A Risk-adjusted and Anatomically Stratified Cohort Comparison Study of Open Surgery, Endovascular Techniques and Medical Management for Juxtarenal Aortic Aneurysms:

The UK COMplex AneurySm Study (UK-COMPASS).

Version 6.0 dated 21st July 2022

Study Sponsor:
Liverpool University Hospitals NHS Foundation Trust
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LIVERPOOL CLINICAL TRIALS CENTRE LCTC

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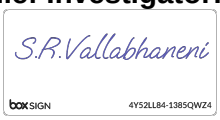
Protocol Approval

I, the undersigned, hereby approve this clinical study protocol:

Authorised by Chief Investigator:

Signature: 

Date: 11 Aug 2022

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Authorised on behalf of the Lead Statistician:

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Date: Aug 10, 2022

Richard Jackson
Lead Study Statistician

Authorised on behalf of the Sponsor:

Signature: 

Date: 10 Aug 2022

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General Information

This document describes the UK-COMPASS study including detailed information about procedures and recruitment. The protocol should not be used as an aide-memoir or guide for the treatment of patients. Every care was taken in its drafting, but corrections or amendments may be necessary. Any amendments will be circulated to the investigators participating in the study, but sites entering patients for the first time are advised to contact the coordinating centre to confirm they have the most up to date version. Clinical problems relating to this study should be referred to the relevant Chief Investigator, via the CTU.

This protocol defines the participant characteristics required for study entry and the schedule of follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements. Waivers to authorise non-compliance are not permitted. Incidence of protocol non-compliance whether reported prospectively or retrospectively noted are recorded as protocol deviations. These are monitored and reported to study oversight committees.

The template content structure is consistent with the SPIRIT (Standard Protocol Item: Recommendations for Interventional Trials 2013) and has regard for the Health Research Authority guidance. Regulatory and ethical compliance information is located in section 13.

The Liverpool Clinical Trials Centre has achieved full registration by the UK Clinical Research Collaboration (www.ukcrc.org) as their standards and systems were assessed by an international review panel as reaching the highest quality. The Liverpool Clinical Trials Centre has a diverse trial portfolio underpinned by methodological rigour, a GCP compliant data management system, and quality management system.

Statement of Compliance

This study is designed to comply with the guideline developed by the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and will be conducted in compliance with the protocol, LCTC Standard Operating Procedures and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004.

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Glossary

AAA	Abdominal aortic aneurysm
A-DQol	Aneurysm – Dependant quality of life questionnaire
A-SRQ	Aneurysm – Symptom rating questionnaire
A-TSQ	Aneurysm – Treatment satisfaction questionnaire
BAR Score	British aneurysm repair Score
BEVAR	Branched endovascular aneurysm repair
CE	Conformité Européenne (Confirmity marking for European Economic Area)
CT	Computerised Tomography
DICOM	Digital Imaging and Communications in Medicine (standard for distributing and viewing medical image regardless of the origin)
DMEC	Data Monitoring and Ethics Committee
EQ-5D 5SL	Euroquol – Five dimension questionnaire
ETTAA	Effective treatments for thoracic aortic aneurysms (Study)
EVAR	Endovascular aneurysm repair
FEVAR	Fenestrated endovascular aneurysm repair
HES	Hospital Episode Statistics
HRA	Health Research Authority
HTA	Health Technology Assessment (programme of NIHR)
HQIP	Health Quality Improvement Partnership
ICER	Incremental cost effectiveness ratio
IEP	Internet exchange portal
IFU	Indications for use (sometimes referred to as 'Instructions for use')
NAAASP	National abdominal aortic aneurysm screening programme
NCAPOP	National clinical audit and patient outcomes programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NVR	National Vascular Registry
ONS	Office for National Statistics
OSR	Open surgical repair (of AAA)
PACS	Picture archiving and communications system
PMG	Programme management group
PPI	Public Patient Involvement
PROMS	Patient-reported outcome measures
RCT	Randomised controlled trial
SD	Standard deviation
SSC	Study Steering Committee
QoL	Quality of life
QUALY	Quality adjusted life years
TAR	Technology assessment report

1. Protocol Summary

Full (Scientific) Title:	A Risk-adjusted and Anatomically Stratified Cohort Comparison Study of Open Surgery, Endovascular Techniques and Medical Management for Juxtarenal Aortic Aneurysms: The UK COMPlex AneurySm Study (UK-COMPASS)
Acronym:	UK-COMPASS
Public Title:	A comparison study of open surgery, minimal invasive surgery and medical management for complex abdominal aortic aneurysms.
Study Type:	Observational study with follow-up.
Health Condition Investigated:	Juxtarenal abdominal aortic aneurysm.
Interventions:	• Fenestrated Endovascular Aneurysm Repair (FEVAR) • Open Surgical Repair • Standard EVAR with adjuncts • Off-label Standard EVAR • Medical Management; Operation Deferred
Sample size:	***Retrieved from routinely collected data:*** estimated minimum of 2000 ***Medically managed cases -Retrospectively identified at sites***: estimated 300 medically managed/operation deferred ***Site collected data (QoL):*** • Operated: approx. 800 • Medical Management- Operation Deferred: approx. 300 N.B Recruitment and follow up to the site collected data (QoL) has been discontinued.
Inclusion Criteria:	***Retrieved from routinely collected data:***

	Abdominal aortic aneurysms ≥ 55 mm in diameter undergoing elective repair in England between Nov 2017 and Oct 2019 and determined in the study Core Lab to have a neck that is: a. shorter than 10 mm, and/or b. Unsuitable for Standard EVAR within Indications for Use. ***Retrospectively Identified Medically Managed Patients at site:*** 1. Patients placed on 'Medical Management – Operation Deferred' in England from November 2017 with an abdominal aortic aneurysm ≥ 55 mm in diameter, and determined by treating physician to have a neck that is: a. shorter than 10 mm, and/or b. Unsuitable for Standard EVAR within Indications for use *OR* 2. Patients fulfilling anatomical inclusion criteria whose operation was delayed due to pandemic disruption – 'Covid delayed'. ***Site collected data:*** Consenting patients undergoing elective repair of abdominal aortic aneurysms in England between Nov 2017 and Dec 2022, that are ≥ 55mm in diameter and determined by treating physician to have a neck that is: • shorter than 10 mm, and/or • Unsuitable for Standard EVAR within Indications for Use. Consenting patients placed on 'Medical Management – Operation Deferred' in England between Nov 2017 and Dec 2022 with an abdominal aortic aneurysm ≥ 55 mm in diameter, and determined by treating physician to have a neck that is: • shorter than 10 mm, and/or • Unsuitable for Standard EVAR within Indications for Use. N.B Recruitment and follow up to the site collected data (QoL) has been discontinued.
Exclusion Criteria: ***(Same for all data streams)***	1. AAA with necks greater than or equal to 10mm in length and considered suitable for Standard EVAR within Indications for Use. Patients treated by surgeon-modified stent-grafts or 'home-made' devices. 2. Emergency operations. 3. Thoracic or thoracoabdominal aneurysms (as defined by an aortic diameter of greater than or equal to 30mm at the level of the SMA). 4. Aneurysm neck anatomy suitable for standard infrarenal EVAR within IFU of CE marked devices. 5. 'Operation Declined' those patients turned down for surgery due to co-morbidity or patient choice.

Study Centres and Distribution:	All arterial vascular centres (secondary and tertiary care) within England.
Study Duration:	• Routinely collected data: 5 years (end date Dec 2023) • Site reported data (QoL): discontinued • Retrospectively identified Medically managed patients at site: 17 months (end date Dec 2023)
Outcome Measures	
Primary clinical endpoints:	***Early:*** Perioperative death: Death within 30 days of operation or within the same admission for the operation. ***Late follow-up (after 30 days or discharge whichever is later):*** all-cause mortality, aneurysm-related mortality*.
Secondary clinical endpoints:	• Time to death from any cause (post baseline to end of follow-up). Post-operative length of hospital stay • Any need for intensive care during hospitalisation post surgery • On-table conversion of EVAR to OSR • Quality of Life (at baseline, 6 month, 1 year, annually for maximum of 5 years) • ***Early (within 30 days of surgery or during hospitalisation post surgery):*** - Perioperative complications and other morbidity (non-specified e.g. wound dehiscence, surgical site infection), stent-graft complications (including target vessel loss, endoleak types 1, 2, 3, endoleak of undetermined type, device kinking, limb occlusion). - Any secondary intervention (specified or non-specified, including return to operating theatre) Conversion of EVAR to OSR • ***Late follow-up (after 30 days or discharge whichever is later):*** - Perioperative complications including, device-related renal failure requiring dialysis, target vessel loss, endoleak types 1, 2, 3, endoleak of undetermined type, aneurysm expansion, device kinking, limb occlusion, device structural disintegration, distal embolisation, graft infection, graft rupture incisional hernia – untreated / operated, anastomotic aneurysm, anastomotic-enteric fistula, renal infarction. -Secondary intervention Conversion of EVAR to OSR

Health Economic measure:	Incremental Cost Effectiveness Ratio in terms of cost per incremental gain in Quality Adjusted Life Years, from an NHS and personal social care perspective.

