Procedural efficiency**, as assessed by:
   Anaesthetic duration
   X-ray dose per procedure
   Contrast dose per procedure
   Consumable use per procedure

2. **Technical effectiveness**, as assessed by proximal and distal seal zones at least 10mm and no evidence of endoleak

3. **Patient outcomes**, as assessed by:
   Length of ITU admission
   Length of HDU admission
   Post-operative length of hospital stay
   30-day mortality
   Re-intervention – primary hospital visit / further admission (HRG/procedure code)
   Adverse events (category, LoS, HDU, ITU, general ward)
   Quality of life (EQ5D)

4. **Cost effectiveness,** as assessed by:
   Total resource use and costs
   Quality-Adjusted Life Years (QALYs)
   Incremental cost per QALY

2.4 TRIAL DESIGN

Multi-centre, open label, two-armed, parallel groups randomised controlled clinical trial that assigns patients with a clinical diagnosis of abdominal aortic aneurysm and/or thoraco-abdominal aneurysm suitable and fit for endovascular treatment, to either repair using standard treatment or treatment using Cydar-EV.

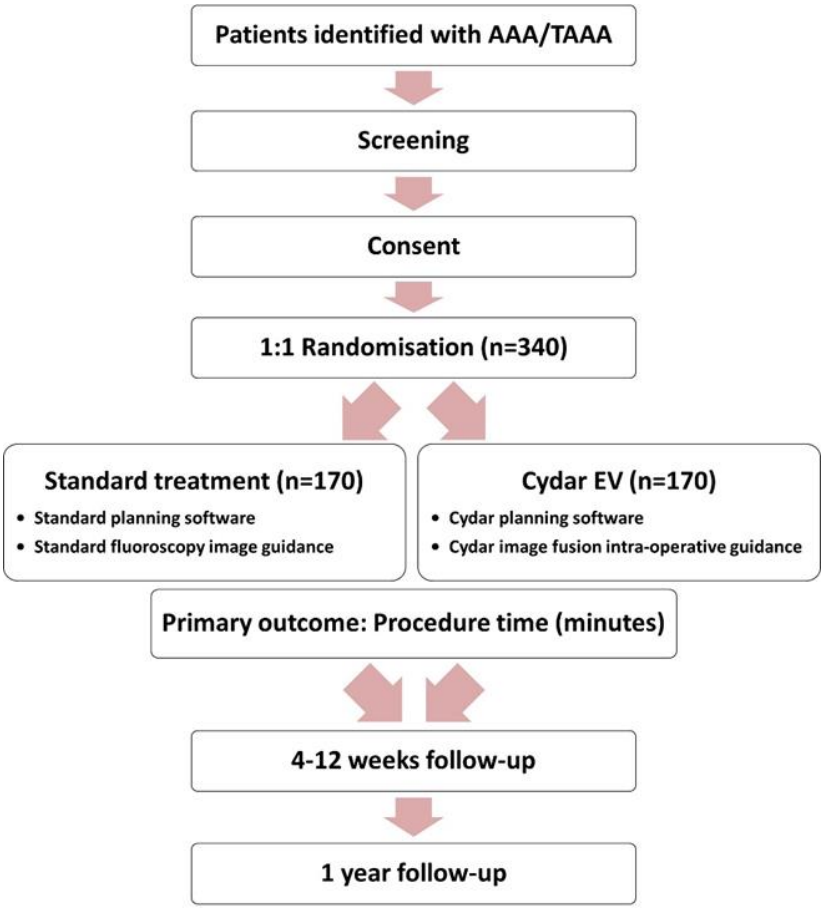

Figure 4. Flow diagram of ARIA trial design

3. PARTICIPANTS

3.1 STUDY SETTING & RECRUITMENT

The trial will be conducted in 10 centres in the UK over 36 months. 340 patients will be recruited.

Asymptomatic patients will be identified for inclusion at the time of their clinic appointment while symptomatic or rupture patients will be identified for inclusion at the time of presentation. Patients that present on an urgent or emergency basis will be required to provide written informed consent, after either reading the patient information leaflet or it being read to them by an individual independent to the trial team and the patient's family.

Expected recruiting sites are

1. Guy's and St Thomas' NHS Foundation Trust, London
2. Imperial Healthcare NHS Trust, London
3. Leeds Teaching Hospitals NHS Trust
4. Liverpool University Hospitals NHS Trust
5. Brighton and Sussex University Hospitals
6. Frimley Health NHS Foundation Trust
7. University Hospital Southampton
8. University Hospital Derby
9. Manchester University NHS Foundation Trust
10. North Bristol NHS Foundation Trust

Relevant study site staff obtaining consent and collecting outcome data will be trained in Good Clinical Practice.

3.2 ELIGIBILITY CRITERIA

3.2.1 INCLUSION CRITERIA

1. Clinical diagnosis of AAA or TAAA suitable for endovascular treatment, as determined by CT imaging and a local treating team multidisciplinary review.
2. Patient is confirmed fit for endovascular repair as determined by the operating team
3. CT imaging must be in accordance with 'Cydar EV: Instructions for Use' i.e. scans should have the same slice thickness and intervals as the original scan acquisition, must not have any missing slices or discontinuities, must include the pelvis and whole vertebrae including the spinous processes and must not use gantry tilt (this will be done post-consent)
4. Written informed consent (patients lacking capacity or unable to speak English will not be enrolled)
5. Age 18 years and above at the time of consent

3.2.2 EXCLUSION CRITERIA

1. Patients unable to provide written informed consent

3.3 INFORMED CONSENT

Written informed consent will be obtained by the Principal Investigator or designee at each site (as listed in the Delegation Log), following explanation of the trial procedures. Discussions about trial participation may take place during an in-person consultation or remotely, i.e. during a telephone or video consultation. The trial must be discussed in detail with the patient, and the patient provided with a copy of the Patient Information Sheet. Patients should be offered sufficient time to consider the trial, allowing time for discussion with family/friends/medical doctor. The patient must be given the opportunity to ask questions and to be satisfied with the responses prior to consent being given. Participant Information Sheet can be sent by post or email ahead of the in-person or remote consultation. Full consent must be given in writing.

