Non-CTIMP Study Protocol

The DAShED (Diagnosis of Aortic Syndrome in the ED) study

An observational cohort study of people attending the ED with symptoms of Acute Aortic syndrome (AAS)

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LIST OF ABBREVIATIONS

AAS	Acute Aortic Syndrome
ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
ADD-RS	Aortic Dissection Detection – Risk Score
CI	Chief Investigator
CRF	Case Report Form
CTA	CT aortogram
ED	Emergency Department
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
PI	Principal Investigator
QA	Quality Assurance
REC	Research Ethics Committee
RCEM	Royal College of Emergency Medicine
SOP	Standard Operating Procedure

1 INTRODUCTION

1.1 BACKGROUND

AAS is a life-threatening emergency condition which presents to the ED. Around 4,000 people suffer per year in the UK **[1]**, many not receiving timely diagnosis and treatment. 25% of patients are not diagnosed until 24 hours after arriving in the ED due to the varied nature of presentation **[2]**. Chest pain is the most common presenting symptom of AAS (80%) although back pain (40%) and abdominal pain are not uncommon **[1]**. These symptoms account for over 2 million ED attendances per year in England [NHS Digital A&E 2021] and are overwhelmingly due to causes other than AAS. The estimated incidence of AAS is 1 in every 980 ED attendances with atraumatic chest pain **[3]**, thus creating a substantial diagnostic challenge.

1.2 RATIONALE FOR STUDY

Prognosis is best when patients are treated early, and mortality increases 2% per hour of delay. **[4]** The misdiagnosis rate during the initial ED visit for AAS is estimated to be between 1 in 3 to 1 in 7 AASs **[5]**, leading to worse outcomes **[6,7]** whilst CTA over testing leads to diagnostic yields as low as 2-3%. **[2,8].** CTA scanning of the aorta has high sensitivity and specificity for diagnosing AAS, but an unrestricted CT strategy will incur significant costs, has ionising radiation risks, resource implications, CT delays for non-AAS patients and the burden of 'incidentalomas'.

Clinicians therefore need to use CTA selectively but there is no validated scoring system to help this decision. Several have been proposed **[1, 9-14]** including the ADD-RS score, the Canadian clinical practice guideline Clinical Decision Aid **[13],** the AORTAs score **[14]** and the Sheffield score **[unpublished]**.

D-Dimer has been suggested as a rule-out biomarker in low pre-test probability patients (95-98% sensitivity) **[15,16]** and has been incorporated into the ADD-RS score to reduce CTA rate in low pre-test probability patients.

None have been studied in truly undifferentiated ED populations, or in the UK where CTA threshold is different compared to North America. It is currently unclear whether any have sufficient sensitivity to be acceptable to clinicians, which is the most accurate, and whether they are likely to lead to CTA and D-Dimer over testing. Assessment of CTA rate and CT positivity has also not previously been studied.

The Royal College of Emergency Medicine has recently released a national guideline advocating any patient with an ADD-RS score of >=1 (no D-dimer incorporated) should have a CT aorta performed (unless other cause for symptoms identified and evidenced). The recommendation is not based on UK-validated clinical evidence, however, and clinical impacts of the recommendation are yet to be seen.

In view of these diagnostic challenges, we aim in our programme of work to ultimately to assess which of the four aforementioned clinical decision tools is most effective, assess external validity, and assess clinical impact. This study (Phase 1; DAShED) will involve prospective data collection on all characteristics of four different risk scores, in addition to evaluation of patient characteristics, potential CT aorta rates with different strategies, and enrolment rates at participating sites. This will inform Phase 2, which will involve full interventional external validation study of the decision aid(s) selected in Phase 1 (including biomarker collection); the main objective being to select the score to subject to assessment of clinical impact (intervention step-wedge trial) in Phase 3.

2 STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

To establish data characteristics of four clinical decision tools (ADD-RS, Canadian Clinical Practice Guideline, AORTAs score and Sheffield score) in patients presenting to the ED with any symptoms potentially attributable to acute aortic syndrome.