* Aneurysm related death is defined as death from aneurysm repair, rupture/exsanguination relating to aneurysm repair, open conversion of endovascular repair or within 30 days of any secondary intervention.

2. Roles and Responsibilities

2.1 Funder

This study/project is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

This funding source had no role in the design of this study but oversee the study through regular progress reports to ensure the study is delivered in accordance with contractual arrangements.

The trial is also registered on the NIHR Portfolio and is eligible for CRN support (CPMS ref: 3635).

2.2 Study Management

Individual / Organisation	**Responsibility**
Sponsor	The Sponsor is legally responsible for the trial. They will formally delegate specific Sponsoring roles to the Chief Investigator and Clinical Trials Unit.
Chief Investigator	Professor S R Vallabhaneni is the Chief Investigator for the trial and is responsible for overall design and conduct of the trial in collaboration with other members of the study team.
Principal Investigators	In each participating centre, a principal investigator will be identified to be responsible for patient identification, consent, enrolment, data collection and completion of CRFs, in adherence with the study protocol.
Clinical Trials Unit*	The Liverpool Clinical Trials Centre (LCTC) at the University of Liverpool in collaboration with the Chief Investigator, will have overall management responsibility and will be responsible for project management activities including (but not limited to) study planning, budget administration, Trial Master File management, data management, enrolment, co-ordinating the collection of follow up QoL data, statistical analysis and participating site coordination.
Core Lab	Liverpool University Hospitals NHS Foundation Trust hosts the study Core Lab and its Vendor Neutral Archive in compliance with regulatory approvals. CT scans retrieved from NHS PACS are analysed in the Core Lab according to set standards to identify aneurysms eligible for inclusion into the study.
National Vascular Registry	NVR provides routinely collected health, procedural, and short-term outcome data of operated patients through a data sharing agreement in compliance with regulatory approvals

NHS Digital	NHSD provides routinely collected demographic, diagnostic, health, procedural and health economic data through a data sharing agreement in compliance with regulatory approvals.
* **Liverpool Clinical Trials Centre Merger** During the management of this study the Liverpool Cancer Trials Unit (LCTU) and the Clinical Trial Research Centre (CTRC) have merged to become the Liverpool Clinical Trials Centre (LCTC).	

2.3 Oversight Committees

2.3.1 Trial Management Group

Membership of the Trial Management Group (TMG) includes:

- Chief Investigator
- Clinical Research Fellow
- Project Manager/Trial Manager
- Project Statistician
- Data Manager
- Lead Research Nurse
- Health Economists
- Core Lab Representative (one or more from Research PACS Clerk, Hospital PACS Manager, IT Network specialist, DICOM software expert)
- Sponsor representative
- Invited Principle Investigators
- Co-applicants
- Director of LCTC

The TMG is responsible for monitoring and delivering all aspects of the progress and conduct of the study, and will be responsible for the day-to-day running and management of the study. The TMG meets on a monthly basis. A sub-group of the TMG consisting of the LCTC internal team, the CI, Clinical research fellow and the lead research nurse meet on a weekly basis.

2.3.2 Trial Steering Committee

The role of the TSC is to provide overall supervision of the study. The TSC considers the recommendations made by the Independent Data Monitoring and Safety Committee (IDMSC) and

steers the Trial Management Group (TMG) responsible for the day-to-day delivery and conduct of the trial.

Membership of the Trial Steering Committee includes the following expertise:

- Independent Chair (Academic expert in the field of aortic research)
- Independent Expert Members x 3 to 5 contributing expertise in the areas of Clinical Surgery, Health Economics, and Statistics/Decision science
- Independent PPI Representative
- Chief Investigator – Non-independent member
- Project Manager – Non-independent member

TSC composition, definition of 'Independent' or 'non-independent' and the ratio of independent to non-independent of quorum will be according to funder's (NIHR) definitions.

Representative of the study sponsor, study co-ordinator and study team may attend TSC as observers or to provide clarification. The ultimate decision for the continuation of the study depends upon recommendations of the TSC to the funding body. The TSC will meet on an annual basis but more regular meetings will be convened if required.

2.3.3 Independent Data and Safety Monitoring Committee

The IDSMC is responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, study conduct and external data.

Membership of the Trial Steering Committee includes:

- Independent Chair (Clinical Academic)
- Independent Member - Expert in the field of clinical vascular surgery
- Independent Member – Expert in the field regulatory aspects
- Independent Statistician

The IDSMC meet at least annually, however more regular meetings may be convened as required. The IDSMC will provide a recommendation to the TSC concerning the continuation of the study.

Full details of Oversight Committee Membership is documented in their respective Charters and membership documents held by the LCTC.

Current composition of the TSC and IDSMC is available from the Project Manager.

3. Background Information

3.1 Introduction

Approximately 6000 people per year, in the UK, undergo elective surgery for an Abdominal Aortic Aneurysm (AAAs) to prevent premature death from aneurysm rupture. The main surgical strategies for AAA treatment are Open Surgical Repair (OSR) and Endovascular Aneurysm Repair (EVAR) techniques. The complexity of aneurysm surgery mainly depends on the structure of the aneurysm 'neck', the segment of aorta below the renal arteries and above the aneurysm. Aneurysms that commence after at least 10mm of good quality neck are described as 'infrarenal' and are usually anatomically suitable for standard EVAR. When the AAA is closer to the renal arteries, called a juxtarenal AAA or when the neck is unsuitable for a standard EVAR, specially made stent-grafts are used to deploy Fenestrated Endovascular Aneurysm Repair (FEVAR).

NHS clinical service commissioners have noted an increasing demand for FEVAR in the absence of evidence to inform which patients benefit from these devices, and whether the substantial cost associated with FEVAR is a good use of NHS resources. The NIHR have commissioned this research in order to resolve this NHS decision problem.

Treatment strategies employed as alternatives to FEVAR include: Open Surgical Repair, Standard EVAR with adjuncts to compensate for the absence of an adequate aneurysm neck (such as Chimney EVAR or Endostaples), as well as Off-label Standard EVAR. Whilst there are proponents for each of these strategies, how they compare with each other has not been established.

Despite the apparent advantages of endovascular techniques, including FEVAR, controversy persists about their role compared with open surgical repair, for two main reasons:

1) ***Long term survival***. Despite its lower perioperative mortality, endovascular repair is not expected to lead to improved survival in the long-term.

2) ***Cost.*** Endovascular devices are expensive and their cost effectiveness is widely questioned, due to a lack of marked improvement in long-term survival.

Open Surgical Repair is also costly, largely on account of longer hospital stay and higher intensive care use when compared to treatment of infrarenal aneurysms.

No medical therapy can prevent aneurysm rupture. However, when the risk of aneurysm rupture is considered to be smaller than the risk of death from an elective repair, a physician and their patient may wish to keep the surgical option available for the future, without imminent surgery, even if the aneurysm is larger than the recognised size 'threshold' of 55 mm. Such patients are observed with a view to offering surgical intervention when the perceived risk of rupture increases through aneurysm enlargement or other intervention to improve operative risk. This is referred to as 'Medical Management – Operation Deferred' in this protocol.

Current clinical practice and commissioning would benefit greatly from evidence of clinical and cost effectiveness of FEVAR and how different treatment strategies for juxtarenal aneurysms compare: this is the remit of the HTA commissioned research call 15/153.

3.2 Rational and why this research is needed

Because of the very high costs of fenestrated stent-grafts, it has become common practice for vascular specialists to use standard stent-grafts outside their Indications For Use (IFU) to deal with adverse anatomy for which fenestrated stent-grafts have been designed. This risks complications, a need for further procedures and the possibility of medico legal consequences of 'off-label' use.

Uncertainty about when to use FEVAR, when to use open surgery, and whether to use infrarenal EVAR devices 'off-label' is currently a real dilemma for vascular surgeons and their patients and is a major source of concern for commissioners. Evidence is needed urgently to inform treatment choices for patients with juxtarenal AAAs. This study would provide the necessary data, based on contemporary UK practice.

