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Carbon dioxide flushing versus saline flushing of thoracic aortic stents for cerebral embolic protection in thoracic endovascular aortic repair (INTERCEPT): protocol for a multicentre randomised controlled trial

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Keywords:
Thoracic aortic endovascular repair; cerebral infarction; stroke; cognitive decline

Abstract:

Introduction

Thoracic endovascular aortic repair (TEVAR) carries a 3%-6.1% stroke risk, including risk of 'silent' cerebral infarction (SCI). SCI do not cause motor, sensory or speech deficits, but have been shown to be a predictor of future development of stroke, dementia and depression.

Stent-grafts are manufactured in room air and retain air. IFU recommends saline flushing to 'de-air' the system prior to insertion, but substantial amounts of air are released when deploying them, potentially leading to downstream neuronal injury and SCI. Carbon dioxide (CO_2) is more dense and soluble in blood than air, without risk of bubble formation, so could be used in addition to saline to de-air stents.

The current pilot RCT aims to answer the question 'Is there a neuroprotective benefit against SCI with the use of CO_2 flushed aortic stent-grafts?'

Methods and Analysis
Patients identified for TEVAR will be enrolled after informed written consent. Participants will be randomised to a TEVAR-CO_2 or TEVAR-Saline group, stratified according to TEVAR landing zone.

Participants will undergo pre-operative neurocognitive tests and quality of life assessments, which will be repeated at 6 weeks and 6 months. Inpatient neurological testing will be performed on day 1, 3 and 7 to screen for clinical stroke or delirium. DW-MRI will be undertaken within 72 hours post-operatively and at 6 months to look for evidence and persistence of SCI. We aim to recruit 120 participants (60 per group) based on our sample size calculation.

Ethics and dissemination (including registration details)

There is ethical approval for recruitment in UK (ClinicalTrials.gov Identifier NCT03886675), and New Zealand (21/STH/192).

Article summary

Strength & Limitations of this study

Limitations:

- Incomplete blinding as the surgeons carrying out the procedure cannot be blinded to stent graft flushing.

Strengths:

- Unprecedented levels of neurocognitive data, neuroimaging and follow up for patients undergoing TEVAR to determine the clinical impact of cerebral infarction complicating thoracic aortic endovascular repair.
- Multicentre RCT providing generalizable results.
- A cheap and readily available intervention is being studied, and results could be rapidly implemented. The study has potential far reaching ramifications for TEVAR and potentially other forms of endovascular intervention.
- The results of our study will be used to gather further information regarding the neurological risk associated with TEVAR and the clinical significance of SCI, where a paucity of literature exists.

Patient and Public involvement

Patients will be involved throughout this trail, with initial informed consent to be randomised into one of the two arms for preparing the stent-grafts, the blood test, MRI scans, transcranial doppler studies and neurocognitive testing throughout the trial.

Introduction

There has been a significant increase in the number of thoracic endovascular aortic repairs (TEVARs) performed in the last decade. TEVAR is offered as preventative treatment to prevent rupture and death from aneurysmal aortic disease, aortic dissection and traumatic aortic injury. It has been adopted as the standard method for thoracic aortic repair as the avoidance of thoracotomy and aortic cross-clamping means morbidity is reduced and hospital stay is significantly decreased [1]. Although TEVAR has successfully reduced peri-procedural morbidity and mortality, stroke remains a significant risk. Several studies have identified risk factors contributing to neurological injury [2, 3] and further work is needed to investigate these risk factors to predict more accurately the patients at higher risk of neurological injury.

There is a reported 3%[4] to 6.1%[5] risk of stroke with TEVAR. Our own observational study has detected a 13% stroke rate in patients undergoing TEVAR[6]. Furthermore, 68% of the patients developed covert brain injury as evidenced by new areas of brain infarction (BI) seen on diffusion weighted MRI following TEVAR[6]. Covert brain injury occurs in aortic surgical and cardiovascular catheter-based interventions [6, 7] and because these lesions do not manifest as clinical stroke with motor, sensory or speech deficits, they are termed 'silent' cerebral infarction (SCI). The American Heart and Stroke Association[8] and the Neurological Academic Research Group (NeuroARC)[9] now recognise the evolving definition of 'stroke' into a tissue-based diagnosis even in the absence of clinical symptoms. Incidentally identified SCI is a predictor of future development of clinically overt stroke[10], dementia[11] and depression[12]. There is also a direct clinical consequence of SCI with cognitive deficits demonstrated by neuro-psychometric testing[11] and in our own study, 88% of patients with SCI suffered with neurocognitive decline[6]. Indeed, several studies have shown that radiologically detected cerebral infarcts tend to occur in those parts of the brain responsible for memory, mood and cognition. These procedurally related lesions are therefore not 'silent' but have clinically significant consequences.

Aetiological mechanisms of SCI in TEVAR remain uncharacterised, although several neuroimaging studies have detected evidence of SCI within a few days post-procedure, suggesting that peri-procedural cerebral embolisation may be a cause[7, 13]. Further support for this hypothesis comes from continuous TCD monitoring of the cerebral vessels for microembolic signals (MES) during TEVAR whereby high-risk phases for cerebral embolization have been shown to occur at specific time points during TEVAR[6, 14]. Stent-graft deployment is the phase most associated with embolisation , followed by wire manipulation in the aortic arch[6].

Through the use of embolic differentiation software, we have deduced that >90% of MES throughout TEVAR are gaseous in nature, with 81% of gaseous MES apparent at stent-graft deployment. Once deployment is complete, TCD monitoring typically detects no further embolic activity. We also found a positive association between number of gaseous MES and number of new DW-MRI BI [15]. This suggests that cerebral air embolization may be a significant cause of SCI in TEVAR and provides us with a basis on which to target preventative strategies.

Stent-grafts are manufactured in room air conditions and retain air. According to instructions for use (IFU), saline flushing is recommended to de-air the system. Emerging experimental studies have shown a substantial amount of air release from all commercially available grafts with bubbles ranging from 0.34-0.79ml, despite saline flushing (see Figure 1) [16, 17]. This is a cause for concern given that cerebral arterioles are 40-250μm in diameter[18]. Large bubbles would be expected to cause downstream ischaemia and neuronal injury, while smaller bubbles may incite endothelial damage and activation of inflammatory and clotting cascades that may then cause secondary ischaemia[19]. These small bubbles have been implicated in causing post-operative cognitive delirium (POCD)[20].

Carbon-dioxide (CO_2) is 1.5 times denser than air and can fill an enclosed space and displace air. It is 25 times more soluble in blood than air and does not lead to bubble formation[21]. CO_2 has been used extensively in cardiac surgery and shown to significantly reduce intracardiac air[22] and POCD[23]. CO_2 can also significantly reduce the average amount of released air from am TEVAR stent in an experimental setting (0.79 vs 0.51 mL, p=0.005)[17], and has been used clinically in a small series of TEVAR patients where the authors describe a 3% clinical stroke rate. However, none of these patients underwent any formal cognitive or neuroimaging assessment and there was no control group, which has prompted the INTERCEPT trial [24, 25].

We know that more proximal zones are associated with higher stroke rates. What remains unknown is whether CO_2 flushing is enough to prevent neurological brain injury in these riskier zones, or whether solid embolisation from the manipulation of instruments close to atherosclerotic aortic valves and carotid vessels in more proximal zones is the main risk factor for neurological injury. This information will be used to aid refinement of the inclusion/exclusion criteria for the full-scale RCT and will be used to refine the sample-size calculation for use in the final trial.

We carried out a pilot study of 20 TEVAR patients who underwent CO_2 flushing and used TCD to detect cerebral embolization rates and DW-MRI to assess for SCI. Intra-operatively, there were no MES detected at stent graft deployment. The SCI rate was 25% and there was no clinical stroke in any of the patients (in comparison to 81% SCI and 13% stroke rate in patients with saline flushing)[6]. Although encouraging, we recognize the need for level 1 evidence in the form of a robust randomised controlled trial to answer the question 'is there a neuroprotective benefit against SCI and POCD with the use of CO_2 flushed aortic stent-grafts.'

A review of registries on 28/01/2019 (www.clinicaltrials.gov and www.isrctn.com) found but no similar studies in TEVAR.