2.1.2 Secondary Objectives

To establish:
1. Patient characteristics
2. Potential CTA rates with different clinical decision tools
3. Patient enrolment rates at participating sites

2.2 ENDPOINTS

2.2.1 Study Endpoints

1. Enrolment rate at each participating site
2. Proportion of patients in whom the ED clinician thinks AAS is a possible differential who have confirmed AAS
3. Proportion of patients in whom ED clinician considers AAS NOT a possible differential who had confirmed AAS
4. Number of AAS patients not enrolled due to lack of clinical/research support
5. CTA ordering and positivity rate
6. Test characteristics of clinical acumen, ADD-RS score, AORTA score, Canadian guideline score and Sheffield AAS decision rule, and D-dimer (separately and in combination)
7. Median time from hospital presentation to imaging diagnosis and median time from symptom onset to hospital presentation (hours)
8. 30-day mortality in proven AAS
9. Proportion of alternative diagnoses found on CTA and final hospital diagnosis
10. Identification of barriers to enrolment

3 STUDY DESIGN

This is an observational cohort study of all people attending the ED with symptoms of possible AAS, including new-onset chest, back or abdominal pain, syncope or symptoms related to malperfusion.

A case report form (CRF) may be placed in the notes of all patients with these presenting symptoms by reception or triage staff. The clinical team (including research staff where part of clinical team) will also screen in person and prospectively using Electronic Patient Records (EPRs). We anticipate that medical student teams will play a role in identifying potential patients and alerting the treating clinician to them. Clinicians will be asked if they suspect AAS as a possible diagnosis and will also be able to include patients who don't fit these symptoms in whom they suspect AAS.

Data will be collected prospectively on all characteristics of the ADD-RS, Canadian clinical practice guideline Clinical Decision Aid, the AORTAs score, and the Sheffield score. Where appropriate patients are not prospectively enrolled by the treating clinician, the clinical team (including research staff where part of clinical team) will perform daily searches of EPRs to identify patients in whom AAS is mentioned and where presenting complaint is of new-onset chest, back or abdominal pain, syncope or symptoms related to perfusion deficit. The clinical team will also perform daily searches of Radiology-ordering EPRs to identify all patients

undergoing CTA in the ED. These patients will be enrolled retrospectively. The treating clinician will be approached by members of the clinical team as soon after the consultation as possible to complete missing information.

Participants will be followed up at 30 days by the clinical team using routine data from EPRs. The clinical team will perform searches of Radiology ordering systems to identify all patients undergoing CTA within 30 days of ED presentation. All sites will separately provide data on confirmed AAS during the study period through routine clinical data collection (e.g. M&M, post mortem, ED/hospital coding).

Remaining non-identifiable CRF data will be entered into Redcap once the 30- day outcome and CTA data are reviewed. No patient-identifiable data will be inputted in Redcap, leave the local NHS Trust, or be viewed outside the clinical team.

4 STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

This is an exploratory study recruiting a convenience sample of participants from at least 5 EDs for 1 month, and, as such, no power calculation has been undertaken. We estimate that around 5000 people will attend the ED with symptoms of AAS, including those with new-onset chest, back or abdominal pain, syncope or symptoms related to perfusion deficit during this one-month study period, of whom 125 will undergo CTA and 6 patients will have confirmed AAS.

4.2 INCLUSION CRITERIA

- People attending the ED with symptoms of AAS, including those with new-onset chest, back or abdominal pain, syncope or symptoms related to malperfusion.
- ≥16 years old

4.3 EXCLUSION CRITERIA

- No symptoms of AAS.
- <16 years old

4.4 CO-ENROLMENT

Co-enrolment will be permitted to CTIMPs and non-CTIMPs where doing so is not expected to burden the participant in line with the Sponsors co-enrolment policy.

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

We will prospectively identify people attending the ED with symptoms of AAS through a variety of methods including but not limited to: reception staff and triage teams placing a focussed one page paper Case Report Form (CRF) in the patient notes of those persons presenting with new-onset chest, back or abdominal pain, syncope or symptoms related to perfusion deficit, local clinical staff advertising and recruitment campaigns, appointment of local champions, utilisation of local TERN networks through the adoption of DAShED as a TERN Supported Project (https://ternresearch.co.uk/tern-projects), research (where part of clinical team) screening in person and prospectively using Electronic Patient Records (EPRs),

and use of medical student teams identifying potential patients and alerting the treating clinician to them.