3.3 Objectives

The aim of UK-COMPASS is to answer the research question identified by the NIHR HTA Commissioning Board: '*What is the clinical and cost-effectiveness of strategies for the management of juxtarenal abdominal aortic aneurysm, including fenestrated endovascular repair?*' The evidence generated by this research should be adequate to resolve the NHS decision problem arising from the use of FEVAR as described within the terms of the HTA research commissioning brief.

Objective 1: To compare different treatment strategies for their perioperative mortality and morbidity, corrected for confounding physiological and anatomical characteristics, in order to account for baseline risk and indication biases.

Objective 2: To identify whether particular physiological and/ or anatomical baseline characteristics are associated with better clinical outcomes or better health economic efficiency using one or other treatment strategy.

Objective 3: To compare different treatment strategies in terms of overall survival and in terms of treatment failure in the long-term (5 year) follow-up (stent-graft related complications, secondary interventions, aneurysm-related mortality*).

Objective 4: To perform cost effectiveness analyses from NHS and personal social care perspective to establish incremental cost effectiveness ratios, comparing different treatment strategies in terms of cost per incremental gain in and quality adjusted life years.

Objective 5: To establish the clinical and cost utility of FEVAR and alternatives, in patients who are considered physiologically unfit for OSR, and to compare these against medical managements.

* Aneurysm related death is defined as death from aneurysm repair, rupture/exsanguination relating to aneurysm repair, open conversion of endovascular repair or within 30 days of any secondary intervention.

4. Study Design

UK-COMPASS is an empirical cohort study to compare clinical and cost effectiveness of different management strategies used in the study population, incorporating statistical methods of correcting for confounding by physiological risk and anatomical complexity.

4.1 Efficient Study Design

The study incorporates aspects referred to by NIHR as "efficient study design", where a substantial proportion of data required for the analysis is retrieved from routinely collected sources. This not only reduces the cost of conducting research, but also more importantly, facilitates inclusion of a larger number of patients within a shorter time. The study has two streams of data collection:

1. **Routinely collected data:** Health data, demographic data and health care resource use data relating to operated patients will be retrieved from the National Vascular Registry, Hospital Episode Statistics and the NHS Picture Archiving and Communication System. This data will be retrieved by the LCTC through data sharing agreements.

2. **Site reported data:**
   a. **(QoL): Quality of Life:** data reported by consenting patients (both Operated and Medical Management – Operation Deferred) from participating vascular centres in England will supplement the routinely collected data. Participating centres will be required to obtain the baseline QoL Questionnaire with the patient. Completion of follow up questionnaires and collection of completed patient diaries will be co-ordinated by the LCTC.
   b. **Baseline Clinical Data:** Participating centres will be required to report baseline health and demographic data for Medically Managed - Operation Deferred patients only as this data is not available for this group of patients through NVR and HES data streams.
   c. **Remote follow-up**: participating patients will be asked to consent to Health data, demographic data and health care resource use data being retrieved from the National Vascular Registry, Hospital Episode Statistics and the NHS Picture Archiving and Communication System

N.B. Site reported data collection (recruitment and follow up) has been discontinued.

The decision to discontinue site reported data collection (recruitment and follow up) early has been made in view of the following:

- recruitment to this stream has been slower than anticipated
- there are anticipated difficulties in recovering recruitment
- disruptions related to the COVID-19 pandemic and potential effect of the pandemic on quality of life.
- return rates of the QoL data is low and the value of continuing to collect QoL data on patients already recruited is considered to be limited.

Medically Managed Cases – Retrospectively Identified at Site

Identification, recruitment and data collection of medically managed patients was done prospectively solely through site reported data. As this arm under recruited and there is no routinely collected data source currently available (as there is for the operated arm), an extension to CAG251 approval has been made to allow the retrospective identification of 'medically managed / operation deferred' patients at all participating sites. With the identification of these patients, the central team at Liverpool can request routinely collected data from NHS digital. This has been done to help meet the objectives of the study.

5. Study Population and Interventions

Population and interventions included in this research have been selected to ensure delivery of the purpose stated in the NIHR commissioning brief - HTA no 15/153 (Appendix 1), which was to generate evidence that would resolve the NHS decision problem arising from increasing demand for FEVAR in the absence of reliable evidence of its comparative effectiveness. Therefore, the study population should encompass the range of patients for whom FEVAR has been developed and used. This includes patients with aneurysm neck shorter than 10 mm as well as those with aneurysm neck that is 10 mm or longer, but unsuitable for Standard EVAR within manufacturers' IFU. Interventions evaluated in the study should include all of the strategies employed in routine clinical practice as alternatives to FEVAR.

5.1 Inclusion and Exclusion Criteria

5.1.1 Routinely collected data

5.1.1.1 Inclusion criteria:

Juxtarenal aneurysms (that have reached a threshold of 55mm in diameter) as determined in the study Core Lab to have a neck that is:

a) shorter than 10 mm, and/or
b) Aneurysm neck unsuitable for Standard EVAR within Indications for Use.

Surgery must have taken place between 1st November 2017 and 31st October 2019.

5.1.1.2 Exclusion criteria:

1) AAA with necks greater than or equal to 10mm in length and considered suitable for Standard EVAR within Indications for Use. Patients treated by surgeon-modified stent-grafts or 'home-made' devices.
2) Emergency operations.
3) Thoracic or thoracoabdominal aneurysms (as defined by an aortic diameter of greater than or equal to 30mm at the level of the SMA).
4) Aneurysm neck anatomy suitable for standard infrarenal EVAR within IFU of CE marked devices.
5) 'Operation Declined' those patients turned down for surgery due to co-morbidity or patient choice.

5.1.2 Site collected data (Quality of Life study)

5.1.2.1 Inclusion Criteria

1) Consenting Patients undergoing elective repair of abdominal aortic aneurysms in England, and determined by treating physician to be ≥ 55mm in diameter with a neck that is:
   a) shorter than 10 mm, and/or
   b) Aneurysm neck unsuitable for Standard EVAR within Indications for Use.

2) Consenting patients placed on 'Medical Management – Operation Deferred'* in England with an abdominal aortic aneurysm ≥ 55mm in diameter, and determined by the treating physician to have a neck that is:
   a) shorter than 10 mm, and/or
   b) Aneurysm neck unsuitable for Standard EVAR within Indications for Use.

*** NB for the purpose of this study protocol 'medical management – operation deferred patients' are defined as those patients whom a decision to operate or not has yet to be made.**

5.1.2.2 Exclusion Criteria

1) AAA with necks greater than or equal to 10mm in length and considered suitable for Standard EVAR within Indications for Use and patients treated by surgeon-modified stent-grafts or 'home-made' devices.
2) Emergency operations
3) Thoracic or thoracoabdominal aneurysms (as defined by an aortic diameter of greater than or equal to 30mm at the level of the Superior Mesenteric artery [SMA])]
4) Aneurysm neck anatomy suitable for standard infrarenal EVAR within IFU of any CE marked device.
5) 'Operation Declined Medical Management' patients, due to co-morbidity or patient choice.

N.B. Recruitment to this aspect of the study has been discontinued. See section 4.1.

5.1.3 Retrospectively Identified Medically Managed Patients at site

*5.1.3.1 Inclusion Criteria**

1) Patients placed on 'Medical Management – Operation Deferred'* from 1st November 2017 in England with an abdominal aortic aneurysm ≥ 55mm in diameter, and determined by the treating physician to have a neck that is:
   c) shorter than 10 mm, and/or
   d) Aneurysm neck unsuitable for Standard EVAR within Indications for Use.
   OR
2) Patients fulfilling anatomical inclusion criteria whose operation was delayed due to pandemic disruption – 'Covid delayed'.

*** NB for the purpose of this study protocol 'medical management – operation deferred patients' are defined as those patients whom a decision to operate or not has yet to be made.**

5.1.3.2 Exclusion Criteria

1) AAA with necks greater than or equal to 10mm in length and considered suitable for Standard EVAR within Indications for Use
2) Thoracic or thoracoabdominal aneurysms (as defined by an aortic diameter of greater than or equal to 30mm at the level of the Superior Mesenteric artery [SMA])]
3) 'Operation Declined Medical Management' patients, due to co-morbidity or patient choice.

5.2 Study Setting

5.2.1 Routinely Collected Data

As detailed in section 4, data will be sourced from National Vascular Registry, Hospital Episode Statistics (from NHS digital) and the NHS Picture Archiving and Communication System. This will encompass all vascular centres in England.

5.2.2 Site Collected Data (Quality of Life)

5.2.2.1 Centre/clinician study inclusion criteria

Centres that meet the following criteria are eligible for inclusion in the study:

- All vascular centres in England that perform arterial surgery
- Confirmation of capacity and capability from NHS trust

5.2.2.2 Centre clinician study exclusion criteria

Those centres that do not fulfil the above (section 5.3.2.1) inclusion criteria will not be permitted to participate in the study.