Written informed consent will be signed before any study specific procedures are undertaken. The local Principal Investigator or designee receiving consent must countersign the consent form. The Patient Information Sheet and Consent Form are available in electronic format to facilitate printing onto local headed paper. Signed original consent forms must be retained on site and should be stored in the trial site file with a copy filed in the patient's hospital notes. A copy of the fully signed consent form and, where applicable, the documentation of verbal consent form, must be given to the patient. Sites must ensure that patients' participation in the trial is recorded in the patient notes.If the Patient Information Sheet and/or Consent Form are modified during the course of the trial, sites will be notified of any required procedure to follow for patients already consented.

3.3.1 POSTAL CONSENT

Postal consent can also be used alongside a telephone conversation with the patient, where a face-to-face consultation is not possible (e.g. where clinics are being held remotely due to COVID-19). In this circumstance, the patient will be provided with a study Patient Information Sheet, postal consent form, return envelope and invitation letter in the post. Within a few days of posting the study information, a member of the local research team will contact the patient via telephone to ask if they are interested in participation. If so, the patient will have the opportunity to ask any questions and discuss their participation. If the patient is happy to enter the study, they will complete the postal consent form and return this to the local research team in the provided

envelope. Randomisation will only take place once the completed consent form has been received and countersigned, as close as possible to the day of surgery.

4. INTERVENTIONS

For all patients the type of fluoroscopy imaging system used (with associated settings) and type of planning software(s) used and timing of each (MDT, planning session etc.) will be noted in the caset record form.

4.1 EXPLANATION FOR THE CHOICE OF COMPARATORS

Standard treatment is the use of standard endovascular aortic aneurysm repair planning software and X-ray fluoroscopy imaging during endovascular repair. These represent the reference standard in England.

4.2 INTERVENTION AND COMPARATOR DESCRIPTION

4.2.1 INTERVENTION DESCRIPTION

Patients will undergo endovascular aneurysm repair guided by Cydar-EV. Cydar EV provides tools to:

- Import and visualise CT data
- Segment and annotate vascular anatomy from CT data
- Place and edit virtual guidewires and measure lengths on them
- Make measurements of anatomical structures on planar sections of the CT data
- Produce an operative plan from measurements and segmentation of preoperative vessel anatomy
- Overlay planning information such as preoperative vessel anatomy onto live fluoroscopic images, aligned based on the position of anatomical features present in both
- Non-rigidly transform the visualisation of anatomy when intra-operative vessel deformation is observed
- Post-operatively review data relating to procedures where the system was used

The version of the product used will be noted.

4.2.2 INTERVENTION TRAINING

Cydar-supervised training cases will be performed at each site to demonstrate and document surgeon competence in using Cydar EV, as per the Cydar CE marking and Quality Assurance procedures, and to ensure the sites are trained in the use of the data entry platform and procedures for the trial. A maximum of 3 clinicians will be allowed to undertake the procedures per site and each must undertake a minimum of 3 training cases and be signed off by the Cydar team as competent. Written confirmation of surgeon competence will be kept in the trial master file.

4.2.3 COMPARATOR DESCRIPTION

Patients will undergo endovascular aneurysm repair using standard technology and X-ray fluoroscopy imaging intra-operatively as defined under standard treatment above. The CT imaging for the patients randomised to standard treatment will be uploaded to Cydar EV at the time of randomisation, in case of cross-over (see section 4.5).

4.2.4 INTERVENTION DELIVERY

Procedures will be performed under local, regional or general anaesthesia (likely ratio: 1:1:8). Procedures can be undertaken using either a mobile C-arm in a surgical operating theatre, a dedicated fixed fluoroscopy set, or in a hybrid operating room. Patients may go to the ward, HDU or ITU according to local protocol.

Routine pre-operative CT aortic imaging will be used to determine general suitability for endovascular repair, including assessment of landing zones for fixation and sealing, and procedure type and device

selection. After randomisation in all patients the pre-randomisation CT images will be uploaded to Cydar EV.

In the Cydar limb of the trial, Cydar EV will be used to plan the procedure including making appropriate measurements, map creation, procedural annotations, and device selection/verification. At operation, the Cydar equipment will be set-up and switched on in theatre prior to 'knife-to-skin'. Participant's information will have been pre-loaded to the system (according to 'Cydar EV: Instructions for Use') and will be available for selection. The machine must be positioned according to surgeon preference. Machine use will be recorded on the Cydar intervention record form. The patient's information will be loaded on the system anytime up until the day of surgery prior to induction of the anaesthetic.

4.3 INTERVENTON ACCOUNTABILITY

Details of the participant being treated must be selected on the Cydar system at the start of the procedure.

4.4 INTERVENTION MAINTENANCE

Cydar will liaise directly with recruiting sites to ensure the Cydar technology is correctly installed and managed.

4.5 CRITERIA FOR DISCONTINUING OR MODIFYING ALLOCATED INTERVENTIONS

Cross-over to Cydar EV will only be permitted in the context of a procedure duration greater than 8 hours or where the patient is in extremis and the surgeon believes that using the Cydar technology may be beneficial to complete the procedure. In these circumstances, the Cydar equipment may be used at the discretion of the operating surgeon and this information must be captured in the Source Data Worksheets and transcribed to the MACRO EDC system.

4.6 STRATEGIES TO IMPROVE ADHERENCE TO INTERVENTIONS

Reasons for non-compliance could include Cydar EV device failure, internet failure, surgeon error, failure to communicate correct randomisation allocation to the surgeon, cross-over (section 4.5), and failure to upload images to Cydar EV, or a non-Cydar-trained surgeon performs the procedure.

The patient could only impact compliance if they express a wish to withdraw between randomisation and surgical procedure or in the event of death.

All study sites will receive training in the use of Cydar-EV and will require all users mandatory training sign off of the CYD 7.5 -205 form to include training cases prior to the study commencement.

Training cases will include all research data collection on the day of the procedure when possible, to ensure local processes are working efficiently prior to randomising the first trial participant.

4.7 RELEVANT CONCOMITANT CARE PERMITTED OR PROHIBITED DURING THE TRIAL

No restriction on concomitant care during the trial.

4.8 PROVISIONS FOR POST-TRIAL CARE

Post-trial care will follow routine NHS practice. In centres where ultrasound imaging is used as the 4–12-week follow-up and/or at one year, these patients will be required to undergo CT angiography. This deviation from standard care has been noted in the application for ethical approval for the study.