The clinical team will perform daily searches of EPRs to identify all patients in whom AAS is mentioned and where presenting complaint coding is available, we will identify all patients with a presenting complaint of new-onset chest, back or abdominal pain, syncope or symptoms related to perfusion deficit.

The clinical team will perform daily searches of Radiology ordering EPRs to identify all patients undergoing CTA in the ED. All these patients will be recruited retrospectively and will have a focussed one-page CRF completed including the presence of characteristics of existing clinical probability scores along with D-Dimer and CTA results, where performed, ED clinician rating as to likelihood of AAS, time of ED presentation, time of symptom onset in hours and time of CTA, and at 30 days, whether patient is alive; whether AAS has been diagnosed and final hospital diagnosis.

When able, the treating clinician will be approached by members of the clinical team as soon after the consultation as possible to complete missing information. If the ED clinician thinks that there is a negligible likelihood of AAS, the patient will still be enrolled, and data collected with 'Acute aortic syndrome/dissection a possible diagnosis?' coded as 'no'. This will allow us to know what proportion of presentations with symptoms suggestive of AAS have no clinical concern of AAS.

Remaining non identifiable CRF data will be entered into Redcap once 30-day outcome and CTA data has been reviewed. No identifiable data will be inputted in Redcap, leave the local NHS Trust, or be viewed outside the clinical team.

5.2 CONSENTING PARTICIPANTS

This study involves no change in clinical care and no study specific interventions for participants. It carries minimal clinical risk. We will be collecting routinely collected data and wish to maximise recruitment to produce a study with maximal generalisability, so will not approach individual participants for written consent. We will be adopting a zero-consent strategy. No personal information will be collected, and data will remain fully anonymised. All access to data before anonymisation will be undertaken by the direct care team.

We will seek approval from a REC Committee. This strategy has been previously approved by REC committees for similar studies (e.g. An observational Study of E-scooter impacts upon ED in the United Kingdom; SEED-UK; https://ternresearch.co.uk/seed-uk).

Information posters informing patients we are collecting fully anonymised data will be displayed around individual sites and a patient information sheet (PIS) will be available to participants and recruiting sites to be available upon request.

5.2.1 Withdrawal of Study Participants

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator. The study poster and PIS will advise participants wishing to withdraw to contact their treating clinician or local PI. If withdrawal occurs, data collected up to that point will be retained as locally stored linkage between hospital number and study number is likely to have been deleted.

6 STUDY ASSESSMENTS

6.1 STUDY ASSESSMENTS

Assessment	Screening	30 days
Assessment of Eligibility Criteria	☐	
CRF completion including demographic data, clinical details	☐	
30 day follow-up clinical information		☐

6.2 LONG TERM FOLLOW UP ASSESSMENTS

There will be no follow-up of patients. Electronic health records will be checked for any outstanding data items (such as 'Length of hospital stay in days' and the 'Hospital Discharge Diagnosis').

7 DATA COLLECTION

All patients whether recruited prospectively or retrospectively will have a focussed CRF completed. This can either be completed directly onto the eCRF or recorded on a paper CRF and then later transferred to the eCRF by the local study team.

The local study team, who will be part of the clinical care team, will keep an up to date record on a password protected NHS computer linking the patient's hospital number with their study number until such time as the patient is discharged from hospital (this may be within a few hours up to many days) in order that the 'Length of hospital stay in days' and the 'Hospital Discharge Diagnosis' can be obtained and entered onto the CRF and eCRF. At that point the hospital number/study number linkage record will be removed.

No identifiable data will be entered onto the CRF and eCRF, leave the local NHS Trust, or be viewed outside the clinical team.

7.1 Source Data Documentation

The patient's electronic patient record will be the only source document.

7.2 Case Report Forms

All patients whether recruited prospectively or retrospectively will have a focussed CRF completed. This can either be completed directly onto the Redcap eCRF or recorded on a paper CRF and then later transferred to the eCRF by the local study team.