N.B. Recruitment and follow up to this aspect of the study has been discontinued. See section 4.1.

5.2.3 Retrospectively Identified Medically Managed Patients at site

5.2.3.1 Centre/clinician study inclusion criteria

- Having participated in Site Collected Data (Quality of Life)
- Confirmation of capacity and capability from NHS trust

6. Study Outcomes

6.1 Primary Endpoints

- ***Early:*** Perioperative death: Death within 30 days of operation or in-hospital mortality during the same admission for the operation.

- ***Late:*** all-cause mortality, aneurysm-related mortality that is not peri-operative, during the rest of following up (approximately 5 years).

Aneurysm related death is defined as death from aneurysm repair either in hospital and/or within 30 days, rupture/exsanguination relating to aneurysm repair, open conversion of endovascular repair or in hospital and/or within 30 days of any secondary intervention or death from secondary aneurysm rupture.

6.2 Secondary Endpoints

- Time to death from any cause (post baseline to end of follow-up)
- Post-operation length of hospital stay
- Quality of Life at baseline, 6 months, 1 year, and annually for a maximum of 5 years

- ***Early (within 30 days of surgery or prior to discharge):***
  Any need for intensive care
  - Any perioperative complications or other morbidity (non-specified e.g. wound dehiscence, surgical site infection), stent-graft complications (including target vessel loss, endoleak types 1, 2, 3, endoleak of undetermined type, device kinking, limb occlusion).
  - Any secondary intervention (specified/non-specified, including return to operating theatre non-specified).

- ***Late follow-up (after 30 days or discharge whichever is later):***
  - Any complication after the perioperative period including, device-related renal failure requiring dialysis, target vessel loss, endoleak types 1, 2, 3, endoleak of undetermined type, aneurysm expansion, device kinking, limb occlusion, device structural disintegration, distal embolisation, graft infection, graft rupture incisional hernia – untreated / operated, anastomotic aneurysm, anastomotic-enteric fistula, renal infarction.
  - Any secondary intervention after the perioperative period.

6.3 Health Economic Outcome measures

Health Economic outcome measures include perioperative death, morbidity, intensive care usage, hospital stay, long-term (5 year) survival, complications arising from each procedure and QoL. In order to inform the cost utility analysis and generate information on which to base the ICER analysis, a

subgroup of patients will be requested to fill in the EQ-5D-5L questionnaire both before and after their treatment. Selection of patients, together with the comparative survival data will form the basic building blocks for our assessment of comparative outcome in terms of Quality Adjusted Life Years (QALYs).

7. Data Sources

7.1 Data Sources

7.1.1 National Vascular Registry

The National Vascular Registry (NVR) is run by the Clinical Effectiveness Unit of the Royal College of Surgeons of England as a national clinical audit. NVR includes a wide range of data pertinent to this study encompassing demographics, comorbidity, preoperative assessment, intraoperative detail, postoperative complications, duration of hospital stay, and critical care use for all types of repair.

Specifically, NVR data permits the calculation of a British Aneurysm Score for each patient. This is a validated statistical measure of pre-operative fitness that will enable physiological stratification during the comparative analysis stage.

Data is retrieved under a Data Sharing Agreement. Data flow and all data processing is performed in compliance with regulatory approvals. List of data points retrieved from NVR are included in Appendix 2.

7.1.2 Hospital Episode Statistics (HES)

HES is a data warehouse containing details of all admissions, outpatient appointments, investigations and A&E attendances at NHS hospitals in England. This data is collected during a patient's time at hospital and is used to allow hospitals to be paid for the care they deliver. HES is a records-based system and is designed to enable secondary use of this administrative data for non-clinical purposes, medical research being an explicitly stated one. In addition to health and resource use data during the primary admission for aneurysm repair, follow-up data will be collected for five years after the operation to identify late complications, treatment of complications and re-interventions. Survival data will be retrieved via linked ONS data.

7.1.3 CORE laboratory

Detailed anatomical measurements of relevant aneurysm neck anatomy are generated in the study Core Lab. Core Lab refers to a combination of infrastructure and methodology of warehousing radiological imaging and methodical interpretation according to predetermined reporting standards to reduce subjectivity inherent to clinical radiological reporting. Imaging is retrieved from NHS PACS in the study Core Lab, anonymised and subjected to measurements to identify aneurysms fulfilling

inclusion criteria accurately and to stratify anatomical complexity of aneurysms. Core Lab Standard Operating Procedure is provided as Appendix 3.

7.1.4 Patient Reported Outcome Measures (PROMs)

PROMS data collected are from the UK-COMPASS patient diary and Quality of Life measures using validated tools.

N.B. Data collection for this aspect of the study has been discontinued. See section 4.1.

7.1.5 Micro-costing Exercise

In order to assess variations in endovascular consumables and local practice, a micro-costing exercise will be conducted to establish a detailed cost profile of at least 10 each of Open Repair, Fenestrated EVAR* and off-label Standard EVAR. The template used for collection of data is included as Appendix 4.

*BEVAR will be combined with FEVAR unless the branch bridges a gap between the stent-graft main body and target vessel ostium, when it will be excluded.

7.2 Data Set

The data set is extensive. The data that are retrieved from NVR and various administrative data sets of NHSD commonly referred to as HES data are given in Appendix 2. The data retrieved from these sources can be summarised as follows:

- Demographic data
- Baseline health data, including data for BAR Score generation
- Operative details
- Perioperative complications
- Discharge
- Complications noted during follow-up
- Secondary interventions, early and late
- NHS and personal social care resource use during the primary operation, subsequent follow-up and management of secondary interventions.

7.2.1 Data Flow

Please see Appendix 5 for a description of the data flow of UK-COMPASS.

8. Aneurysm Stratification

8.1 Physiological Stratification

8.1.1 Operated patients

Physiological fitness of operated patients is stratified according to British Aneurysm Repair (BAR) Score. Parameters required for this are available within the data set and listed in Appendix 6.

Patients are stratified into two groups based on physiological fitness: 1) Standard risk, and 2) High risk. This is done by estimating the risk of perioperative death of each patient using BAR score, under the assumption that Open Repair is not carried out. [This is a measure of risk of in-hospital death arising from non-treatment related baseline characteristics]. The cohort is ordered by risk score, and those falling into the highest risk quartile are considered 'High Risk' and the remainder 'Standard Risk'.

8.1.2 Medical Management - Operation Deferred

Patients considered best managed by continued medical management with a view to consideration of repair in future as determined by local MDT are considered eligible for inclusion.

N.B. Recruitment and data collection to the site reported data stream of the study has been discontinued early. See section 4.1.

8.2 Anatomical Stratification

For the routinely collected data, patients are stratified into subgroups depending primarily upon aneurysm neck morphology. Length of aneurysm neck and suitability for Standard EVAR within Indications for Use are the primary determinants. Stratification is as follows:

- Group 1: Aneurysm neck length 0-4 mm
- Group 2: Aneurysm neck length 5-9 mm
- Group 3: Aneurysm neck length 10 mm or more and unsuitable for Standard EVAR within IFU due to adverse anatomical features.

Physiological and anatomical stratification was determined by a clinical consensus group which was described in Appendix 6.

9. Study Risks

The study has undergone a bespoke risk assessment. There are few potential risks directly arising from the study because this is an observational study of existing clinical practice and patient care will not be altered based on their data being included in analysis.

- Clinical Risk: No significant clinical risk has been identified and has been assessed as low risk.
- Data Security Risk: There are measures in place to minimise risk to data security. These are detailed in Appendix 2 that describes Data Set and Data Management.

10. Participant timelines and assessments

10.1 Participant Identification

10.1.1 Identification from routinely collected data

All patients who underwent an elective AAA repair in England during the between November 2017 and October 2019 will be identified from HES Admitted Patient Care dataset. Preoperative CT scans of all of these patients will be retrieved from the NHS PACS system for review in the study Core Lab for accurate identification of AAAs fulfilling anatomical inclusion criteria.

Patients confirmed in the Core Lab to have anatomy according to inclusion criteria will be included in the study. Routinely collected data from HES and NVR will be retrieved for these patients only for duration of the study.

It is not possible to identify patients who are Medically Managed - Operation Deferred from HES data because diagnostic codes for aortic aneurysms do not distinguish small aneurysms (<55 mm and hence excluded) from those reaching diameter threshold for inclusion in the study (> 55 mm).