Research influence:
We have produced the largest case series to date regarding SCI in TEVAR and continue to highlight the magnitude of the problem by our ongoing study of neuroimaging, TCD, neurological and neurocognitive data on these patients. These data initially led us to believe that solid embolization of particulate atherosclerotic matter dislodged from the thoracic aorta was responsible for SCI. Accordingly, we trialed the use of a cerebral embolic protection device designed to capture particulate matter 'en-route' to the brain in a cohort of 20 patients. This established feasibility and safety, and a 98% capture rate of embolic debris and a reduction in the number of lesions on DW-MRI. However, all patients still had lesions, with the majority concentrated in the posterior circulation territory [15].

We suspect that both solid and gaseous emboli cause SCI. However, our TCD data continuously demonstrates an overwhelming occurrence of gaseous MES at stent-deployment in TEVAR patients with and without filters, that amounts to a greater contribution of total MES than cumulative solid MES throughout TEVAR. Particulate embolism appeared to numerically correlate with the size of infarct, whilst gaseous

emboli numerically correlated with the number of infarcts. These findings warrant our attention into investigating cerebral air embolism (CAE) as a cause of SCI and into CO2 flushed stent-grafts as a stand-alone intervention first, particularly as it is cheap, safe and easily implemented.

Whilst the different ultrasonic reflective properties of solid and gaseous emboli provide the basis for discriminating between the two, we are aware of skepticism regarding the sensitivity and specificity of TCD embolic differentiation software during an embolic shower.[26] We have sufficient recorded TCD data to demonstrate that the 'shower' of emboli seen at stent-graft deployment with resultant SCI on DW-MRI with saline flushing is reduced when stent-grafts are flushed with CO2, even when cerebral embolic protection devices are used to capture solid emboli. Reducing the contribution of gaseous embolic events will pave the way for future studies to tackle the residual problem of solid emboli, which will likely require the use of invasive devices, rather than a simple bench-top flushing procedure.

The results of our study will be used to gather further information regarding the neurological risks associated with TEVAR and the clinical significance of SCI, where a paucity of literature currently exists. It will also facilitate a more comprehensive and individualised consent process, allowing patients to make more informed decisions. We hope to inform the cardiovascular community about a potential prevention strategy against SCI. Stroke, dementia and neurocognitive decline are enormous burdens on healthcare resources, and any reduction in the incidence of these complications will have a positive effect on health economics, which is vital in the current financial climate.

(please see attached documents for images)

Figure 1. A) Air bubble release during stent-graft deployment from the proximal end of the stent-graft as it opens in a benchtop experiment carried out by our group
B) Air bubble release during stent-graft deployment from the distal end of the stent-graft as it opens in a benchtop experiment carried out by our group.

Methods & analysis

Type of study: Multi-centre pilot randomised controlled superiority trial (see Figure 2 for flow chart for RCT).
Duration: Estimated duration is 36 months for patient recruitment.
Number and type of subjects: All elective patients undergoing TEVAR for aortic pathology.
Target total sample size: 120, (60 in each intervention arm).

Enrolment

Patients suitable for TEVAR as decided upon by a vascular multi-disciplinary meeting will be invited to participate and enrolled after informed written consent. Participants will be recruited by the research team at each site before surgery before their procedure (Box 1).

Randomisation and Interventions

Participants will be randomly assigned to TEVAR-CO2 or TEVAR-S group (Box 1) providing they fulfil the entry criteria at screening (Box 2). Participants will be randomized 1:1 via computerized randomization tool via the INTERCEPT Redcap database with stratification by zone of TEVAR. The latter has been chosen because more proximal landing zones in the aortic arch for stent-graft placement are closer to the cerebral vessels and represent a greater risk factor for stroke (Zone 0>1>2>3> 4). Stratification by zones will ensure the groups are similar with respect to this potential confounding factor. Randomisation will occur on the day of surgery. The surgical team delivering the intervention in theatre will be unblinded but are not involved in assessing the outcomes of the study. Participants and outcome assessors will be blinded to group allocation. For sheathed devices, there is a side-port for flushing with saline and/or CO_2. For unsheathed devices (e.g. CTAG, Gore), bench top-models have shown that using a dry seal, can allow sufficient flushing of the stent with CO2 and saline.

Box 1 Intervention and Control treatment

TEVAR-S group

- **ALL** Stent-grafts used in a patient randomised to TEVAR-S are prepared according to their IFU including flushing of the device through the side flush port and with 60mls physiological saline solution.

TEVAR-CO2 group

- **ALL** Stent-grafts used in a patient randomised to TEVAR-CO2 are prepared according to their respective IFU. Flushing of the stent-graft will be performed first by flushing 100% CO_2 at 2l/min, 4 bar from a pressurized cylinder with 1.4inch tubing connected to the side flush port for 1 minutes followed by 60mls of physiological saline

Box 2 Inclusion and Exclusion Criteria

Inclusion criteria

- All patients suitable for TEVAR for any thoracic aortic pathology in zones 0-4

Exclusion criteria

- Stroke within the last 12 months
- Pregnancy
- <18yrs
- Unwilling or unable to provide informed consent
- Type II thoracoabdominal aneurysms

Withdrawal criteria

- Any patient has the right to withdraw from the study at any point; their treatment and management will not be altered in any way.

(please see attached documents for images)

Figure 2. Patient Flow chart for the pilot RCT

Primary objectives: Evaluation of pilot RCT processes

Conduct an evaluation of the processes described in this pilot RCT for a full-scale RCT including:

1. Recruitment (number eligible and willing to be randomised, identify challenges to randomisation)
2. Retention in follow-up assessments
3. Study design for the full RCT (appropriateness of inclusion/exclusion criteria, study outcomes) and identification of important stratification variables
4. Sample size refinement for a future full RCT

Secondary objectives: Neurological end-points

1. *Primary outcome: Incidence of **DW-MRI SCI***

MRI scans will be performed at each site where the patient is recruited from. DW-MRI will be performed within 72hrs postoperatively to look for new lesions using a 3-Tesla Discovery MR750w system (GE healthcare, UK) or equivalent system, and at 6-months routine outpatient appointment to look for residual disease. We have previously published the MRI protocol[15] that we will use and these sequences may have to be modified where only a 1.5T scanner is available and discussions with the local MR department will be undertaken to ensure image accuracy. Chronic small vessel ischemia will be classified using the Fazekas Scale[27]. Pre-op MRI will not be carried out, with a Fazekas score carried out on their post-op MRI to give an estimation of their chronic small vessel disease. This decision was made due to previous experience of loss of patients for follow-up scans, and the focus of the MRIs being on acute lesions, which will be easily identifiable using the MRI sequences chosen. MRIs will be compared for number, laterality and vascular territory (anterior or posterior

circulation, or border zone territory) of lesions. Maximum diameter and surface area of lesions will also be recorded and lesion surface area as measured on the slice of largest lesion diameter. Lesions are considered as separate if there is no continuity between them on the same slice and adjacent slices.

2. *Secondary outcome: Detection of* **periprocedural cerebral solid and gaseous emboli**

Continuous bilateral TCD insonation of the middle cerebral artery (MCA) will be used to detect rates of intraoperative solid and gaseous cerebralMES throughout all stages of TEVAR. For logistical reasons, this will likely be carried out at London centres only. Accepted criteria for emboli detection will be used[28]. MES will be differentiated between solid and gas through software using multi-frequency TCD instrumentation which insonates simultaneously between 2.0MHz and 2.5MHz (EmboDop DWL, Compumedics Ltd, Germany). Manual offline analysis of the number of solid and gaseous emboli will be performed by trained assessors independent of each other. As it is impossible to characterise a solid or gas embolus manually during an 'embolic shower', the automated observations of the TCD equipment will be used.

3. *Secondary outcome:* ***neurological assessment****, delirium,* ***neurocognitive and quality of life testing***

- Pre-operatively all patients will undergo:

a) Neurological assessment and outcome measurement with the National Institutes of Health Stroke (NIHSS) [29] and disability assessment on modified Rankin scale (mRS) [30-32].
b) Baseline delirium test with the 4AT [33].
c) Screening test for cognitive impairment with Montreal Cognitive Assessment (MOCA) [34]
d) Detailed neurocognitive assessment with a battery of validated tests categorized into visual memory, executive function, attention and decision-making. These have been devised after review of the literature, they are tests which we have used in our previous studies [35] and have been pragmatically chosen in collaboration with a clinical psychologist
    a. (i). Rey Auditory Verbal Learning [36]
    (ii). 'FAS'- Verbal fluency test (paper-based test) [37]
    (iii). Grooved Pegboard Test (instrumentation based test to assess manual dexterity) [38]
    (iv). Trail making test TMT [39] (paper-based test to assess attention and switching)
    (v). Hospital Anxiety and Depression Scale (HADS) [40] to detect any psychological influence on the test results (paper-based)
    b. (vi). National Adult Reading Test (NART)[41] to test premorbid intelligence levels
e) Quality of life assessment with SF-36 [42] and EQ5D5L[43].