Data collected through the DAShED Case Report Form will include:

- ED attendance time: hh:mm
- Symptom onset time: hh (nearest hour)

Presenting complaint:

- Chest pain / Back pain / Abdominal pain / Syncope / Malperfusion (central nervous system, cardiac, mesenteric, limb)?
- Other (none of the above, if so what)?
- Neurology: paraparesis, hemiparesis/acute confusion (can be transient)?
- Acute aortic syndrome/dissection a possible diagnosis?
- if Y, ED clinician rating of likelihood of AAS
- Acute aortic syndrome/dissection the most likely diagnosis?
- Suspicion for an alternative diagnosis?

- Pain severe intensity or worst ever?
- Pain thunderclap/abrupt onset (including worst when awoke)?
- Pain Tearing or ripping?
- Pain Migrating or radiating?
- Pregnant?
- Recent significant trauma (i.e., high speed deceleration injury)
- Recent recreational drugs (cocaine, crack, other sympathomimetics)?

Past Medical History:

- Marfan syndrome / Connective tissue disease / Ehler Danlos / Giant cell arteritis?
- Known aortic dissection/syndrome, aortic disease/Coarcation?
- Aortic valve disease (Bicuspid /Dilated aortic root)?
- Recent aortic manipulation / Instrumentation?
- Known Thoracic Aortic Aneurysm?
- Known Abdominal Aortic Aneurysm?

Family History:

- Family history of AAS/ aortic disease)?

Physical Examination findings:

- Pulse deficit?
- Systolic BP differential (>20mHg difference in SBP)?
- Focal Neurological deficit?
- New aortic insufficiency/AR murmur?
- Hypotension (SBP < 90mmHg)/shock/ pericardial effusion?
- Poorly controlled hypertension (SBP >140 or DBP> 90)?

Investigations:

- D-Dimer performed?
- if so; Value of D-Dimer/ ng/mL
- CXR performed in ED?
- If so; abnormal Mediastinum?
- CT chest performed?
- If Y; was this a CT Angiogram?
- If Y; Time of CT: hh:mm;
- If Y; CT positive for AAS?
- If Y; Alternative diagnoses found on CTA?
- Confirmed AAD?
- If Y then Time of Confirmed AAS (hh:mm)
- If Y; Location of patient when AAS confirmed?

Routinely collected EPR data:

- Alive at 30-days
- AAD diagnosed
- Final hospital diagnosis

8 DATA MANAGEMENT

8.1.1 Personal Data

Personal data will be collected as part of the study by the local direct clinical care team and held until the 30 day outcome data entry is completed, at which point, it will be destroyed.

8.1.2 Data Information Flow

The patient's hospital number and corresponding study number will be kept on a password protected NHS computer until such time as the patient is discharged from hospital. Identifiable data will not leave the NHS Trust/Board.

8.1.3 Transfer of Data

Non-identifiable data collected and generated by the study will be transferred into a specially designed password protected online accessed secure database (REDCAP; http://www.project-redcap.org) the server of which is held within the University of Edinburgh. No participant identifiable information will leave the recruiting NHS hospital or be entered onto REDCAP. Participants will be identified on REDCAP by study number alone. Study data will be collected by local clinicians who would have access to this data as part of routine clinical care. Study ID numbers only will be entered into the online database with anonymised data.

8.1.4 Data Controller

NHS Lothian and the University of Edinburgh (ACCORD) will be the data controllers in accordance with applicable laws.

8.1.5 Data Breaches

Any data breaches will be reported to the NHS Lothian and University of Edinburgh (ACCORD) Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

9 STATISTICS AND DATA ANALYSIS

9.1 SAMPLE SIZE CALCULATION

This is an exploratory study recruiting a convenience sample of participants from at least 5 EDs for 1 month, and, as such, no power calculation has been undertaken. We estimate that around 5000 people will attend the ED with symptoms of AAS, including those with new-onset chest, back or abdominal pain, syncope or symptoms related to perfusion deficit during this one-month study period, of whom 125 will undergo CTA and 6 patients will have confirmed AAS.