10.1.2 Identified at site

Participating investigators will approach eligible patients to contribute to QoL data who fulfil the anatomical inclusion criteria, and are either:

a. Undergoing an elective AAA repair, or
b. Medically Managed - Operation Deferred*

*Newly medically managed patients AND existing medically managed patients are eligible for inclusion.

N.B. Recruitment and data collection to the site reported data stream of the study has been discontinued early. See section 4.1.

10.1.3 Retrospectively identified at site

Participating investigators will identify eligible patients who were diagnosed with AAA fulfilling anatomical inclusion criteria whose treatment is classed as medically managed/operation deferred from their surveillance programmes from 1st November 2017.

Patients whose operations were delayed due to the COVID-19 pandemic will also be identified.

These patients will not be consented but will be included with an expansion of the CAG section 251 approvals currently in place for the study (see section 4.1).

10.2 Data Collection

10.2.1 Routinely Collected Data – data collection schedule

	screening	baseline	1 month	1 year	Annually
Eligibility Assessment: preoperative scan	✓				
Procedural scan images		✓			
Post-operative scan images			✓	✓	✓
Demographic data (from HES and/or NVR)		✓			
Baseline health Data (from HES and/or NVR BAR score	✓				
Operation Details including operation type, post-operative complications, discharge	✓				
Follow-up complications (from HES)			✓	✓	✓

Secondary interventions, early and late (from HES)			✓	✓	✓
NHS and personal social care resource use during the primary operation, subsequent follow-up and management of secondary interventions (from HES)					✓

10.2.2 Site Collected Data

Recruitment to the site collected data (QoL) stream of the study has been discontinued (see section 4.1).

10.2.2.1 Confirmation of date of surgery (site collected cohort)

For patients already randomised, a further information CRF should be completed once the patient has undergone surgery. This will record both the type of operation undergone and the date on which it took place.

10.2.3 Medically Managed Cases – Retrospectively Identified at Site

For eligible patients whose treatment is classed as medically managed/operation deferred, who were diagnosed with AAA from 1st November 2017 or whose operation was delayed due to the COVID-19 pandemic, the following details should be provided to the central team at Liverpool:

- Name
- NHS number
- Date of Birth
- Management category: Medically Managed – Operation Deferred /Operation delayed due to COVID Pandemic disruption

The central team at Liverpool will provide these details to NHS digital for the inclusion of their data in the routinely collected datasets.

These patients DO NOT need to be consented as included in an extension to CAG section 251 approval.

10.3 Data triangulation and contradictory data

Routinely collected data is retrieved in the form of codes from which clinical information is inferred. When the same information is available from both NVR and HES, the data is cross-checked to ascertain accuracy. On occasions of data concordance, the data is accepted as corroborated. When data is available from only one source, it is accepted as received. However, when the data is ambiguous or contradictory between different sources, clarification will be sought from the clinical team providing the treatment. The information sought will be limited to confirmation of the procedure dates, free text title of the procedure/s and any postoperative complications. Request to the patients' clinical team will require identifiable data to ascertain accuracy.

11. Statistical Considerations

11.1 Method of randomisation

As UK-COMPASS is an observational study of existing clinical practice randomisation is not required.

11.2 Sample size

11.2.1 Routinely collected data sets – sample size

HES data will be collected from NHS digital and used to identify all patients, in England, undergoing AAA elective surgery between November 2017 and October 2019.

CT scans of these patients (approximately 8000 in number) will be analysed in the Core Lab resulting in the inclusion of an estimated 2000 patients to UK COMPASS that are confirmed to have been treated for aneurysms and to meet the inclusion criteria. Evaluations of the accumulation data will be conducted at least annually to assess this assumption.

11.2.2 Site collected data (Quality of Life) – sample size

Because this is an observational cohort study, power calculations are difficult to obtain since precise allocation between different treatment strategies is not known. Power calculations are therefore based on conservative estimates of likely case numbers, derived from available information.

11.2.2.1. Sample size of Operated patients Quality of Life

We will obtain PROMs from a representative sample of patients undergoing AAA surgery during the study period. This will equate to 800 patients (40% of the total expected AAA surgeries detailed in

section 13.2.1). We expect a 50% loss to follow-up. Patients will be followed up for a minimum of 3 years to a maximum of 5 years.

N.B. Recruitment to this aspect of the study has been discontinued short of reaching the patient target. See section 4.1.

11.2.2.2 Sample size for Medically Managed/Operation Deferred patients' quality of Life

We plan to obtain PROMS from 300 medically managed patients. 300 patients will give a 95% confidence interval of maximum width 12.5 for the difference in mean EQ-VAS values between baseline and later time points based on a standard deviation equal to 20. The standard deviation was calculated after an evaluation of EQ-VAS scores across a wide range of LCTC trials.

Participants will be followed up for a minimum of 1 year1 to a maximum of 5 years.

N.B. Recruitment to this aspect of the study has been discontinued short of reaching the patient target. See section 4.1.

11.2.3 Retrospectively Identified at Site – sample size

A target of 300 patients will be identified retrospectively from participating sites. We will obtain the diagnosis data and use this to make quantitative assessment of patient outcomes using routinely collected data. Baseline characteristics will be used to match these patients to those who underwent surgery and outcomes compared using the same methodology as for the analysis of the routinely collected data (11.2.1)

11.3 Interim monitoring and Analyses

Data accumulated from the study will be assessed at regular intervals (at least annually) for review by an Independent Data Monitoring and Safety Committee (IDMSCS). These analyses will be performed at the Liverpool Clinical Trials Centre. The IDMSCS will be asked to give advice on whether the accumulated data from the study, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the study and the general clinical community. If a decision is made to continue, the IDMSCS will advise on the frequency of future reviews of the data on the basis of accrual and event rates.

11.4 Analysis Plan

11.4.1 Patient Groups for Analysis

All patients in England undergoing elective repair (between November 2017 and October 2019) of an aortic aneurysm fulfilling the anatomical inclusion criteria will be included in the study, as well as those whose aneurysm size is >55mm, but are medically managed. Analyses will be carried out on an intention to treat basis, retaining all patients in the primary surgery group to which they are assigned irrespective of any procedural issues.

11.4.2 Levels of significance, multiplicity adjustments

In keeping with the study design, for the primary objective of perioperative mortality, two comparisons of interest will be assessed (FEVAR. vs. Open Repair and off-label standard EVAR vs. Open Repair). In order to keep the family-wise error rate at 5% a Bonferroni corrected level of 0.025 will be used for each comparison with results presented with two-sided 97.5 confidence intervals. All other analyses will be evaluated at the nominal $p<0.05$ level and reported with two-sided 95% confidence intervals.

11.4.3 Adjustment for co-variates

As an analysis of observational cohort data, all attempts to present a measure of effectiveness free from confounding bias will be undertaken. A propensity score analysis approach will be taken here. With all outcomes derived from routine data sets following this approach.

Propensity score estimation is chosen for the analysis of the primary endpoints instead of multivariable regression techniques because it is considered the most appropriate means of reducing selection bias at the low level of perioperative death rates anticipated. Full details of the statistical procedures to be taken will be included in the statistical analysis plan.

As an overview, the propensity score is the probability of a patient being given each treatment based on baseline clinical and demographic characteristics. This will be estimated for each patient, and for each possible treatment strategy. Patients will then be stratified based on their propensity to receive each treatment strategy and an estimate of treatment effect is obtained which adjusts for selection bias associated with known risk factors in the data.

Models to estimate the propensity for each patient shall be generated using multi-variable multi-nomial modelling techniques using as candidate covariates only variables that influence simultaneously the treatment assignment and the outcome variable. Covariates shall be retracted to demographic/clinical data available at the point of treatment decision with the aim of producing a propensity model that satisfies the assumptions of conditional independence.

The minimum set of covariates that shall be considered for inclusion in the propensity are the covariates which contribute towards the calculation of the British Aneurysm Risk (BAR) score, with the

exception of the 'Open Repair' identifier. Assessment of the balance of covariates across propensity groups will be tabulated and balance scores produced across treatment groups.

The final analysis will be carried out using regression modelling approaches with the form of the model dependent on the outcome being used (e.g. logistic regression for binary outcomes, full details available in the study SAP). These models will adjust for the estimate propensity scores through a number of approaches (e.g. Stratification, covariate adjustment and inverse probability weighting). Full justification of the final approach will be included in the study SAP with sensitivity analyses presented alongside the final analysis using alternative methods for propensity score adjustment.

11.4.4 Planned subgroup analysis

Special attention is given to the role of clinical subgroups which are defined by neck anatomy and risk of perioperative death. These sub-groups are defined by patient anatomy and risk as follows:

Anatomy is categorised based on:

Group 1: Neck length 4 mm or shorter
Group 2: Neck length 5-9 mm
Group 3: Neck length 10 mm or more and unsuitable for Standard EVAR within IFU (due to adverse neck characteristics)

Risk of perioperative group is derived from baseline BAR score:

Standard Risk: Lower 75 percentile of the cohort.
High Risk: Highest 25 percentile of the entire cohort.