5. OUTCOMES

5.1 PRIMARY OUTCOME

Primary efficacy parameter of the study is procedure duration, measured as the time between insertion of the first wire (after percutaneous access achieved, if applicable) at the beginning of the endovascular procedure to the last frame of the completion angiogram. This will be recorded (in minutes) at the time of the procedure by the local research team.

5.2 SECONDARY OUTCOMES

1. Procedural efficiency**:**
   a) Anaesthetic duration – the time between the beginning of induction and the end of emergence. This will be documented at the time of the procedure by the local research team in minutes.
   b) X-ray dose per procedure –fluoroscopy time (FT) (seconds), dose area product (DAP) ($Gy.cm^2$) and cumulative air kerma (CAK) (mGy) should be recorded and documented at the time of the procedure by the local research team. The imaging system used should also be recorded.
   c) Contrast dose per procedure – the volume (ml) and concentration (mgI/ml) of the iodinated contrast material used should be recorded by the local research team at the time of the procedure in minutes.
   d) Consumable use in the operating theatre for endovascular aortic aneurysm repair – name of device, unit and quantity used, blood products used; details to be completed by nurse in the operating theatre or research nurse at the time of the procedure using a Source Data Worksheet.

2. Technical success:
   e) Proximal and distal seal zone at least 10mm and no evidence of endoleak. This will be documented by the imaging CoreLab team on review of the CT images acquired post-operatively and at 4-12 weeks and at 52 weeks.

3. Patient outcomes:
   f) Length of ITU/HDU admission – date and time from admission to date and time of discharge from ITU/HDU; documented by the local research team during the time of admission; ITU and HDU admissions should be documented separately
   g) Postoperative length of hospital stay – date of procedure to date of discharge from hospital (nights); documented by the local research team during the time of admission.
   h) 30-day mortality – death of the participant within 30 days of the primary procedure; documented by the local research team; to include date of death (dd/mm/yy) and cause.
   i) Re-intervention – any procedure open surgical or endovascular undertaken within one year of the primary endovascular aortic aneurysm repair procedure (binary outcome). The type, timing and number of procedures should also be recorded by the local research team.
   j) Adverse events – hospitalisation for any reason within one year of the primary endovascular aortic aneurysm repair; the type of event should be documented and classified as one of the following: musculoskeletal, urological, neurological, ophthalmological, cardiovascular, gastro-intestinal, hepato-pancreato-biliary, dermatological or other by the local research team, with information captured to understand if linked to re-intervention (section 'i' above). For each hospitalisation the following should also be captured:
      i. Day case, Elective, Non-elective
      ii. Length of hospital stay - date of admission to date of discharge (nights)
      iii. Length of ITU/HDU admission (if applicable) - date and time from admission to date and time of discharge from ITU/HDU; ITU and HDU admissions should be documented seperately
   k) Quality of life – differences in quality of life between intervention and the comparator group, and changes in quality of life post-surgery will be measured using data from the patient-completed EQ5D-3L (15) instrument. EQ-5D-3L is a validated measure of health-related quality of life, consisting of a five-dimension health status classification system and a separate visual analogue scale. EQ-5D-3L data will be obtained through face-to-face or telephone interview

with the participant at baseline, pre-discharge, 4-12 weeks and at 12-months follow up. Patients will complete the questionnaires with the support of the local research team

4. Cost effectiveness, as assessed by:

l) Total resource use and costs
m) Quality-Adjusted Life Years (QALYs) - Quality of life will be measured by the EQ-5D-3L instrument as described above. In order to be used in the calculation of quality-adjusted life years (QALYs), the EQ-5D-3L dimension scores will be converted to utilities using the relevant value set for England. Quality-adjusted life years (QALYs) gained in both groups, over the time horizon of the trial, will be calculated using the area under the curve method.
o) Incremental cost per QALY

5.3 PARTICIPANT TIMELINE

Timepoint	Screening	Randomisation	Pre-surgery	Surgery	Pre-discharge	Week 4-12	Week 52	Ongoing
Registration Form & Consent	**X**							
Check Inclusion Criteria (if CT Image suitable for CYDAR)	**X**							
Full medical history and baseline demographics (smoking, ethnicity, routine bloods)	**X**							
EQ-5D-3L	**X**		**X***		**X**	**X**	**X**	
Intra-operative data				**X**				
ITU/HDU admission record					**X**			
Hospital admission record					**X**			
Post-operative CT aorta assessment						**X**	**X**	
30 day mortality				X	X	**X**		
Re-intervention record								**X**
Adverse event log								**X**
Status								**X**
Withdrawal								**X**
Concomitant treatment								**X**

**If more than 28 days since last EQ5D-3L*

Table 1. Schedule of events

5.3.1 SCREENING

Participants will be screened for the study after signing an ethically approved Informed Consent Form.

Patient will undergo a baseline CT as per normal clinical care, and in accordance with 'Cydar EV: Instructions for Use'. These images will be used to plan the endovascular case and be used for model generation after randomisation. Baseline measures will be collected as per Table 1, Schedule of events.

5.3.2 RANDOMISATION

The randomisation procedure will commence after informed consent has been given and as close to the procedure as possible. All participants will have their inclusion and exclusion criteria checked on the day of randomisation. A full medical history will be taken and an EQ-5D-3L questionnaire will be completed. EQ-5D-3L and other screening assessments will be repeated if the baseline assessment was taken >1month since the previous basline assessment (see 5.3 Particpant timelines).

The consent form and randomisation result must be made available for the operating surgeon to review on the day of surgery. The research team will complete the relevant study procedures and data collection using the Source Data Worksheets provided.

5.3.3 PRE-DISCHARGE

Data will be collected as per table 1 above in the post-operative period. Every effort will be made to collect the data via the self-complete version of the EQ-5D-3L questionnaire. EQ-5D-3L telephone interview will be used on the day of discharge, should it need to be done by telephone. In the event the data cannot be collected on the day of discharge, attempts will be made to collect the data by telephone as soon as possible thereafter.

5.3.4 WEEK 4-12 POST-RANDOMISATION

Participants will return for follow up between 4 and 12 weeks post-operatively. Data will be collected as per table 1 above.

5.3.5 WEEK 52 POST-RANDOMISATION / END OF STUDY VISIT

Participants will return for follow up between 48 and 56 weeks post-operatively. Data will be collected as per table 1 above.

6. ASSIGNMENT OF INTERVENTIONS: ALLOCATION

6.1 SEQUENCE GENERATION

6.1.1 METHOD OF ALLOCATION SEQUENCE

The allocation sequence will be generated dynamically using the method of minimisation.