This will provide sufficient power to estimate key measures with an acceptable degree of precision, e.g. 0.12% prevalence of confirmed AAS with 95% CI 0.04 to 0.26%; 2.5% prevalence of CTA use with 95% CI 2.1 to 3.0%. However, it will not be problematic to this specific study if we don't recruit 5000 patients.

9.2 PROPOSED ANALYSES

A descriptive analysis will be performed. Categorical variables will be summarised using frequencies and percentages; continuous variables will be summarised using the mean, standard deviation (SD), median, lower quartile, upper quartile, minimum and maximum values. Exact binomial 80% confidence intervals will be constructed around enrolment proportions and other key proportions such as the proportion of patients in whom the clinician considers AAS is not a possible differential. We will use exact methods (e.g. Clopper-Pearson) to calculate the confidence intervals. The confidence intervals will inform us as to the likely proportions we will expect to observe in Phases 2 & 3.

10 OVERSIGHT ARRANGEMENTS

10.1 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

10.2 STUDY MONITORING AND AUDIT

The ACCORD Sponsor Representative will assess the study to determine if an independent risk assessment is required. If required, the independent risk assessment will be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and, if so, at what frequency.

Risk assessment, if required, will determine if audit by the ACCORD QA group is required. Should audit be required, details will be captured in an audit plan. Audit of Investigator sites, study management activities and study collaborative units, facilities and 3rd parties may be performed.

11 GOOD CLINICAL PRACTICE

11.1 ETHICAL CONDUCT

Ethical approval will be sought. The study will not commence until REC Approval is confirmed. The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained, and any conditions of approvals will be met.

11.2 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

11.2.1 Informed Consent

This study involves no change in clinical care and no study specific interventions for participants. It carries minimal clinical risk. We will be collecting routinely collected data and wish to maximise recruitment to produce a study with maximal generalisability, so will not approach individual participants for written consent. We will be adopting a zero-consent strategy. No personal information will be collected, and data will remain fully anonymised. All access to data before anonymisation will be undertaken by the direct care team.

Information posters informing patients we are collecting fully anonymised data will be displayed around individual sites and a patient information sheet will be available to participants and recruiting sites to be available upon request.

11.2.2 Study Site Staff

The Investigator must be familiar with the protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the protocol and their trial related duties.

11.2.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

11.2.4 Investigator Documentation

The Principal Investigator will ensure that the required documentation is available in local electronic Investigator Site files ISFs.

11.2.5 GCP Training

The CI and local PIs will undertake GCP training to understand the principles of GCP.

11.2.6 Confidentiality

All records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished information, which is confidential or identifiable, and has been disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

11.2.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information.

Computers used to collate the data will have limited access measures via user names and passwords. Published results will not contain any personal data and be of a form where individuals are not identified and re-identification is not likely to take place.

STUDY CONDUCT RESPONSIBILITIES

11.3 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Amendments will be submitted to a sponsor representative for review and authorization before being submitted in writing to the appropriate REC, and local R&D for approval prior to participants being enrolled into an amended protocol.

11.4 MANAGEMENT OF PROTOCOL NON COMPLIANCE

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, and local R&D for review and approval if appropriate.

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation. All protocol deviation logs and violation forms should be emailed to QA@accord.scot

Deviations and violations are non-compliance events discovered after the event has occurred. Deviation logs will be maintained for each site in multi-centre studies. An alternative frequency of deviation log submission to the sponsors may be agreed in writing with the sponsors.

11.5 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:
(a) the safety or physical or mental integrity of the participants of the trial; or
(b) the scientific value of the trial.
If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (seriousbreach@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value

of the trial, to determine whether the incident constitutes a serious breach and report to research ethics committees as necessary.

As there is no change to diagnostic processes or treatment, and as all information is recorded as in routine clinical care, there is no additional clinical risk over standard care.

11.6 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 3 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

11.7 END OF STUDY

The end of study is defined as the 30 day outcome point of the last recruited participant. The Investigators or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, and R+D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot

A summary report of the study will be provided to the REC within 1 year of the end of the study.

11.8 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.

Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.

Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.

12 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

12.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the DAShED central study team. All publications and presentations must be approved by the DAShED study steering committee.

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