The combination of these two clinical factors creates a 6-level factor which define our sub-groups of interest. The prevalence of all outcomes shall be presented within each sub-group to measure the impact that each clinical subgroup has upon patient outcome. Further, analysis of the primary outcomes shall be reported within each level of the subgroup provided at least 20 events are observed.

12. Health Economics Evaluation

12.1 Review of health economics literature

A preliminary literature search identified the HTA report that did not include cost analysis and an additional three l international publications undertaking cost analyses of FEVAR from Canada (2009), Republic of Ireland (2011) and France (2015). Unfortunately, none of these incorporated comparative clinical effectiveness into their analysis and hence they offer limited guidance in this respect.

Further searching identified a number of additional publications of economic analyses of infrarenal AAA treatment (15 primary sources, three pooled analyses and one clinical modelling analysis). Each of these analyses has been reviewed to identify potential methodological issues that may arise in developing our more relevant economic model. The NICE Clinical Guideline 'Abdominal Aortic

Aneurysm – Diagnosis and Management (NG156) has been published during course of UK-COMPASS. A systematic literature review will be carried out prior to the health economic analysis.

12.2 Population for Health Economic analysis

The population covered within the economic analysis will be the population covered by the clinical analysis. As such the study population to be incorporated into the economic model will include all patients fulfilling the anatomical inclusion criteria undergoing elective treatment in England during the study recruitment period and all site recruited patients under Medical Management who have either had their surgical treatment delayed or eventually denied. Sub group analysis will be considered based on i) physiological fitness and ii) anatomical stratification to estimate incremental cost effectiveness ratios (ICERs) associated with the use of FEVAR in comparison to alternative surgical strategies (i.e. open surgical repair, standard EVAR and off-label EVAR) and medical management. Sub-groups will be constituted as described earlier in this protocol and detailed in Appendix 6.

12.3 Health Economics Model Development

We plan to adapt the NICE health economic model developed for NG156 and use data from UK-COMPASS to update information relevant to the population suitable for complex EVAR. The NICE model has been developed from a UK NHS and Personal Social Services (PSS) perspective, appraised by a NICE Committee and scrutinised during consultation. As such, we see little value in developing a de novo model. Use of the NICE model will also facilitate use of the UK-COMPASS study results in any future updates of NG156.

One of the key recommendations for research in NG156 was “What is the effectiveness and cost effectiveness of complex endovascular aneurysm repair (EVAR) versus open surgical repair in people for whom open surgical repair is suitable for elective repair of an unruptured AAA?” The analysis was based on data from a proxy population and duly noted that “In deterministic sensitivity analysis, there are 3 parameters that, when varied between plausible bounds, cause the EVAR ICER to be better than £20,000 per QALY gained: the complex EVAR device cost, the 30-day mortality odds ratio and the post-perioperative mortality hazard ratio. Each of these parameters is subject to substantial uncertainty (in the case of device cost because no reliable data are available; in the case of peri- and post-perioperative mortality because data are extrapolated from the infrarenal RCTs in our base case).”

UK-COMPASS is collecting data that will provide more certainty in the estimates for all relevant parameters.

At the outset, QoL data was planned to be obtained from patients recruited through multiple hospitals in England. Progress of this has been hampered by the COVID Pandemic with little prospect of recovery within a meaningful timeframe. Therefore it is now envisaged that QoL data from historic and other sources will inform health economic modelling.

12.3.1 Perspective

Our economic analysis will be undertaken from an NHS and PSSPSS perspective. This will enable direct costs and benefits to the UK healthcare providers to be evaluated.

12.3.2 Time Horizon

Because the impact of treatment is likely to extend throughout the remaining life of the patient, lifetime model will be used to identify, measure and evaluate the impact on comparative resource use and quality of life in early, mid and late follow-up. This reflects in the time horizon used in the economic model for NG156. ThisNG156This will ensure that we will capture late complications that may vary in intensity and severity between each of the treatment modalities being evaluated. The full impact of such complications on the quantity and quality of life experienced by the patient may extend well beyond the duration of study follow up and therefore a range of techniques will be employed to extrapolate the anticipated survival and quality of life impacts over the lifetime of the patients.

12.3.3 Health Economic Outcome Measures

A comprehensive assessment of the comparative benefits arising from each procedure will be examined utilising a wide range of outcome measures. These measures will include perioperative death, morbidity, intensive care usage, hospital stay, long-term (5 year) survival, complications arising from each procedure and QoL. In order to inform the cost utility analysis and generate information on which to base the ICER analysis a subgroup of patients will be requested to fill in the EQ-5D-5L questionnaire both before and after their treatment. Selection of patients, together with the comparative survival data will form the basic building blocks for our assessment of comparative outcome in terms of Quality Adjusted Life Years (QALYs).

12.3.4 Input parameters

A range of evidence typically informs decision analytic models. The information generated by the proposed research project will be used to update relevant parameters of the NICE NG156 economic model. Transition probabilities to update the model will be derived from the clinical study, by available literature and, if necessary, by consultation with clinical experts. Any assumptions made will be checked for plausibility with clinical experts.

12.3.5 Cost of stent-grafts, ancillary implants and consumables

There is variation in the choices of implantables and consumables made by physicians, potentially resulting in wide variations in FEVAR costs. There is also opacity in actual prices charged for standard as well fenestrated stent-grafts, varying between hospitals due to volume discounts and variability of manufacturers' expenses in servicing each hospital. A method of 'micro-costing' in a sample of procedures will be used. The micro-costing template is provided in appendix 4. Procedure costs will be compiled by ensuring that any sampling is adequately representative of variations between centres and physicians.

12.3.6 Sensitivity analyses

A wide range of sensitivity analyses will be undertaken to evaluate the impact of both structural and parameter uncertainty on the results obtained in the analysis. Parameter uncertainty will be analysed through the use of both Tornado diagrams and probabilistic sensitivity analyses. In this manner the robustness of the results obtained can be ascertained in order to determine their use as the basis of future clinical and policy development in this therapeutic area.

12.3.7 Discounting

In accordance with NICE guidance all future costs and outcomes will be estimated over the anticipated lifetime for each patient and will be discounted at 3.5% per year. The discount rate will be varied in the sensitivity analysis to assess the sensitivity of the results to variations in the time flows of costs and benefits.

12.4 Generalisability of the results obtain: External validity review of health economics literature

To be of greatest value, any locally based research would normally have to assess its' generalisability to mainstream NHS practice through the construction of an ‘impact model’. Such a model would evaluate the extent to which the results obtained in the research can be transferred to other locations and generalised throughout the NHS. However, this study undertakes a national analysis of actual clinical practice using patient level data that is already being routinely collected and hence automatically evaluates the comparative clinical and cost effectiveness of the different procedures in the context of actual clinical practice. As such the study exhibits the best possible external validity as it evaluates all patients undergoing treatment for the specified condition in the UK.

Wherever possible the potential impact of potential confounding factors will be controlled in order to maximise, as far as possible, the internal validity of the results obtained. Strategies used in the clinical outcome analysis to improve internal validity will be replicated.

In addition, a range of statistical techniques will be employed in order to ensure that a ‘like for like’ comparison is undertaken between the competing procedures generating results to guide clinical development at the national level.

13. End of study and patient withdrawal

13.1 Patient withdrawal

13.1.1 Routinely collected data

Patients may choose not to have their confidential patient data used for the purpose of research. This would be processed through the National Data Opt-Out Scheme (https://digital.nhs.uk/services/national-data-opt-out). This can be done at https://www.nhs.uk/your-nhs-data-matters/.

This process is managed by NHS digital, who will not provide UK-COMPASS with details of any opt-outs.

13.1.2 Retrospectively collected data

Patients may choose not to have their confidential patient data used for the purpose of research. This would be processed through the National Data Opt-Out Scheme (https://digital.nhs.uk/services/national-data-opt-out). This can be done at https://www.nhs.uk/your-nhs-data-matters/.

This process is managed by NHS digital, who will not provide UK-COMPASS with details of any opt-outs

13.2 End of Study

The end of the trial is defined to be the date on which data for all participants is frozen and data entry privileges are withdrawn from the trial database. The trial may be closed prematurely by the Trial Steering Committee (TSC), on the recommendation of the Independent Data and Safety Monitoring Committee (IDSMC).