- Day 1, 3, 7 and at discharge (if patient remains an inpatient throughout this time):

a) NIHSS and mRs
b) 4AT
c) MOCA

- 6-week, 6 month and 1 year follow-up:

a) NIHSS and mRS
b) 4AT
c) MOCA and neurocognitive battery as above
d) SF-36 and EQ5D5L

4. *Secondary outcome: Serial **biomarker** blood tests e.g. S100B*
   A sample of the patient's blood will be taken along with routine blood tests preoperatively, at the end of procedure and 24hrs later. We will study the upregulation of proinflammatory mediators in response to TEVAR between the two groups. Serial measurement of biomarkers will look at inflammatory pathway upregulation, modification of low-density lipoprotein (LDL) moieties inducing the modification of LDL into oxidised LDL and consumption of protection antibodies that work on maintaining homeostasis against danger associated molecular patterns (DAMPS)[44]. S100B is regarded as a marker of brain damage. Reduced serum levels have been detected in patients who underwent carbon-dioxide field flooding in mitral valve operations with cardiopulmonary bypass where there is a risk of CAE [45]. Further analysis will be done via a proteomic inflammatory panel analysis [46]. We will also study the extent of neurological injury using S100B and markers of cell death: TNF receptor 1 (TNFR-1), TRAIL receptor 2 (TRAILR-2) and Fas [47, 48].
   Levels of biomarkers will be correlated with DW-MRI SCI, neurological and neurocognitive assessments. For pragmatic reasons including transportation this test will only be conducted in participants recruited at London hospitals.

5. *Secondary outcome: **Risk factor assessment***
   Procedural risk factors such as conventional proximal landing zones for the stent (PLZ)[45], coverage of arch vessel origins and intraoperative factors such as but not limited to, number of digital subtraction angiography (DSA) runs and length of time of hypotension, stent type, length of procedure and post stent ballooning will be recorded for multivariate analysis to allow risk factor assessment.

Sample Size: Observational data indicate that the incidence of SCI from TEVAR is 81%[6]. Based on our CO2-pilot study that reduced SCI to 25%, a 50% reduction in SCI is possible. Taking a pragmatic and realistic approach to recruitment we aim for an effect size of 40% reduction in incidence of SCI. Considering a 10% MRI dropout rate from our observational study, a total of 76 (38 per group) would be sufficient to detect an effect size. However, given that randomisation will be by zone of TEVAR, of which there are 5, and we expect a 20% MRI drop-out rate, we are aiming to recruit 120 cases (60 in each arm). This number has been chosen to ensure 10-12 patients in each of 5 arch landing zones in each of the two intervention groups, to allow us to quantify brain injury by zone between the two interventions in addition to establishing an overall measure of effect between the two interventions.

Statistical analysis
Statistical analysis will be by intention to treat. Standard descriptive statistics will be used throughout (mean, range, standard deviation, and median, IQR), with

comparative statistics for normally and non-normally distributed data with $p<0.05$ considered as significant. Cronbach's alpha will be used to assess inter-rater reliability of MRI and TCD data. Subgroup analysis will be used to examine SCI and TCD MES rates with respect to PLZ, atheroma grade and stent-graft type.

Ethics and dissemination

The study coordination centre has obtained approval from the London Fulham Research Ethics Committee and Southern Health and Disability Ethics Committee (NZ) and UK's Health Regulator Authority (HRA). The study will be conducted in accordance with declaration of Helsinki.

ClinicalTrials.gov Identifier NCT03886675

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Competing interests statement

There are no competing interests in this study

Data statement

The results of this study will be kept on an anonymized Redcap database, and will be published in full on completion of the study. Data requests can be made to corresponding author.

Monitoring

The data monitoring committee will be made up of SC & LH. They will carry out interim analysis on an ad hoc basis, with no specific stopping guidelines. Any adverse events will be recorded in the trial management folder, and serious adverse events will be reviewed by the CI, with involvement of the local ethics committee if indicated. There will be no planned audits, but any audits will be undertaken by Imperial R&D if required.

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3833 words

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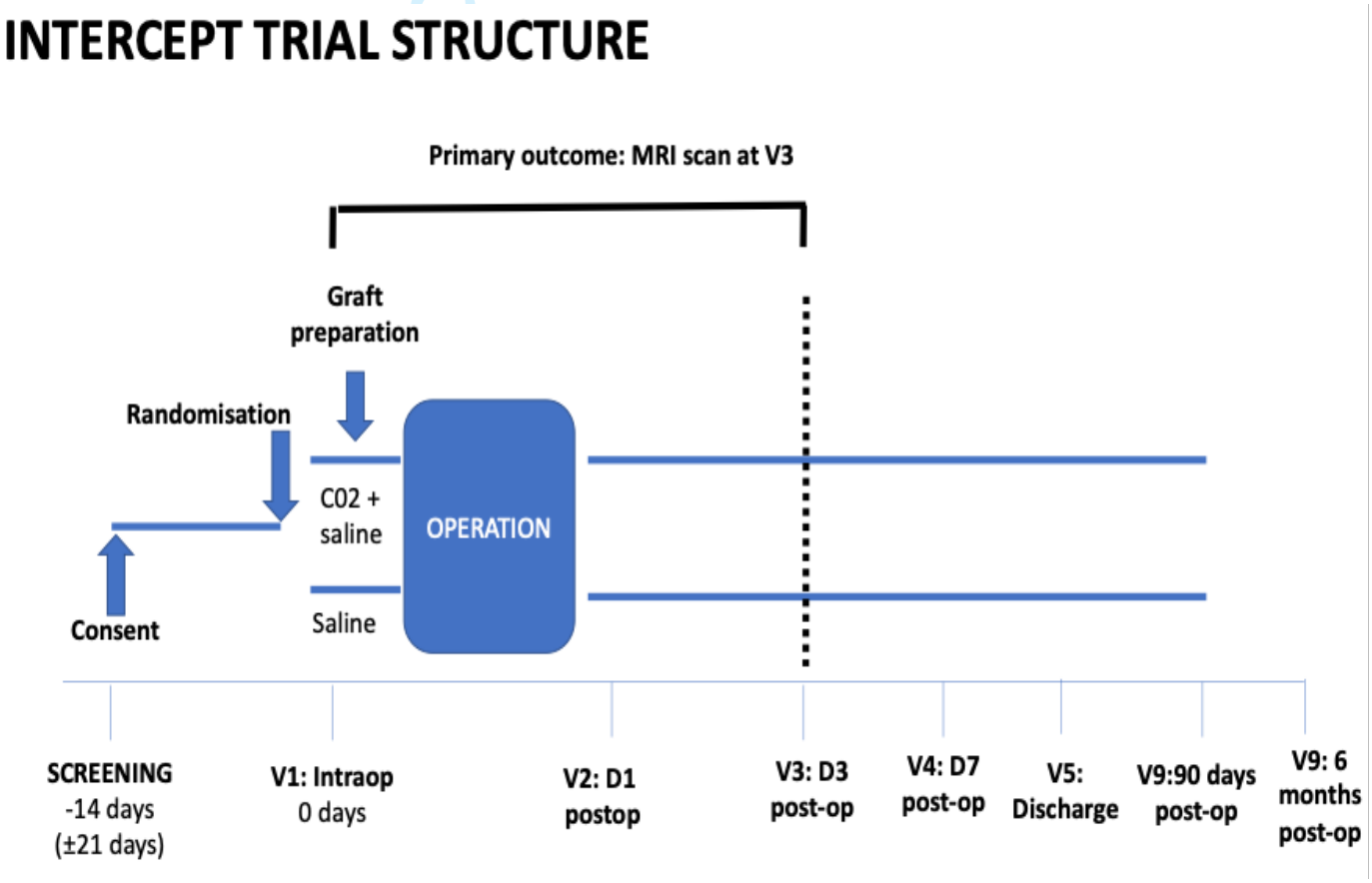
Figure 1A