6.1.2 STRATIFICATION FACTORS (WHERE MINIMIZATION OR STRATIFIED BLOCK)

Name of stratification	Stratification groups
Surgeon	Surgeons from all sites 01, 02, 03, 04 etc.
Procedure urgency	01. Emergency | 02. Elective
Procedure type	01. Simple (repair of infra-renal aneurysm +/- internal iliac embolisation)

	02 Complex (all other types of AAA and TAAA repair, to include branched and fenestrated devices)

Table 2. Stratification factors

Minimisation will be balanced using the factors detailed in table 2.

6.2 CONCEALMENT MECHANISM

Minimisation will incorporate a random component to assure allocation concealment.

6.3 IMPLEMENTATION

6.3.1 ALLOCATION SEQUENCE GENERATION

Implemented via the KCTU web-based randomisation system.

6.3.2 RANDOMISATION OF PATIENTS

Participants will be randomised post-consent, after checking their eligibility. The signed consent form must be made available for the operating team to review, along with the randomisation result.

6.3.3 ASSIGNMENT OF PARTICIPANTS TO INTERVENTIONS

Participants will be randomised to Cydar-EV image fusion for guidance or standard imaging techniques in a ratio of 1:1 post-consent and confirmation of eligibility.

6.3.4 RANDOMISATION PROCEDURE

Study site staff delegated to undertake the randomisation procedure will be sent unique login details. Requests for user access is via the KCTU ARIA Trial Manager.

- Prior to randomisation but after consent, obtain a unique Patient Identification Number (PIN) from the Elsevier MACRO EDC system.
- Ensure the initials, dob and stratification information above for the participant are available.
- Log on to the website: go to www.ctu.co.uk, click 'randomisation' and select ARIA
- Enter your username and password
- Click on the Randomisation tab at the top of the page and choose *Randomisation Request*
- The study site selection will open. Choose the relevant site and click on **Randomise.**
- Under Profile Details, enter the:
    - Participant Identification Number (PIN). This is a 6-digit number which is obtained from MACRO.
    - Participants initials. This will consist of 2 or 3 letters. Enter in upper case. Do not put a dash between the letters.
    - Participants date of birth (DOB).
- Under Data Collection, answer the question with a Yes or No. To answer the question, click on Edit, choose the appropriate response and then save. Once the question is answered click on submit.
- You will receive a randomisation notification by email. This will provide details of the treatment arm assigned to the participant.
- Print a copy for the surgeon treating the participant and file a copy in the Investigator Site File.
- Show the randomisation email to the surgeon, along with a copy of the signed consent form.

6.4 Blinding Status of Researchers

Individual blinding status	Blinded	Unblinded
Chief Investigator	x	
Principal Investigators at site		x
Trial Manager/monitor		x
Senior Statistician	x	
Junior Statistician		x
Independent image reader	x	
Cydar project manager		x
Trial Participants		x
Outcome Assessors/Research Nurses		x
Treating clinicians		x
Trial Steering Committee (TSC)	x	
Data Monitoring Committee (DMC)		x

**For roles not listed please refer to study delegation logs.*

Table 3. Blinding status of research team

The planned blinding of the research team and committees is detailed in table 3 above.

6.5 Procedure for unblinding if needed

Emergency unblinding is not required in this study.

7. Laboratory Tests

No laboratory tests outside those needed for routine clinical care will be required for the trial. In the event of abnormal results, consideration should be given to recording an adverse event relating to the abnormal results.

8. Withdrawal

8.1 Procedure for withdrawal

Participants have the right to withdraw from the study at any time for any reason.

The investigator also has the right to withdraw patients from the study for any reason.

An excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Should a patient decide after randomisation that they do not wish to receive the allocated treatment:

- if randomised to Cydar-EV the participant will be treated with standard X-ray fluoroscopy imaging alone
- if randomised to treatment as usual, the participant cannot be offered Cydar-EV

Efforts will be made to continue to obtain follow-up data to month 12, even if the participant did not receive their randomised allocation and with the permission of the patient. Patients randomised and not treated will be excluded from the analysis.

If the participant refuses to undergo AAA repair after randomisation, efforts will be made to continue to obtain follow-up data to month 12.

Should a patient decide to withdraw from follow up data collection, all efforts will be made to report the reason for withdrawal as thoroughly as possible.

9. DATA COLLECTION AND MANAGEMENT

9.1 PLANS FOR ASSESSMENT AND COLLECTION OF OUTCOMES

9.1.1 SOURCE DATA WORKSHEETS

Sites will be provided with source data worksheets containing the relevant data required to be transcribed to the MACRO EDC system and the randomisation system. Training will be provided by the ARIA Trial Manager.

9.1.2 CT AORTA IMAGE READING

CT imaging data will be uploaded to the ARIA trial image anlysis virtual CoreLab, which is a cloud-based system. Images will be read in a blinded manner by the Chief Investigator (KCL) and Research Fellow (KCL). They will securely log into the cloud-based Cydar vault where the CT image data will be housed, and analyse the pre- and post-operative CTs.. Data from this analysis will be entered onto the MACRO EDC system inaccessible to sites. Twenty image data sets will be used to assess the inter- and intra- observer repeatability coefficients for each of the anatomical variables in the CT read protocol.

9.2 PLANS TO PROMOTE PARTICIPANT RETENTION AND COMPLETE FOLLOW-UP

Participants will be seen in routine NHS follow up clinics. If visits have not been scheduled by the end of the week 4-12 and week 52 visit windows, the study site staff will contact the participants by telephone to collect the EQ-5D (telephone version) and attempts will continue to schedule a follow up visit. Data will be collected and entered, even if follow up clinic assessments are outside the optimal visit windows.

9.3 DATA MANAGEMENT

There are two datasets in the trial; the KCTU randomisation dataset and the KCTU Elsevier Macro 4 EDC system dataset. The CI will act as custodian for the trial data.

9.3.1 DATA ENTRY

Randomisation data will be entered as per section 6.3.4.

Study site staff will be delegated by the site PI to access the eCRF and randomisation systems via a Study Site Delegation Log. The request for user access must go to the ARIA Trial Manager, who will submit user requests for all sites to the KCTU team upon receipt of completed Study Site Delegation Logs. Requests for user access will be processed within a maximum of 5 working days.