Site and closure activities will be centrally coordinated and conducted in accordance with CTU processes regardless of whether the trial closes as planned or prematurely. This includes activities such as:

- End of Trial notification to REC and
- All site data entered onto the study database, discrepancies raised and satisfactory responses received
- Quality Control checks of the Investigator Site Files and Trial Master File as appropriate.

13.3 Study Discontinuation

As this is an observational study there are no significant implications for the normal care of patients. Patients who have consented to provide QoL data will be informed with acknowledgement of appreciation.

14. Data Management and Trial Monitoring

For the UK-COMPASS study the responsibilities for Data Management and monitoring are delegated to LCTC. Separate Data Management and Trial Monitoring Plans have been developed which provide detail regarding the internal processes that will be conducted at LCTC throughout the study. Justification for the level of monitoring is provided within those documents and the study-specific risk assessment. All data will be managed as per local CTU processes and in line with all relevant regulatory, ethical and legal obligations.

14.1 Source documents

The case report form (CRF) will be considered the source document for data where no prior record exists and which is recorded directly in the bespoke CRF. A UK-COMPASS source document list will be produced for each site to be kept in the ISF and provide detail of what constitutes UK-COMPASS-specific source data.

Date(s) of informed consent processes (including date of provision of patient information, randomisation number and the fact that the patient is participating in a clinical study should be added to the patient's medical record chronologically

14.2. Data Collection methods

14.2.1 Data collection methods for routinely collected data sets

HES Data from NHS Digital are accessed using secure electronic file transfer methods via NHS Digital's SEFT account. NVR data are also received via NHSD similarly as a Trusted Third-party. See Appendix 5 data flow.

14.2.2 Data collection methods for patients identified at site

Further information case reports forms (CRFs) will be made available to participating sites via the PORTAL. Study staff at site should print these prior to use, Study staff named at each site will enter data from source documents corresponding to a participant's visit onto the relevant CRF. The CRF is the primary data collection instrument for the study so all data requested on the CRF must be recorded and all missing data must be explained. A copy of all CRFs should be retained at site. Any corrections should be made in accordance with GCP. Copies of the CRF should be forwarded to LCTC electronically by WeTransfer by encrypted NHS email

Baseline questionnaires are a source document and sites should maintain copies at site. Originals should have been provided to CTU.

14.2.3 Data Collection methods for Retrospectively Identified Medically Managed Patients

Participating sites will compile a list of patients fulfilling anatomical criteria whose management falls under one of the following two categories:

1) Medically Managed – Operation Deferred
2) Operation has been delayed due to COVID Pandemic disruption.

Details of these patients will be transmitted to the central team at Liverpool via secure transfer using the CRF available via the Portal.

HES Data from NHS Digital are accessed using secure electronic file transfer methods via NHS Digital's SEFT account. See Appendix 5 data flow

14.3 Monitoring

Monitoring is conducted to ensure protection of patients participating in the trial and all aspects of the trial (procedures, laboratory, trial intervention administration and data collection) are of high quality and conducted in accordance with sponsor and regulatory requirements.

A detailed Trial Monitoring Plan will be developed and agreed by the TMG and CI to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted. This will be dependent on the documented risk assessment of the trial which determines the level and type of monitoring required for specific hazards. All processes may be subject to monitoring, e.g. enrolment, consent, adherence to trial interventions, accuracy and timeliness of data collection etc.

14.3.1 Central monitoring

There are a number of monitoring features in place at the CTU to ensure reliability and validity of the trial data, to be detailed in the trial monitoring plan. Data will be entered into a validated database and during data processing there will be checks for missing or unusual values (range checks) and for consistency within participants over time. Other data checks relevant to patient rights and safety will also be regularly performed as per CTU processes. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at the CTU from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond the queries providing an explanation/resolution to the discrepancies and return the data query forms to the CTU. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database.

Site monitoring visits may be 'triggered' in response to concerns regarding study conduct, participant recruitment, outlier data or other factors as appropriate.

14.3.2 Clinical site monitoring

In order to perform their role effectively, the trial coordinator (or monitor) and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient medical records, laboratory reports, appointment books, etc. Since this affects the participant's confidentiality, this fact is included on the PISC. In agreeing to participate in this study, a PI grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation. The purposes of site monitoring visits include, but are not limited to:

- assessing compliance with the study protocol;
- discussing any emerging problems that may have been identified prior to the visit;
- checking CRF and query completion practices.

As most of the data forming the basis of this study is from routinely collected sources, no routine central site monitoring visits are planned.

14.4 Confidentiality

This study will collect personal data (e.g. participant names), including special category personal data (i.e. participant medical information) and this will be handled in accordance with all applicable data protection legislation. Data (including special category) will only be collected, used and stored if necessary for the study (e.g. evidencing provision of consent, for data management and central monitoring, statistical analysis, regulatory reporting, etc.). At all times, this data will be handled confidentially and securely.

CRFs will be labelled with the participant's initials and unique study ID. Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent forms being supplied to the CTU by recruiting sites. This transfer of identifiable data is disclosed in the PISC.

Site-specific study-related information will be stored securely and confidentially at sites and all local relevant data protection policies will be adhered to.

The LCTC will store personal data to allow posting of QoL questionnaires. The LCTC as part of The University of Liverpool will preserve the confidentiality of participants taking part in the study.

14.5 Quality assurance and Quality control of data

To assure protocol compliance, ethical standards, regulatory compliance and data quality, as a minimum, the following will occur:

- The PI and other key staff from each centre will attend initiation training, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol.
- The TMG will determine the minimum key staff required to be recorded on the delegation log in order for the centre to be eligible to be initiated.
- The TC at the LCTC will verify appropriate approvals are in place prior to initiation of a centre and the relevant personnel have attended the trial specific training. A greenlight checklist will verify all approvals are in place prior to trial initiation at LCTC and the individual centre.
- The trial will be conducted in accordance with procedures identified in the protocol.
- The IDSMC and independent members of the TSC will provide independent oversight of the trial.
- The TMG will monitor screening, randomisation and consent rates between centres and compliance with the protocol.
- Data quality checks and monitoring procedures will be undertaken in line with the trial Data Management Plan.

Quality Assurance of Core Lab is described in Appendix 3 Core lab SOP. Quality assurance of NVR data, NHS Digital data and site collected data is performed by separate measures due to distinct requirements. This is further detailed in the UK-COMPASS Statistical Analysis Plan.

14.6 Records Retention

The retention period for the UK-COMPASS data and information is 15 years from the official End of Trial date (defined in section 13.2 above).The investigator at each investigational site must make arrangements to store the essential study documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Trial File, until the Sponsor or the LCTC informs the investigator that the documents are no longer to be retained. In addition, the investigator is responsible for archiving of all relevant source documents so that the study data can be compared against source data after completion of the study (e.g. in case of inspection from authorities).

The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing. The LCTC undertakes to store originally completed CRFs and separate copies of the above documents for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only. At the point where it is decided that the study documentation is no longer required; the Investigator will be responsible for the destruction of all site study specific documentation and the Sponsor/LCTC will be responsible for the destruction of all study related materials retained by the Sponsor/LCTC.

15. Regulatory Approvals

15.1 Ethical considerations

The UK-COMPASS The protocol has undergone ethical review by an independent Research Ethics Committee and has received a favourable opinion. UK-COMPASS is a purely observational study capturing outcomes of standard clinical practice. Treatment is not affected by study and therefore there are no major ethical implications.

15.2 Regulatory Approvals

The study protocol, ICF, PIS and all other patient facing study documentation has received the favourable opinion of the North West - Preston Research Ethics Committee (REC) and HRA approval.

Details of approvals:

- National Research Ethics Committee (REC) - 30/11/2017
- Confidential Advisory Group (CAG) - 13/12/2017
- Health Research Authority (HRA) - 18/12/2017
- NHS Digital Data Sharing Agreement (initial): 10/08/2018
- NHS Digital Data Sharing Agreement (superseding the previous): 27/09/2019
- HQIP Data Sharing Agreement (for NVR Data): 04/12/2018

Any substantial amendments to the original approved documents will be submitted and, where necessary, approved by the above parties before use.

15.3 Hospital/Site Approvals

15.3.1 Site R&D approvals

All sites participating in the Quality of Life study/Site Collected data aspect of the study must undergo site specific assessment and confirm capacity and capability before participating in the study.

15.3.2 Caldecott Guardian Approvals

Caldecott Guardians at all hospitals within England will be written to, by the study team, and advised that anonymous data in the form of CT Scans of their patients will be accessed via the NHS Picture Archiving and Communications System (PACS). As this data will be coming directly from NHS PACS hospitals will not be required to provide capacity and capability for this aspect of the study. Approval to collect this data without consent has been provided by CAG (see section 15.2)

16. Indemnity

UK-COMPASS is sponsored by The Liverpool University Hospitals NHS Foundation Trust and co-ordinated by the LCTC in the University of Liverpool.