Figure 1B

Figure 2


INTERCEPT TRIAL STRUCTURE
Primary outcome: MRI scan at V3
Graft preparation
Randomisation
C02 + saline
Saline
OPERATION
Consent
SCREENING -14 days (±21 days)
V1: Intraop 0 days
V2: D1 postop
V3: D3 post-op
V4: D7 post-op
V5: Discharge
V9:90 days post-op
V9: 6 months post-op

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	12
Funding	#4	Sources and types of financial, material, and other support	12
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	12

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	12
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3-5
Objectives	#7	Specific objectives or hypotheses	9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8-9
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7-9

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	2
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	2
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	8

		provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-10
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9-10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	p.1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	p.2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	p.2-4
	2b	Specific objectives or hypotheses	p.7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	p.6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	p.6
Participants	4a	Eligibility criteria for participants	p.6
	4b	Settings and locations where the data were collected	p.6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	P,.6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	p.7-8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	p.9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	p.10
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	p.6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	p.6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	p.6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	p.6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	p.2

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	p.2-4
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	p.7-8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	n/a
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	p.7-8
	13b	For each group, losses and exclusions after randomisation, together with reasons	p.7-8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	p.6
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	n/a
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	n/a
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	n/a
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	n/a
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	n/a
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	n/a
Other information			
Registration	23	Registration number and name of trial registry	p.10
Protocol	24	Where the full trial protocol can be accessed, if available	n./a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	p.10

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Intervention with cerebral embolic protection in TEVAR (INTERCEPT): 'Carbon dioxide flushing versus saline flushing of thoracic aortic stents: a multi-centre pilot randomised controlled trial'

Journal:	*BMJ Open*
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Complete List of Authors:	Crockett, Stephen; Imperial College London, Hanna, Lydia; Imperial College London Singh, Abhinav; Imperial College London Gunning, Stephen; Imperial College London Nicholas, Richard; Imperial College Healthcare NHS Trust, Bicknell, Colin; Imperial College London Hamady, Mohamad; Imperial College London Gable, Dennis; Baylor Scott & White Health Sallam, Morad; Guy's and St Thomas' Hospitals NHS Trust Modarai, Bijan ; Guy's and St Thomas' Hospitals NHS Trust, Surgery Abisi, Said; Guy's and St Thomas' Hospitals NHS Trust Lyons, Oliver; Canterbury District Health Board Gibbs, Richard; Imperial College London
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Surgery
Keywords:	Vascular surgery < SURGERY, Stroke medicine < INTERNAL MEDICINE, GERIATRIC MEDICINE, VASCULAR MEDICINE

Title:
Intervention with cerebral embolic protection in TEVAR (INTERCEPT):
'Carbon dioxide flushing versus saline flushing of thoracic aortic stents: a multi-centre pilot randomised controlled trial'

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Keywords

Thoracic aortic endovascular repair; cerebral infarction; stroke; cognitive decline

Abstract word count

528 words

Word Count

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Number of references

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Title:
Intervention with cerebral embolic protection in TEVAR (INTERCEPT):
'Carbon dioxide flushing versus saline flushing of thoracic aortic stents: a multi-centre pilot randomised controlled trial'

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Keywords:
Thoracic aortic endovascular repair; cerebral infarction; stroke; cognitive decline

Abstract:

Introduction

Thoracic endovascular aortic repair (TEVAR) carries a 3%-8% stroke risk, including risk of 'silent' cerebral infarction (SCI). SCI do not cause focal motor, sensory or speech deficits, but have been shown to be a predictor of future development of stroke, dementia and depression. Stent-grafts are manufactured in room air and retain air. IFU recommends saline flushing to 'de-air' the system prior to insertion, but substantial amounts of air are released when deploying them, potentially leading to downstream neuronal injury and SCI. Carbon dioxide (CO_2) is more dense and soluble in blood than air, without risk of bubble formation, so could be used in addition to saline to de-air stents. The current pilot RCT aims to answer the question 'Is there a neuroprotective benefit against SCI with the use of CO_2 flushed aortic stent-grafts?'

Methods and Analysis
This is a multicenter pilot RCT, which is taking place in vascular centres in the UK, USA and New Zealand. Patients identified for TEVAR will be enrolled after informed written consent. Participants will be randomised to a TEVAR-CO_2 or TEVAR-Saline group, stratified according to TEVAR landing zone.

Participants will undergo pre-operative neurocognitive tests and quality of life assessments, which will be repeated at 6 weeks and 6 months. Inpatient neurological testing will be performed on day 1, 3 and 7 to screen for clinical stroke or delirium. DW-MRI will be undertaken within 72 hours post-operatively and at 6 months to look for evidence and persistence of SCI. We aim to recruit 120 participants (60 per group) based on our sample size calculation.

Ethics and Dissemination
The study coordination centre has obtained approval from the London Fulham Research Ethics Committee (19/LO/0836) and Southern Health and Disability Ethics Committee (NZ) and UK's Health Regulator Authority (HRA). Consent for entering into the study will be taken using standardised consent forms by the local study team, led by a local PI. The results of the trial will be published in an open access journal.

Article summary

Strength & Limitations of this study

- Unprecedented levels of neurocognitive data, neuroimaging and follow up for patients undergoing TEVAR to determine the clinical impact of cerebral infarction complicating thoracic aortic endovascular repair.
- Multicentre RCT providing generalizable results.
- A cheap and readily available intervention is being studied, and results could be rapidly implemented.
- The results of our study will be used to gather further information regarding the neurological risk associated with TEVAR and the clinical significance of SCI, where a paucity of literature exists.
- Incomplete blinding as the surgeons carrying out the procedure cannot be blinded to stent graft flushing.

Introduction

There has been a significant increase in the number of thoracic endovascular aortic repairs (TEVARs) performed in the last decade. TEVAR is offered as a treatment to prevent rupture and death from aneurysmal aortic disease, aortic dissection and traumatic aortic injury. It has been adopted as the standard method for thoracic aortic repair as the avoidance of thoracotomy and aortic cross-clamping means morbidity is reduced and hospital stay is significantly decreased [1]. Although TEVAR has successfully reduced peri-procedural morbidity and mortality, stroke remains a significant risk. Several studies have identified risk factors contributing to neurological injury [2, 3] and further work is needed to investigate these risk factors to predict more accurately the patients at higher risk of neurological injury.

There is a reported 3%[4] to 8%[5] risk of stroke with TEVAR. Our own observational study detected a 13% stroke rate in patients undergoing complex TEVAR[6]. Furthermore, 68% of these patients developed covert brain injury as evidenced by

new areas of brain infarction (BI) seen on diffusion weighted MRI following the intervention.[6] Covert brain injury occurs in aortic surgical and cardiovascular catheter-based interventions [6, 7] and because these lesions do not manifest as clinical stroke with motor, sensory or speech deficits, they have been erroneously termed 'silent' cerebral infarction (SCI). The American Heart and Stroke Association[8] and the Neurological Academic Research Group (NeuroARC)[9] now recognise the evolving definition of 'stroke' into a tissue-based diagnosis even in the absence of clinical symptoms. Incidentally identified SCI is a predictor of future development of clinically overt stroke[10], dementia[11] and depression[12]. There is also a direct clinical consequence of SCI with cognitive deficits demonstrated by neuro-psychometric testing[11] and in our own study, 88% of patients with SCI suffered with neurocognitive decline[6]. Indeed, several studies have shown that radiologically detected cerebral infarcts tend to occur in those parts of the brain responsible for memory, mood and cognition. These procedurally related lesions are therefore not 'silent' but have clinically significant consequences.

Aetiological mechanisms of SCI in TEVAR remain uncharacterised, although several neuroimaging studies have detected evidence of SCI within a few days post-procedure, suggesting that peri-procedural cerebral embolisation may be a cause[7, 13]. Further support for this hypothesis comes from continuous TCD monitoring of the cerebral vessels for microembolic signals (MES) during TEVAR whereby high-risk phases for cerebral embolization have been shown to occur at specific time points during TEVAR[6, 14]. Stent-graft deployment is the phase most associated with embolisation , followed by wire manipulation in the aortic arch[6].