Authorised staff at sites will transcribe baseline and follow up data from the source data worksheets (SDWs) by going to www.ctu.co.uk and clicking the link to access Macro Version 4. A full audit trail of data entry and any subsequent changes to entered data will be automatically date and time stamped, alongside information about the user making the entry/changes within the system.

Training videos for data entry staff, study site monitors and trial managers are available at www.ctu.co.uk under the 'Training' section. Users can self-register and should select the MACRO related training videos.

9.3.2 SECURITY (EDC)

The CI delegate (e.g Trial Manager) will request usernames and passwords from KCTU on behalf of recruiting sites. Systems access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested and a request for access to be revoked must be requested when staff members leave the project.

Participant initials and partial date of birth (mm/yyyy) will be entered into the systems. Hospital number, email address, participant names and addresses, and full postcodes will not be entered into the EDC system. Trial sites will maintain a master patient log linking participant identifiers to study numbers. No data will be entered unless a participant has signed a consent form to participate in the trial.

9.3.3 DATA QUALITY PROCESSES

At the database design stage, validations will be programmed into the systems to minimise data entry errors by querying the data entered in real time with sites.

The CI team will undertake appropriate reviews of the entered data, in consultation with the project analyst, where appropriate for the purpose of data cleaning and will request amendments to the MACRO EDC system data as required. No data will be amended independently of the study site responsible for entering the data.

No data can be amended in the randomsation system, however CI or delegate (e.g. Trial Manager) may request King's Clinical Trials Unit to add notes against individual participant entries to clarify data entry errors. Any errors should be reported by site staff to the Trial Manager as soon as possible once they are detected. The trial manager will onward report errors to KCTU and retain records in the TMF.

The KCTU will provide the Trial Manager with Data Management Plans for both the Elsevier Macro EDC system and the randomisation system once the systems are made live. Those documents will be filed in the Trial Master File.

A regular Data Management Report will be produced by a grant-funded KCTU data manager and passed to the Trial Manager, who will raise Data Clarification Requests (DCRs) with sites in the EDC system. Study sites will periodically review raised DCR's and respond to the queries raised.

Site monitoring visits will be conducted by the Trial Manager. The first monitoring visit will occur 3 months after the first patient has been enrolled and then at least once a year to review adherence to the protocol, consent procedures, and to raise any queries with sites via the Source Data Verification (SDV) function. The

Trial Manager, CI and the CTU will create a study specific standard operating procedure that guides the trial manager's monitoring processes (Risk-based Monitoring Plan).

We will ask the DMC to take on the role of monitoring patients at recruitment. Our KCTU has Standard operating procedures that guide the trial statistician's reporting to the DMC.

9.3.4 Database Lock

At the end of the trial, the site PI's will review all the data for each participant in the MACRO EDC system and provide electronic sign-off to verify that all the data are complete and correct.

The trial manager will confirm all checks are complete and all monitors queries have been resolved prior to database lock. At this point, with the agreement of the senior statistician, all data can be formally locked for analysis.

When the final data extract is requested, KCTU will remove all data entry user access prior to data extract and will retain only 'monitor' access for site PI's and other relevant individuals.

Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will onward distribute to sites as appropriate. Once sites have received copies of their individual datasets and confirmation of receipt has been received, the Trial Manager will request that all user access is removed from the MACRO EDC system. A copy of the database is to be stored in the TMF

9.4 End of trial

The end of the trial will be defined as last patient last visit.

9.5 Confidentiality

When consent forms are signed, a copy will be provided to the patient, a copy will be filed in the medical records and the original will be retained in the Investigator Site File. Participant initials and date of birth will be entered into the study database, but no more identifying information will be collected outside the recruiting study site.

Within site, an Investigator Site File will be maintained by the site PI. Participants will be fully identifiable within these files.

When the study is complete, a data sharing dataset will be created from the raw data by the study analyst, which will not include patient initials, date of birth or any other identifiable data and study ID will be altered so that individuals are not recognisable from the dataset.

10. Statistical methods

10.1 Sample size justification

We are not aware of any known minimum clinically important difference (MCID) and part of the aim of the study is to better characterise the clinical benefit to patients. The study is instead powered on the basis of a minimum economically meaningful difference. Previous work at Duke (11) reported data on the primary

outcome, procedure time, and found a mean difference of 22.5 minutes (17%) for patients with an abdominal aortic aneurysm treated with Cydar-EV 109.6 (34.2) and standard 2D fluoroscopy imaging 132.1 (69.2) minutes. This is a meaningful difference in the NHS context as this time reduction per case would allow four rather than three EVAR procedures to be performed per day, which is a productivity increase of 33% at the same capacity. The SD for procedure time increases with the mean and so we have assumed a t-test for ratio of means 1.2 (fold change), assuming a lognormal distribution for the calculations. Therefore, a sample size of 153 patients per arm with a 1:1 allocation ratio (2 x 153 = 306) would give us 90% power at the 2-sided 5% significance level to detect this difference (PASS 15 Power Analysis and Sample Size Software (2017)). Since our primary outcome measure requires the procedure to be completed, we need to inflate the sample size for possible: i. loss post randomisation, pre-procedure (est 7.5%); and ii. on-table death and cross-overs (where surgeons may use the intervention in a control arm patient (see section 4.5) and additional assistance is required to complete the operation) (est 2.5%). These inflate the sample size to 170 per arm. The final randomisation target is therefore 2 x 170 = 340. The Duke data also showed using Cydar-EV in TAAA showed larger reductions in operating time than for AAA. We have powered on the more conservative difference since the relative proportions of AAA/TAAA patients anticipated in our proposed trial is unknown.

10.2 STATISTICAL METHODS FOR PRIMARY AND SECONDARY OUTCOMES

The analyses will be carried out according to the statistical analysis plan written before any outcome data are inspected. A CONSORT diagram will describe the patient flow and exclusions. Baseline demographic and clinical data will be summarised by randomisation trial arm.

10.2.1 STATISTICAL METHODS FOR PRIMARY OUTCOME

As the primary outcome is procedure duration and we envisage 7.5% loss of patients between randomisation and procedure, the primary analysis will be a per-protocol (PP) analysis based on procedure time. The primary analysis will be conducted after completion of first follow-up (at 4-12 weeks) which will include procedure time as well as the secondary outcome data available at this time. Sensitivity analysis with multiple imputation for missing data will also be conducted alongside the per-protocol analysis. No significance tests will be performed for baseline comparison. The primary outcome measure is likely to have a skewed distribution and therefore if necessary and possible the data will be normalised using an appropriate transformation. The data will then be analysed using linear regression techniques with stratification (minimisation) factors included as covariates. If a suitable transformation cannot be found the data will be analysed using quantile regression to allow us to include the addition of the stratification factors as covariates.