The sponsor holds insurance against claims from participants for harm caused by their participation in this clinical study. However, the treating hospital continues to have a duty of care to the participant and the Sponsor does not accept liability for any breach in the hospital's duty of care, or any negligence of the part of hospital employees. In these cases, clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

As this is an observational study, there is little risk of injury caused by participation in this study.

17. Financial Arrangements

This study is funded by the NIHR Health Technology Assessment (NIHR_HTA) Board of the Department of Health.

There are no payments made to patients for participation in the study.

As the study has been funded by the NIHR HTA it has been adopted to the NIHR portfolio which will allow sites to apply to their local Clinical Research Network for service support costs.

18. Publication and Dissemination

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.

Publications will be sought in peer-reviewed journals of high impact factor, presentations and lectures in scientific meetings, as well as releases to non-peer reviewed medical press.

Due to the major impact the findings of this study are likely to have, investigators will seek to present the findings of the study at the annual conferences of The Vascular Society of GB & I, the British Society of Interventional Radiology, The British Society for Endovascular Therapy and The Society for Vascular Nursing, all representing professionals with an interest in the welfare of patients with juxtarenal AAA.

The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants, and if there are named authors, these will include the Chief Investigator(s), Statistician(s) and Project Manager(s). If there are no named authors (i.e. group authorship) then a writing committee will be identified. The ISRCTN allocated to this study should be attached to any publications resulting from this study.

The members of the TSC and IDSMC will be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

On completion of the research, a Final Study Report will be prepared and submitted to the REC. The results of UK-COMPASS will be published regardless of the magnitude or direction of effect.

19. References

1. Cepeda, M. S., Boston, R., Farrar, J. T., & Strom, B. L. (2003). Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. American journal of epidemiology, 158(3), 280-287.
2. Health Quality Ontario. Fenestrated endovascular grafts for the repair of juxtarenal aortic aneurysms: an evidence-based analysis. Ont Health Technol Assess Ser 2009;9:1–51.
3. Sultan S, Hynes N. Clinical efficacy and cost per quality-adjusted life years of pararenal endovascular aortic aneurysm repair compared with open surgical repair. J Endovasc Ther 2011;18:181–96.
4. Michel M, Becquemin JP, Clément MC, Marzelle J, Quelen C, Durand-Zaleski I; WINDOW Trial Participants. Editor's choice - thirty day outcomes and costs of fenestrated and branched stent grafts versus open repair for complex aortic aneurysms. Eur J Vasc Endovasc Surg 2015;50:189-96.

20. Protocol Version History

Version 6.0 dated 21/07/2022

section number	Section	short description of change
	Protocol Approval	Change in lead study statistician from Barbara Arch to Richard Jackson; Authorised on behalf of LCTC removed
	Contact details	Change in study statistician from to Barbara Arch to Anna Rosala-Hallas; Change in Project Manager from Claire Taylor to Nadia Ismail; Change in Health Economist from Rui Duarte to inter-regnum
1	Protocol summary	Changes made to sample size, inclusion criteria, exclusion criteria and study duration
2.3.1	Trial Management Group	Membership details updated
4.1	Efficient study design	Rationale provided for discontinuing the site reported data collection (recruitment and follow up) and for the addition of retrospectively identified medically managed cases at site
5.1.2	Site Collected Data (Quality of Life Study)	Clarification that recruitment to site reported data collection stream has been discontinued
5.1.3	Retrospectively Identified Medically Managed Patients at Site	Section added
5.2.2	Site Collected Data (Quality of Life)	Clarification that recruitment to the site reported data collection stream has been discontinued
5.2.3	Retrospectively Identified Medically Managed Patients at site	Centre/clinician study inclusion criteria added
7.1.4	Patient Reported Outcome Measures (PROMs)	Clarification that the site reported data collection stream has been discontinued
8.1.2	Medical Management - Operation Deferred	Clarification that the site reported data collection stream has been discontinued.
10.1.2	Identified at site	Clarification that the site reported data collection stream has been discontinued
10.1.3	Retrospectively identified at site	Section added
10.2	Data Collection	Section updated

10.3	Informed consent by participating sites	Section deleted as no longer applicable
10.4	Eligibility Assessment and Confirmation	Section deleted as no longer applicable
10.5	Baseline Data	Section deleted as no longer applicable
10.6	Patient Registration	Section deleted as no longer applicable
11.2.2	Site collected data (Quality of Life) – sample size	Section updated
11.2.3	Retrospectively Identified at Site – sample size	Section added
12.3	Health Economics Model Development	Section updated
13.1.2	Site Collected Data	Updated to remove references to site reported data. Addition of option to opt out of retrospectively collected data
13.1.2.1	Loss to follow up	Section on site reported data deleted
14.2.2	Data collection methods for patients identified at site	Section updated
14.2.3	Data Collection methods for retrospectively identified medically managed patients	Section added

Version 5.0 dated 26/10/2021

section number	section	short description of change
	Protocol Approval	Change in lead study statistician from Eftychia Psareli to Richard Jackson
	Contact details	Change in lead study statistician from Eftychia Psareli to Barbara Arch
	Protocol summary	Rephrasing of secondary endpoints
3.1	Introduction	Typographical errors fixed
3.3	Objectives	Clarified that objective 3 is over 5 years
4.1	Efficient study design	Clarification that patients identified at site will also be having data collected from routine sources

5.1	Inclusion/exclusion criteira	Criteria added for routinely collected data group
6	Study endpoints	Rephrasing of endpoints
8	Physical stratification	Text added to clarify terms
10.8	Schedule of follow up	Table updated
10.8.4	QoL completion	Updated to allow participants to complete data electronically as well as by phone and post
10.9	Data collection methods	Moved to section 14
11.4	Analysis plan	updated
12.3	Health Economic Model Development	updated
13	End of study and withdrawal	Updated to show patients can opt out from routinely collected data collection using the NHS opt out service

Version 4.0 dated 12/03/2020

A reformat of protocol layout to fit LCTC template:

section number	section	short description of change
	N/A	branding added
	protocol approval	signature page added
	General statement	general statement added
	Contact details	reformatted
	List of abbreviations	changed to glossary
1	Protocol Summary	Table added
1	Roles and Responsibilities	Section added. Included funder statement. Replaces project management text, previously found at the end of the protocol
2	Background Information	new title - replaces background and rationale
3.1	Introduction	Text redrafted
3.2	Rationale	Text redrafted
3.3	Objectives	Added statement on what the evidence generated from the study will do.
3.3	objective 4	slightly rephrased
	objective 5	slightly rephrased
4	Study design	Title study design replaces 'pilot study'. Pilot study text deleted
4.1	Efficient study design	new text

5	Study population and interventions	Re-titled. Redrafted
5.1 and 5.2	Inclusion and exclusion criteria	rephrased and split into routinely collected data, and quality of life study
5.3	Study Setting	replaces study period
6	study outcomes	subheading of outcomes given section in its own right
6.1	early endpoint	term 'perioperative death' added
6.2	secondary endpoints	aneurysm expansion replaces endotension
6.3	Health Economic outcome measures	new sub section added
7.1.1	NVR	moved from design and framework section of v3.0
7.1.2	HES	moved from design and framework section of v3.0
7.1.3	CORE lab	New section
7.1.5	micro costing	new section
7.2	Data set	New section
8	Aneurysm stratification	New section
9	Study Risks	New section
10	participant timelines and assessments	replaces old section on PROMS
10.3.1	Telephone consent	added
10.8.3	Telephone QoL completion	added
11	Statistical considerations	Text redrafted
12	Health Economic evaluation	Some text redrafted
13	End of Study and patient withdrawal	section added
14	Regulatory approvals	replaces prior section of approval by ethics committees
15	Indemnity	new section
16	Financial arrangements	new section
17	Publication and dissemination	New section
18	References	New Section
19	Protocol version history	New section
20	Appendices	New section

Version 3.0 dated 11/12/2017

Changes N/A as first REC approved version of protocol.

Version 2.0 dated 11/07/2017

Changes N/A as unapproved version.

Version 1.0 dated 19/12/2016

Changes N/A as unapproved version.

21.List of appendices as separate documents

- Appendix 1 Commissioning Brief
- Appendix 2 Data sets
- Appendix 3 Core lab Standard Operating Procedure
- Appendix 4 Micro costing Template
- Appendix 5 Data Flow
- Appendix 6 Stratification of Anatomical Complexity and Physiological Fitness