Through the use of embolic differentiation software, we have deduced that >90% of MES throughout TEVAR are gaseous in nature, with 81% of gaseous MES apparent at stent-graft deployment. Once deployment is complete, TCD monitoring typically detects no further embolic activity. We also found a positive association between number of gaseous MES and number of new DW-MRI BI [15]. This suggests that cerebral air embolization may be a significant cause of SCI in TEVAR and provides us with a basis on which to target preventative strategies.

Stent-grafts are manufactured in room air conditions and retain air. According to instructions for use (IFU), saline flushing is recommended to de-air the system. Emerging experimental studies have shown a substantial amount of air release from all commercially available grafts with bubbles ranging from 0.34-0.79ml, despite saline flushing (see Figure 1) [16, 17]. This is a cause for concern given that cerebral arterioles are 40-250μm in diameter[18]. Large bubbles would be expected to cause downstream ischaemia and neuronal injury, while smaller bubbles may incite endothelial damage and activation of inflammatory and clotting cascades that may then cause secondary ischaemia[19]. These small bubbles have been implicated in causing post-operative cognitive delirium (POCD)[20].

Carbon-dioxide (CO_2) is 1.5 times denser than air and can fill an enclosed space and displace air. It is 25 times more soluble in blood than air and does not lead to bubble formation[21]. CO_2 has been used extensively in cardiac surgery and shown to

significantly reduce intracardiac air[22] and POCD[23]. CO_2 can also significantly reduce the average amount of released air from am TEVAR stent in an experimental setting (0.79 vs 0.51 mL, p=0.005)[17], and has been used clinically in a small series of TEVAR patients where the authors describe a 3% clinical stroke rate. However, none of these patients underwent any formal cognitive or neuroimaging assessment and there was no control group, which has prompted the INTERCEPT trial [24, 25].

We know that more proximal zones are associated with higher stroke rates. What remains unknown is whether CO_2 flushing is enough to prevent neurological brain injury in these riskier zones, or whether solid embolisation from the manipulation of instruments close to atherosclerotic aortic valves and carotid vessels in more proximal zones is the main risk factor for neurological injury. This information will be used to aid refinement of the inclusion/exclusion criteria for the full-scale RCT and will be used to refine the sample-size calculation for use in the final trial.

We carried out a pilot study of 20 TEVAR patients who underwent CO_2 flushing and used TCD to detect cerebral embolization rates and DW-MRI to assess for SCI. Intra-operatively, there were no MES detected at stent graft deployment. The SCI rate was 25% and there was no clinical stroke in any of the patients (in comparison to 81% SCI and 13% stroke rate in similar patients undergoing TEVAR with standard saline flushing)[6]. Although encouraging, we recognize the need for level 1 evidence in the form of a robust randomised controlled trial to answer the question 'is there a neuroprotective benefit against SCI and POCD with the use of CO_2 flushed aortic stent-grafts.'

A review of registries on 28/01/2019 (www.clinicaltrials.gov and www.isrctn.com) found but no similar studies in TEVAR.

Research influence:
We have produced the largest case series to date regarding SCI in TEVAR and continue to highlight the magnitude of the problem by our ongoing study of neuroimaging, TCD, neurological and neurocognitive data on these patients. These data initially led us to believe that solid embolization of particulate atherosclerotic matter dislodged from the thoracic aorta was responsible for SCI. Accordingly, we trialed the use of a cerebral embolic protection device designed to capture particulate matter 'en-route' to the brain in a cohort of 20 patients. This established feasibility and safety, and a 98% capture rate of embolic debris and a reduction in the number of lesions on DW-MRI. However, all patients still had lesions, with the majority concentrated in the posterior circulation territory [15].

We suspect that both solid and gaseous emboli cause SCI. However, our TCD data continuously demonstrates an overwhelming occurrence of gaseous MES at stent-deployment in TEVAR patients with and without filters, that amounts to a greater contribution of total MES than cumulative solid MES throughout TEVAR. Particulate embolism appeared to numerically correlate with the size of infarct, whilst gaseous emboli numerically correlated with the number of infarcts. These findings warrant our attention into investigating cerebral air embolism (CAE) as a cause of SCI and into

CO2 flushed stent-grafts as a stand-alone intervention first, particularly as it is cheap, safe and easily implemented.

Whilst the different ultrasonic reflective properties of solid and gaseous emboli provide the basis for discriminating between the two, we are aware of skepticism regarding the sensitivity and specificity of TCD embolic differentiation software during an embolic shower.[26] We have sufficient recorded TCD data to demonstrate that the 'shower' of emboli seen at stent-graft deployment with resultant SCI on DW-MRI with saline flushing is reduced when stent-grafts are flushed with CO2, even when cerebral embolic protection devices are used to capture solid emboli. Reducing the contribution of gaseous embolic events will pave the way for future studies to tackle the residual problem of solid emboli, which will likely require the use of invasive devices, rather than a simple bench-top flushing procedure.

The results of our study will be used to gather further information regarding the neurological risks associated with TEVAR and the clinical significance of SCI, where a paucity of literature currently exists. It will also facilitate a more comprehensive and individualised consent process, allowing patients to make more informed decisions. We hope to inform the cardiovascular community about a potential prevention strategy against SCI. Stroke, dementia and neurocognitive decline are enormous burdens on healthcare resources, and any reduction in the incidence of these complications will have a positive effect on health economics, which is vital in the current financial climate.

(please see attached documents for images)

Figure 1. A) Air bubble release during stent-graft deployment from the proximal end of the stent-graft as it opens in a benchtop experiment carried out by our group
B) Air bubble release during stent-graft deployment from the distal end of the stent-graft as it opens in a benchtop experiment carried out by our group.

Methods & analysis

Type of study: Multi-centre pilot randomised controlled superiority trial (see Figure 2 for flow chart for RCT).
Duration: Estimated duration is 36 months for patient recruitment, from June 2021 to June 2024
Number and type of subjects: All elective patients undergoing TEVAR for aortic pathology.
Target total sample size: 120, (60 in each intervention arm).

Patient and Public involvement

None

Enrolment

Patients suitable for TEVAR as decided upon by a vascular multi-disciplinary meeting will be invited to participate and enrolled after informed written consent. Participants will be recruited by the research team at each site before surgery before their procedure (Box 1).

Randomisation and Interventions

Participants will be randomly assigned to TEVAR-CO2 or TEVAR-S group (Box 1) providing they fulfil the entry criteria at screening (Box 2). Participants will be randomized 1:1 via computerized randomization tool via the INTERCEPT Redcap database with stratification by zone of TEVAR. The latter has been chosen because more proximal landing zones in the aortic arch for stent-graft placement are closer to the cerebral vessels and represent a greater risk factor for stroke (Zone 0>1>2>3> 4). Stratification by zones will ensure the groups are similar with respect to this potential confounding factor. Randomisation will occur on the day of surgery. The surgical team delivering the intervention in theatre will be unblinded but are not involved in assessing the outcomes of the study. Participants and outcome assessors will be blinded to group allocation. For sheathed devices, there is a side-port for flushing with saline and/or CO_2. For unsheathed devices (e.g. CTAG, Gore), bench top-models have shown that using a dry seal, can allow sufficient flushing of the stent with CO2 and saline.

Box 1 Intervention and Control treatment

TEVAR-S group

- **ALL** Stent-grafts used in a patient randomised to TEVAR-S are prepared according to their IFU including flushing of the device through the side flush port and with 60mls physiological saline solution.

TEVAR-CO2 group

- **ALL** Stent-grafts used in a patient randomised to TEVAR-CO2 are prepared according to their respective IFU. Flushing of the stent-graft will be performed first by flushing 100% CO_2 at 2l/min, 4 bar from a pressurized cylinder with 1.4inch tubing connected to the side flush port for 1 minutes followed by 60mls of physiological saline

Box 2 Inclusion and Exclusion Criteria

Inclusion criteria

- All patients suitable for TEVAR for any thoracic aortic pathology in zones 0-4

Exclusion criteria

- Stroke within the last 12 months
- Pregnancy
- <18yrs
- Unwilling or unable to provide informed consent

Withdrawal criteria

- Any patient has the right to withdraw from the study at any point; their treatment and management will not be altered in any way.