10.2.2 STATISTICAL METHODS FOR SECONDARY OUTCOMES

A similar analysis will be undertaken for the secondary outcomes including quality of life scores. Binary outcomes will be compared between arms using logistic regression adjusting for stratification factors. Outcomes will be reported as adjusted differences in means (or median) or odds ratios for continuous and binary data respectively. All tests will be two sided and will be assessed at the 5 % significance level. Safety outcomes will be reported as patient proportions and rates within and between arms with 95 % confidence intervals using exact methods where appropriate.

10.3 INTERIM ANALYSES (STATISTICAL)

There will be no planned formal interim analyses of the primary and secondary outcomes. However, we will conduct further analyses of secondary outcomes at the completion of 52 weeks follow-up for all the patients.

10.4 METHODS FOR ADDITIONAL ANALYSES (E.G. SUBGROUP ANALYSES)

- Image analysis – CoreLab – analysis of technical outcome

CT image data acquired pre-operatively and at the two post-operative intervals will be uploaded into the CoreLab system for analysis. All image data will be reviewed independently by two experienced clinicians blinded to the image guidance method used during endovascular aortic repair. Anatomical measurements will be performed with central luminal line reconstructions using dedicated software. Measurements will include: aneurysm size, aortic neck (diameter, length,α and β angulation), iliac diameter and stenosis, distance from the lowermost renal artery to the beginning of the covered part of the endograft; the length of the proximal sealing zone, length of the distal sealing zone and detection of endoleak. Technical success will be defined as proximal and distal seal zone at least 10mm with no evidence of endoleak (2).

- Health economic analysis

The design, conduct and reporting of the cost-effectiveness analysis will be undertaken in accordance with the requirements of the National Institute for Health and Care Excellence (NICE) reference case. The perspective of the analysis will be from the perspective of the UK NHS. The health economic analysis will evaluate:

a) The direct NHS costs over the 12-month follow up period of using endovascular treatment augmented with Cydar-EV compared to endovascular treatment using standard X-ray fluoroscopy imaging alone.
b) A 'within trial' analysis of the cost-effectiveness of using Cydar-EV, compared to standard fluoroscopy, over a 12-month follow up.
c) An exploratory 'model based' analysis of the cost-effectiveness of using Cydar-EV, compared to standard fluroscopy, over a lifetime time horizon.

The evaluation of the direct costs of using Cydar-EV, in comparison to standard fluoroscopy, will be assessed over the time horizon of the trial (12-months). Resource utilisation collected during the initial index admission will include the duration of the initial procedure (and other aspects of procedural efficiency including anaesthetic duration, X-ray and contrast dose), any additional procedures and consumables and the duration of the initial index admission (including any periods in ITU/HDU). Information on post-discharge resource use up to week 52 will also be collected. Post-discharge resource use collected in the trial will include re-intervention (including type of procedure), inpatient readmissions (day case, elective and non-elective inpatient stay) and length of subsequent admissions, including any periods in ITU/HDU. Resources will be costed using standard national NHS tariffs such as the National Schedule of Reference Costs and the Unit Costs of Health and Social care. In addition, the cost of the initial set-up (including training for technical, engineering and clinical staff), and the annual costs of software licences and maintenance for Cydar-EV will also be included.

Quality of life will be measured by the EQ-5D-3L instrument. EQ-5D-3L is a validated measure of health-related quality of life, consisting of a five-dimension health status classification system and a separate visual analogue scale. EQ-5D-3L data will be obtained through face-to-face or telephone interview with the participant at baseline, pre-discharge, 4-12 weeks and at 12-months follow up. In order to be used in the calculation of quality-adjusted life years (QALYs), the EQ-5D-3L dimension scores will be converted to utilities using the relevant value set for England. Quality-adjusted life years (QALYs) gained in both groups, over the time horizon of the trial, will be calculated using the area under the curve method.

Cost and QALYs will be analysed as intention to treat and missing data will be imputed using multiple imputation. All statistical tests and CIs will be two sided, with statistical significance inferred at the 0.05 level. Potential differences in costs and health outcomes between the two groups and the 95% CIs will be

presented. Since costs and QALYs are usually non-normally distributed, we will use generalised linear models for adjustment of baseline covariates. Mean values of cost and QALYs will be used to calculate the incremental cost-effectiveness ratio (ICER) based on a 'within trial' analysis over the 12-month follow up. We will use the bootstrapping percentile method to identify the sampling uncertainty of ICER. Cost-effective planes and cost-effectiveness acceptability curves will also be estimated to display and interpret statistical uncertainty and economic decision-making according to the maximum willingness to pay for a QALY.

The primary health economic analysis will focus on the estimation of the 'within trial' cost-effectiveness over the 12-month trial period using assessments of the ICER. If there are found to be differences between the use of Cydar-EV and standard fluoroscopy which are expected to persist beyond the trial period, for example as a result of differences in mortality or the rate of re-intervention, these differences will need to be estimated over the remaining lifetime of patients to appropriately reflect the impact on these on cost-effectiveness. To do so, an exploratory 'model based' analysis will be used to extend the time horizon to a lifetime and to synthesise evidence from the trial with external evidence to estimate the impacts over the remaining lifetime of patients in terms of QALYs, and health care costs. We will explore implications over a longer time horizon using sensitivity and scenario analyses to evaluate the impact of alternative model assumptions.

System efficiency

A key link between the primary outcome measure (procedure time) and the cost-effectiveness of the intervention is measured in terms of improvements in the planning and utilisation of operating theatre resources. The average procedure time in England for a standard EVAR procedure is 110 minutes. Assuming operating theatre capacity of 420 minutes (7 hours) daily, it would currently be possible to complete three EVAR procedures daily with an allowance for turn-around time. Assuming a similar reduction in procedure time as was observed in the Duke University study (18%), with Cydar-EV it would be possible to complete four procedures daily with the same capacity, an increase of 33%. The HRG EVAR tariff can be used as a proxy for the value to the NHS of the additional procedure. Because Cydar-EV is also expected to reduce variability in procedure times there should also be a reduction in the number of cancelled operations because of over-runs, and more predictability in waiting list planning and bed occupancy.