(please see attached documents for images)

Figure 2. Patient Flow chart for the pilot RCT

Primary objectives: Evaluation of pilot RCT processes

Conduct an evaluation of the processes described in this pilot RCT for a full-scale RCT including:

1. Recruitment (number eligible and willing to be randomised, identify challenges to randomisation)
2. Retention in follow-up assessments
3. Study design for the full RCT (appropriateness of inclusion/exclusion criteria, study outcomes) and identification of important stratification variables
4. Sample size refinement for a future full RCT

Secondary objectives: Neurological end-points

1. *Primary outcome: Incidence of **DW-MRI SCI***

MRI scans will be performed at each site where the patient is recruited from. DW-MRI will be performed within 72hrs postoperatively to look for new lesions using a 3-Tesla Discovery MR750w system (GE healthcare, UK) or equivalent system, and at 6-months routine outpatient appointment to look for residual disease. We have previously published the MRI protocol[15] that we will use and these sequences may have to be modified where only a 1.5T scanner is available and discussions with the local MR department will be undertaken to ensure image accuracy. Chronic small vessel ischemia will be classified using the Fazekas Scale[27]. Pre-op MRI will not be carried out, with a Fazekas score carried out on their post-op MRI to give an estimation of their chronic small vessel disease. This decision was made due to previous experience of loss of patients for follow-up scans, and the focus of the MRIs being on acute lesions, which will be easily identifiable using the MRI sequences chosen. MRIs will be compared for number, laterality and vascular territory (anterior or posterior

circulation, or border zone territory) of lesions. Maximum diameter and surface area of lesions will also be recorded and lesion surface area as measured on the slice of largest lesion diameter. Lesions are considered as separate if there is no continuity between them on the same slice and adjacent slices.

2. *Secondary outcome: Detection of* **periprocedural cerebral solid and gaseous emboli**

Continuous bilateral TCD insonation of the middle cerebral artery (MCA) will be used to detect rates of intraoperative solid and gaseous cerebral MES throughout all stages of TEVAR. For logistical reasons, this will likely be carried out at London centres only. Accepted criteria for emboli detection will be used[28]. MES will be differentiated between solid and gas through software using multi-frequency TCD instrumentation which insonates simultaneously between 2.0MHz and 2.5MHz (EmboDop DWL, Compumedics Ltd, Germany). Manual offline analysis of the number of solid and gaseous emboli will be performed by trained assessors independent of each other. As it is impossible to characterise a solid or gas embolus manually during an 'embolic shower', the automated observations of the TCD equipment will be used.

3. *Secondary outcome:* ***neurological assessment****, delirium,* ***neurocognitive and quality of life testing***

- Pre-operatively all patients will undergo:

a) Neurological assessment and outcome measurement with the National Institutes of Health Stroke (NIHSS) [29] and disability assessment on modified Rankin scale (mRS) [30-32].
b) Baseline delirium test with the 4AT [33].
c) Screening test for cognitive impairment with Montreal Cognitive Assessment (MOCA) [34]
d) Detailed neurocognitive assessment with a battery of validated tests categorized into visual memory, executive function, attention and decision-making. These have been devised after review of the literature, they are tests which we have used in our previous studies [35] and have been pragmatically chosen in collaboration with a clinical psychologist
    a. (i). Rey Auditory Verbal Learning [36]
       (ii). 'FAS'- Verbal fluency test (paper-based test) [37]
       (iii). Grooved Pegboard Test (instrumentation based test to assess manual dexterity) [38]
       (iv). Trail making test TMT [39] (paper-based test to assess attention and switching)
       (v). Hospital Anxiety and Depression Scale (HADS) [40] to detect any psychological influence on the test results (paper-based)
    b. (vi). National Adult Reading Test (NART)[41] to test premorbid intelligence levels
e) Quality of life assessment with SF-36 [42] and EQ5D5L[43].

- Day 1, 3, 7 and at discharge (if patient remains an inpatient throughout this time):

a) NIHSS and mRs
b) 4AT
c) MOCA

- 6-week, 6 month and 1 year follow-up:

a) NIHSS and mRS
b) 4AT
c) MOCA and neurocognitive battery as above
d) SF-36 and EQ5D5L

4. *Secondary outcome: Serial **biomarker** blood tests e.g. S100B*
   A sample of the patient's blood will be taken along with routine blood tests preoperatively, at the end of procedure and 24hrs later. We will study the upregulation of proinflammatory mediators in response to TEVAR between the two groups. Serial measurement of biomarkers will look at inflammatory pathway upregulation, modification of low-density lipoprotein (LDL) moieties inducing the modification of LDL into oxidised LDL and consumption of protection antibodies that work on maintaining homeostasis against danger associated molecular patterns (DAMPS)[44]. S100B is regarded as a marker of brain damage. Reduced serum levels have been detected in patients who underwent carbon-dioxide field flooding in mitral valve operations with cardiopulmonary bypass where there is a risk of CAE [45]. Further analysis will be done via a proteomic inflammatory panel analysis [46]. We will also study the extent of neurological injury using S100B and markers of cell death: TNF receptor 1 (TNFR-1), TRAIL receptor 2 (TRAILR-2) and Fas [47, 48].
   Levels of biomarkers will be correlated with DW-MRI SCI, neurological and neurocognitive assessments. For pragmatic reasons including transportation this test will only be conducted in participants recruited at London hospitals.

   The samples will be centrifuged and stored at -80°c. Using Enzyme Linked Immunosorbent Assay (ELISA), we will then analyse for S100B amongst a number of other biomarkers at the National Heart and Lung Institute by SC.

5. *Secondary outcome: **Risk factor assessment***
   Procedural risk factors such as conventional proximal landing zones for the stent (PLZ)[45], coverage of arch vessel origins and intraoperative factors such as but not limited to, number of digital subtraction angiography (DSA) runs and length of time of hypotension, stent type, length of procedure and post stent ballooning will be recorded for multivariate analysis to allow risk factor assessment.

Sample Size: Observational data indicate that the incidence of SCI from TEVAR is 81%[6]. Based on our CO2-pilot study that reduced SCI to 25%, a 50% reduction in SCI is possible. Taking a pragmatic and realistic approach to recruitment we aim for an effect size of 40% reduction in incidence of SCI. Considering a 10% MRI dropout rate from our observational study, a total of 76 (38 per group) would be sufficient to detect an effect size. However, given that randomisation will be by zone of TEVAR, of which there are 5, and we expect a 20% MRI drop-out rate, we are aiming to recruit 120 cases (60 in each arm). This number has been chosen to ensure 10-12 patients in each of 5 arch landing zones in each of the two intervention groups, to allow us to quantify brain injury by zone between the two interventions in addition to establishing an overall measure of effect between the two interventions.

Statistical analysis

Statistical analysis will be by intention to treat. Standard descriptive statistics will be used throughout (mean, range, standard deviation, and median, IQR), with comparative statistics for normally and non-normally distributed data with $p<0.05$ considered as significant. Cronbach's alpha will be used to assess inter-rater reliability of MRI and TCD data. Subgroup analysis will be used to examine SCI and TCD MES rates with respect to PLZ, atheroma grade and stent-graft type.

The data monitoring committee will be made up of SC & LH. They will carry out interim analysis on an ad hoc basis, with no specific stopping guidelines. Any adverse events will be recorded in the trial management folder, and serious adverse events will be reviewed by the CI, with involvement of the local ethics committee if indicated. There will be no planned audits, but any audits will be undertaken by Imperial R&D if required.

Ethics and dissemination (including registration details)

The study coordination centre has obtained approval from the London Fulham Research Ethics Committee and Southern Health and Disability Ethics Committee (NZ) and UK's Health Regulator Authority (HRA). The study will be conducted in accordance with declaration of Helsinki. Any protocol modifications will be undertaken through the local ethics committee. Consent for entering into the study will be taken using standardised consent forms (see supplementary materials) by the local study team, led by a local PI. For St Mary's Hospital, St George's Hospital and St Thomas' Hospital this includes consenting for blood sampling for biochemical marker analysis. Patients will be given an anonymised code upon entering the trial, which will be stored on a secure hard drive to maintain confidentiality throughout.

The authors have no financial or competing interest to declare. The final trial dataset will be accessible by the trial co-ordinators (SC & LH), as well as the CI Professor Richard Gibbs. Post-trial provisions and compensation are covered by the policy with Gallagher insurance company. The results of the trial will be published in an open access journal.

Trial Registration Number

There is ethical approval for recruitment in the UK, which was approved by the Fulham REC (ClinicalTrials.gov Identifier NCT03886675, 19/LO/0836), and New Zealand (21/STH/192).