We will explore the implications of improvements in system efficiency by comparing the distributions of procedure times for Cydar-EV and standard fluoroscopy and assessing these against current capacity constraints (e.g. operating theatre capacity, turn-around times etc). We will also assess the potential implications of any 'learning curve' effects in the procedure times for Cydar-EV. We will use these analyses to develop a series of scenarios which capture the potential impact on Cydar-EV on improving the planning and utilisation of operating resources in terms of costs and potential health consequences. The impact of these scenarios on the overall cost-effectiveness of Cydar-EV will be assessed using sensitivity analysis.

Value of information

Decisions based on 12-month follow up (and the exploratory model based analysis) for Cydar-EV will be subject to uncertainty and there will always be a chance that the wrong decision could be made. If the wrong decision is made, there will be costs in terms of health benefit and resources forgone. The maximum amount the NHS should be willing to invest to further reduce remaining uncertainty in the decision can be informed by the expected value of perfect information (EVPI). EVPI evaluates the expected cost of current decision uncertainty, based on results from the ARIA trial, by accounting for both the probability that a decision based on existing evidence is wrong and for the magnitude of the consequences of making the wrong decision.

The EVPI estimates will be used to assess the potential value of further research and to inform future research priorities. EVPI also represents the maximum amount that a decision-maker should be willing to pay for additional evidence to inform this decision in the future. EVPI provides an upper bound on the value of additional research. This valuation provides an initial hurdle, acting as a necessary requirement for determining the potential efficiency of further primary research. Applying this decision rule, additional research should only be considered if the EVPI exceeds the expected cost of the research.

10.5 METHODS TO HANDLE MISSING DATA

Missingness will be reported and reasons for missingness explored. Although a low percentage of missing data is anticipated a sensitivity analysis of the primary outcome will be undertaken in order to assess the impact of the exclusion of participants with missing intraoperative data in the primary analysis. In this view of the sample size, a modelling approach will be taken rather than multiple imputation.

10.6 POPULATIONS UNDER INVESTIGATION

Patients with a clinical diagnosis of AAA or TAAA suitable and fit for endovascular treatment, as determined by CT imaging and a local multidisciplinary review will be eligible for inclusion. The CT scan must meet requirements in 'Cydar EV: Instructions for Use'. Patients under the age of 18 years will be excluded. Written informed consent will be required from all participants (patients treated in an emergency setting that are not able to consent will not be included).

10.7 METHODS TO HANDLE COMPLIANCE

Compliance with intervention will be recorded in the source data worksheets and transcribed to the EDC system. Reasons for non-compliance would include device failure, surgeon error or failure to communicate correct randomisation allocation to the surgeon.

The patient could only impact compliance if they express a wish to withdraw between randomisation and surgical procedure.

10.8 SENSITIVITY ANALYSIS

For primary analysis, although a low percentage of missing data is anticipated a sensitivity analysis of the primary outcome will be undertaken in order to assess the impact of the exclusion of participants with missing intraoperative data in the primary analysis.

10.9 PLANS FOR ACCESS TO THE PROTOCOL, PARTICIPANT LEVEL-DATA AND STATISTICAL CODE

The Investigator(s) will permit trial-related monitoring, audits and REC review by providing the Sponsor(s), and REC direct access to source data and other documents (e.g. patients' case sheets, blood results, imaging reports, trial protocol, statistical code, and etc).

11. OVERSIGHT AND MONITORING

11.1 COMPOSITION OF THE COORDINATING CENTRE AND TRIAL STEERING COMMITTEE

11.1.1 TRIAL MANAGEMENT GROUP

Title	Name*	Role
KCL Chief Investigator	Dr Rachel Clough	Chair
Cydar Lead Investigator	Dr Tom Carrell	Member
KCTU Operations Director	Ms Caroline Murphy	Member
KCTU Data Centre Lead	Ms Joanna Kelly	Member
ARIA Senior Statistician	Dr Yanzhong Wang	Member
KCTU Junior Statistician	Mr Hatem Wafa	Member
KCTU Trial Manager	Dr Izabela Pilecka	Member
ARIA Health Economist	Prof Stephen Palmer	Member
Cydar Project Manager	Mr Adam Jones	Member
Independent image reader and Clinical Research Fellow	Dr James Budge	Member

**The protocol will not be formally amended to replace individuals who leave the project after ethics approval, unless an amendment is bieng submitted for other reasons*

Table 4. TMG membership

The TMG is responsible for the study co-ordination, data quality and budget management. The TMG members listed in table 4 above will meet at least monthly throughout the trial. The CI will chair the TMG. Minutes will be taken by the trial manager and retained in the TMF. The TMG will review recruitment to the study across all study sites and will take appropriate action in the event the study recruitment rate is lower than anticipated.

11.1.2 TRIAL STEERING COMMITTEE (TSC)

The TSC is an executive committee, reporting to the funder (NIHR) and the sponsor. Independent members will be independent of both the Sponsor organisations and of any recruiting study sites.

Terms of reference of the TSC will be agreed at the first meeting, prior to start of recruitment. Meetings will be scheduled approximately 2 weeks after each Data Monitoring Committee (DMC) meeting. Minutes will be taken by the trial manager and retained in the TMF. The Trial Manager will prepare reports to the TSC.

The trial may be prematurely discontinued by the Co-Sponsors or Chief Investigator on the recommendation of the Trial Steering Committee.

11.1.3 DATA MONITORING COMMITTEE (DMC)

The DMC will be composed of three independent members; a statistician and two clinicians. The DMC is an advisory committee, reporting to the Trial Steering Committee. They will receive a report of recruitment, serious and non-serious adverse events and a summary of accumulated clinical data from the trial statistician, and will meet in person or by telephone. The DMC will meet at least annually during the study, approximately 2 weeks prior to the TSC. Members will be independent of the Sponsor organisations and of any recruiting study sites. The DMC will work to the DAMOCLES guidance and a DMC charter will be

agreed at the first meeting outlining responsibilities, reporting, meeting frequency, documentation and other matters. The Trial Statistician will prepare reports to the DMC.