Based on Protocol version 4 (18/1/2022)

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Competing interests statement

There are no competing interests in this study

Data statement

The results of this study will be kept on an anonymized Redcap database, and will be published in full on completion of the study. Data requests can be made to corresponding author.

Acknowledgements

We would like to acknowledge the research nurses, R&D department, radiology, and theatre staff at all centres involved for their continued hard work in carrying out this trial.

Author contributions

Stephen Crockett has been involved in the set-up, data collection, and write up for this project. Lydia Hanna designed the trial, gained ethical approval, gained funding for the trial. Abhinav Singh developed the MRI protocol, and will be the blinded assessor of the MRIs for the trial. Stephen Gunning has developed the neurocognitive battery with LH, and helped in neurocognitive training for staff. Richard Nicholas, Colin Bicknell, Mohammad Hamady were involved in the study design. Denis Gable was involved in study design and is PI for Baylor Scott & White (Texas). Morrad Sallam is the PI for St Thomas' Hospital. Bijan Modarai has been involved in the study design, and data collection alongside Said Abisi. Oliver Lyons is the PI for CDHB (New Zealand). Richard Gibbs is the chief investigator for the study and led the study design, ethical approval and funding application.

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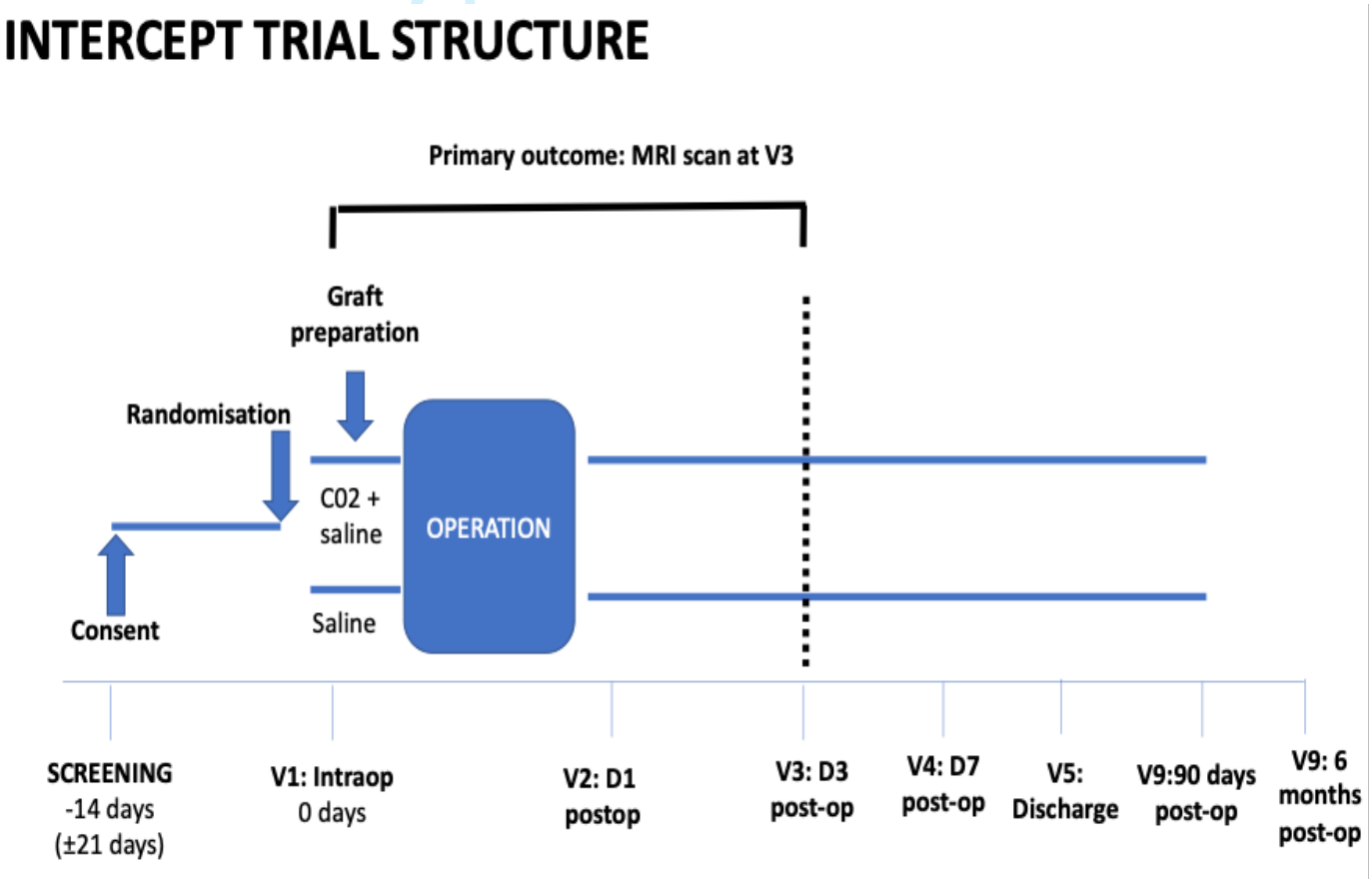
Figure 1A

Figure 1B

Figure 2


INTERCEPT TRIAL STRUCTURE
Primary outcome: MRI scan at V3
Graft preparation
Randomisation
C02 + saline
OPERATION
Consent
Saline
SCREENING -14 days (±21 days)
V1: Intraop 0 days
V2: D1 postop
V3: D3 post-op
V4: D7 post-op
V5: Discharge
V9:90 days post-op
V9: 6 months post-op

Imperial College London

Research Governance and Integrity Team

NHS Imperial College Healthcare NHS Trust

IRAS Number: 262145
Patient Identification Number for this trial:

CONSENT FORM

Title of Project:

INTERCEPTevar; 'Carbon-Dioxide Flushing versus Saline Flushing of Thoracic Aortic Stents: A Multi-centre Randomised Controlled Trial'

Chief Investigator: **Mr Richard Gibbs**

Please initial all boxes

1. I confirm that I have read and understand the information sheet dated **18/01/2022 version 2** for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from **Imperial College London** from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my GP being informed of my participation in the study. ☐

5. I agree to take part in the above study. ☐

6. I give / do not give **(delete as applicable)** consent for samples collected during this study to be used in future ethically approved studies. I give permission for my samples to be sent to other organisations, including these outside of the EEA (European Economic Area) ☐

Consent form date of issue: **18/01/2022**
Consent form version number: **3**
IRAS number: 262145

7. I give/do not give **(delete as applicable)** consent to being contacted to potentially taking part in other research studies. ☐

Name of Participant	Date	Signature
Name of Person taking consent.	Date	Signature

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	p.1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	p.2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	p.2-4
	2b	Specific objectives or hypotheses	p.7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	p.6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	p.6
Participants	4a	Eligibility criteria for participants	p.6
	4b	Settings and locations where the data were collected	p.6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	P,.6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	p.7-8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	p.9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	p.10
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	p.6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	p.6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	p.6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	p.6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	p.2

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	p.2-4
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	p.7-8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	n/a
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	p.7-8
	13b	For each group, losses and exclusions after randomisation, together with reasons	p.7-8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	p.6
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	n/a
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	n/a
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	n/a
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	n/a
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	n/a
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	n/a
Other information			
Registration	23	Registration number and name of trial registry	p.10
Protocol	24	Where the full trial protocol can be accessed, if available	n./a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	p.10

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	12
Funding	#4	Sources and types of financial, material, and other support	12

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	12
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	12
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3-5
Objectives	#7	Specific objectives or hypotheses	9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8-9
Methods: Participants,			

interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7-9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including	2

		clinical and statistical assumptions supporting any sample size calculations	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	2
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate	9-10

		measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9-10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	2
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	2
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	2
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	2, 10
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	10

Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	2
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	See consent v3 document
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	2 & 9 & consent form

BMJ Open

Carbon dioxide flushing versus saline flushing of thoracic aortic stents: protocol for a multicentre pilot randomised controlled trial

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Carbon dioxide flushing versus saline flushing of thoracic aortic stents: protocol for a multicentre pilot randomised controlled trial

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Keywords

Thoracic aortic endovascular repair; cerebral infarction; stroke; cognitive decline

Abstract

Introduction

Thoracic endovascular aortic repair (TEVAR) carries a 3%-6.1% stroke risk, including risk of 'silent' cerebral infarction (SCI). Stent-grafts are manufactured in room air and retain air. Instructions for use recommend saline flushing to 'de-air' the system prior to insertion, but substantial amounts of air are released when deploying them, potentially leading to downstream neuronal injury and SCI. Carbon dioxide (CO_2) is more dense and more soluble in blood than air, without risk of bubble formation, so could be used in addition to saline to de-air stents. This pilot trial aims to assess the feasibility of a full-scale randomised controlled trial (RCT) investigating the neuroprotective benefit against SCI with the use of CO_2-flushed aortic stent-grafts.