11.2 ADVERSE EVENT REPORTING AND HARMS

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

- **Adverse Event (AE)**: Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
- **Adverse Reaction (AR):** Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.
    - **Unexpected Adverse Reaction (UAR)**: An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (SmPC) for that product (for products with a marketing authorisation)
- **Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR):** Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that**:**
    - results in death;
    - is life-threatening;
    - required hospitalisation or prolongation of existing hospitalisation;
    - results in persistent or significant disability or incapacity;
    - consists of a congenital anomaly or birth defect.
- **Important Medical Events (IME) & Pregnancy:** Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious. Although not a serious adverse event, any unplanned pregnancy will also be reported via the SAE reporting system.
- **Device performance errors:** Performance and error data will be collected, with failure case analysis undertaken as required.

11.2.1 EVALUATING AES AND SAES.

- **Assessment of Intensity**
  The Investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the Investigator's clinical judgement. The intensity of each AE and SAE recorded in the CRF should be assigned to one of the following categories:
    - **Mild** An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
    - **Moderate** An event that is sufficiently discomforting to interfere with normal everyday activities.
    - **Severe** An event, which is incapacitating and prevents normal everyday activities.

An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

- **Assessment of Causality**

The Investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated.

The causal relationship to the study product assessed by the Investigator (or medically qualified delegate) should be assessed using the following classifications:

- **Not Related** In the Investigator's opinion, there is not a causal relationship between the study product and the AE.
- **Remote**The temporal association between the AE and study product is such that the study product is not likely to have any reasonable association with the AE.
- **Possible** The AE could have been caused by the study Subject's clinical state or the study product.
- **Probable** The AE follows a reasonable temporal sequence from the time of study product administration, abates upon discontinuation of the study product and cannot be reasonably explained by the known characteristics of the study Subject's clinical state.
- **Definitely** The AE follows a reasonable temporal sequence from the time of study product administration or reappears when study product is reintroduced.

There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always assesses causality for every event prior to transmission of the SAE form to the Sponsor. The Investigator may change his/her opinion of causality considering follow-up information, amending the SAE form accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

- **Assessment of Expectedness**

  A reasonable possibility of a relationship conveys that there are facts, evidence and/or arguments to suggest a causal relationship, rather than a relationship that cannot be ruled out.
  - **Expected** An adverse reaction, the nature or severity of which is consistent with the applicable product information for an unapproved medicinal product).
  - **Unexpected** An adverse reaction, the nature or severity of which is not consistent with information in the relevant source document

11.2.2 FOLLOW-UP OF AES AND SAES

- After the initial AE/SAE report, the Investigator is required to proactively follow each Subject and provide further information to the Sponsor on the Subject's condition.
- All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, until the condition stabilises, until the event is otherwise explained, or until the Subject is lost to follow-up. Once resolved, the appropriate AE/SAE CRF page(s) will be updated. The Investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature

and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. New or updated information will be recorded on the originally completed SAE form, with all changes signed and dated by the Investigator. The updated SAE form should be resent to the Sponsor.

11.2.3 PREGNANCY

- Any pregnancy that occurs during study participation must be reported using a serious adverse event form. To ensure subject safety, each pregnancy must be reported to the Sponsor within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child, which must also be reported to the Sponsor. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.
- Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to the Sponsor.

11.2.4 ADVERSE EVENT REPORTING RESPONSIBILITIES

All SAEs, SARs and SUSARs will be reported immediately (and certainly no later than 24hrs) by the Investigator to KCTU via email to ctu@kcl.ac.uk.

The Chief Investigator will report relevant SAE's to the ethics committee. Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days;
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.

11.3 PLAN FREQUENCY AND PLAN FOR AUDITING TRIAL CONDUCT

Monitoring of this trial to ensure compliance with Good Clinical Practice will be managed by the Trial Manager at King's College London.

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents (e.g. patients' case sheets, blood results, imaging reports, trial protocol, statistical code, and etc).

KCTU will prepare a monitoring plan for approval by the TMG. Recruiting study sites will have a Site Initiation Visit prior to recruitment of the first participant and regular site visits thereafter to verify the data.

11.4 PLANS FOR COMMUNICATING IMPORTANT PROTOCOL AMENDMENTS TO RELEVANT PARTIES (E.G. TRIAL PARTICIPANTS, ETHICAL COMMITTEES)

The Trial Manager will be responsible for preparing and submitting protocol amendments to the ethics committee and the HRA, and circulating updated document versions to recruiting study sites, co-applicants,

the TMG, TSC and DMC and (where relevant) the funder. Site investigators will be responsible for communicating relevant information to study participants.

12. DISSEMINATION PLANS

The primary and 4-12 week secondary outcomes will be published in a peer reviewed open source medical journal as early as possible. The 52 week secondary outcomes will be published in a further paper when all outcome data collection is complete.

Recruiting sites will be informed of the results and will be asked to disseminate the findings to participants.

Patient groups will be informed of the results for dissemination among their members.

The sharing dataset will be passed to the UK Chief Investigator by the analyst and all future data sharing will be managed as per the Head contract and associated collaboration agreements.

13. DISCUSSION

COVID19 CONTINGENCIES

- Travel restrictions and limitations on face-to-face data collection and monitoring visits may necessitate moving to a fully remote trial model to help ensure continuity of the trial

14. FUNDING, DATA SHARING, ETHICS, REGULATORY, INSURANCE, ARCHIVING

14.1 FUNDING

UK funding is a 36 month grant from the NIHR i4i Programme (ref. NIHR201004).

14.2 AVAILABILITY OF DATA AND MATERIALS

Data will be available for sharing upon request for future scientific research, subject to approval by the co-sponsors.

14.3 ETHICS/REGULATORY APPROVAL AND CONSENT TO PARTICIPATE

Individual participants will consent to participate. The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments. This protocol and related documents will be submitted for review to Health Research Authority (HRA), Research Ethics Committee (REC) . MHRA approval is not required as the device is CE Marked as a medical device and is being used as intended.

The Chief Investigator will submit an end of study report at conclusion of the trial to the REC.

14.4 INSURANCE AND INDEMNITY

King's College London provides no fault liability insurance in the event of harm arising from the study design. UK NHS recruiting sites provide indemnity in the event of clinical negligence.

CYDAR has manufacturer liability insurance in place to meet potential legal liability arising in relation to the device.

14.5 ARCHIVING

At the end of the trial, all sites will be asked to archive trial data locally.

15. REFERENCES

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