Methods and analysis

This is a multicentre pilot RCT, which is taking place in vascular centres in the UK, USA and New Zealand. Patients identified for TEVAR will be enrolled after informed written consent. 120 participants will be randomised (1:1) to TEVAR-CO_2 or TEVAR-Saline, stratified according to TEVAR landing zone. Participants will undergo pre-operative neurocognitive tests and quality of life assessments, which will be repeated at 6 weeks and 6 months. Inpatient neurological testing will be performed within 48 hours of return to level 1 care for clinical stroke or delirium. DW-MRI will be undertaken within 72 hours post-operatively (1-7 days) and at 6 months to look for evidence and persistence of SCI. Feasibility will be assessed via measures of recruitment and retention, informing the design of a full-scale trial.

Ethics and dissemination

The study coordination centre has obtained approval from the London Fulham Research Ethics Committee (19/LO/0836) and Southern Health and Disability Ethics Committee (NZ) and UK's Health Regulator Authority (HRA). The study has received ethical approval for recruitment in the UK (Fulham REC, 19/LO/0836), New Zealand (21/STH/192) and the USA (IRB 019- 264, Ref 378630). Consent for entering into the study will be taken using standardised consent forms by the local study team, led by a local PI. The results of the trial will be submitted for publication in an open access journal.

Trial registration number

ClinicalTrials.gov, NCT03886675.

Strength and limitations of this study

- Multicentre pilot randomised controlled trial (RCT) will assess the feasibility and shape the design of a full-scale RCT, which will gather further information regarding the neurological risk associated with thoracic endovascular aortic

repair (TEVAR) and the clinical significance of silent cerebral infarction, where a paucity of literature exists.
- A cheap and readily available intervention is being studied.
- Unprecedented levels of neurocognitive, neuroimaging and follow up data will be collected to determine the clinical impact of cerebral infarction complicating TEVAR.
- Blinding is incomplete, as the surgeons carrying out the procedure cannot be blinded to stent graft flushing.

Introduction

There has been a significant increase in the number of thoracic endovascular aortic repairs (TEVARs) performed in the last decade. TEVAR is offered as preventative treatment to prevent rupture and death from aneurysmal aortic disease, aortic dissection and traumatic aortic injury. It has been adopted as the standard method for thoracic aortic repair as the avoidance of thoracotomy and aortic cross-clamping means morbidity is reduced and hospital stay is significantly decreased [1]. Although TEVAR has successfully reduced peri-procedural morbidity and mortality, stroke remains a significant risk. Several studies have identified risk factors contributing to neurological injury [2, 3] and further work is needed to investigate these risk factors to predict more accurately the patients at higher risk of neurological injury.

There is a reported 3%[4] to 6.1%[5] risk of stroke with TEVAR. Our own observational study has detected a 13% stroke rate in patients undergoing TEVAR[6]. Furthermore, 68% of the patients developed covert brain injury as evidenced by new areas of brain infarction (BI) seen on diffusion weighted MRI following TEVAR[6]. Covert brain injury occurs in aortic surgical and cardiovascular catheter-based interventions [6, 7] and because these lesions do not manifest as clinical stroke with motor, sensory or speech deficits, they are termed 'silent' cerebral infarction (SCI). The American Heart and Stroke Association[8] and the Neurological Academic Research Group (NeuroARC)[9] now recognise the evolving definition of 'stroke' into a tissue-based diagnosis even in the absence of clinical symptoms. Incidentally identified SCI is a predictor of future development of clinically overt stroke[10], dementia[11] and depression[12]. There is also a direct clinical consequence of SCI with cognitive deficits demonstrated by neuro-psychometric testing[11] and in our own study, 88% of patients with SCI suffered with neurocognitive decline[6]. Indeed, several studies have shown that radiologically detected cerebral infarcts tend to occur in those parts of the brain responsible for memory, mood and cognition. These procedurally related lesions are therefore not 'silent' but have clinically significant consequences.

Aetiological mechanisms of SCI in TEVAR remain uncharacterised, although several neuroimaging studies have detected evidence of SCI within a few days post-procedure, suggesting that peri-procedural cerebral embolisation may be a cause[7, 13]. Further support for this hypothesis comes from continuous TCD monitoring of the cerebral vessels for microembolic signals (MES) during TEVAR whereby high-risk phases for cerebral embolization have been shown to occur at specific time points during TEVAR[6, 14]. Stent-graft deployment is the phase most associated with embolisation, followed by wire manipulation in the aortic arch[6].

Through the use of embolic differentiation software, we have deduced that >90% of MES throughout TEVAR are gaseous in nature, with 81% of gaseous MES apparent at stent-graft deployment. Once deployment is complete, TCD monitoring typically detects no further embolic activity. We also found a positive association between number of gaseous MES and number of new DW-MRI BI [15]. This suggests that cerebral air embolization may be a significant cause of SCI in TEVAR and provides us with a basis on which to target preventative strategies.

Stent-grafts are manufactured in room air conditions and retain air. According to instructions for use (IFU), saline flushing is recommended to de-air the system. Emerging experimental studies have shown a substantial amount of air release from all commercially available grafts with bubbles ranging from 0.34-0.79ml, despite saline flushing (see Figure 1) [16, 17]. This is a cause for concern given that cerebral arterioles are 40-250μm in diameter[18]. Large bubbles would be expected to cause downstream ischaemia and neuronal injury, while smaller bubbles may incite endothelial damage and activation of inflammatory and clotting cascades that may then cause secondary ischaemia[19]. These small bubbles have been implicated in causing post-operative cognitive delirium (POCD)[20].

Carbon dioxide (CO_2) is 1.5 times denser than air and can fill an enclosed space and displace air. It is 25 times more soluble in blood than air and does not lead to bubble formation[21]. CO_2 has been used extensively in cardiac surgery and shown to significantly reduce intracardiac air[22] and POCD[23]. CO_2 can also significantly reduce the average amount of released air from am TEVAR stent in an experimental setting (0.79 vs 0.51 mL, p=0.005)[17], and has been used clinically in a small series of TEVAR patients where the authors describe a 3% clinical stroke rate. However, none of these patients underwent any formal cognitive or neuroimaging assessment and there was no control group, which has prompted the present study [24, 25].

We know that more proximal zones are associated with higher stroke rates. What remains unknown is whether CO_2 flushing is enough to prevent neurological brain injury in these riskier zones, or whether solid embolisation from the manipulation of instruments close to atherosclerotic aortic valves and carotid vessels in more proximal zones is the main risk factor for neurological injury. This information will be used to aid refinement of the inclusion/exclusion criteria for the full-scale randomized controlled trial (RCT) and will be used to refine the sample size calculation for use in the trial.

We carried out a pilot study of 20 TEVAR patients who underwent CO_2 flushing and used TCD to detect cerebral embolization rates and DW-MRI to assess for SCI. Intra-operatively, there were no MES detected at stent graft deployment. The SCI rate was 25% and there was no clinical stroke in any of the patients (in comparison to 81% SCI and 13% stroke rate in patients with saline flushing)[6]. Although encouraging, we recognize the need for level 1 evidence in the form of a robust randomised controlled trial to answer the question ‘is there a neuroprotective benefit against SCI and POCD with the use of CO_2 flushed aortic stent-grafts.’

A review of registries on 28/01/2019 (www.clinicaltrials.gov and www.isrctn.com) found but no similar studies in TEVAR.

Research influence

We have produced the largest case series to date regarding SCI in TEVAR and continue to highlight the magnitude of the problem by our ongoing study of neuroimaging, TCD, neurological and neurocognitive data on these patients. These data initially led us to believe that solid embolization of particulate atherosclerotic matter dislodged from the thoracic aorta was responsible for SCI. Accordingly, we trialed the use of a cerebral embolic protection device designed to capture particulate matter 'en-route' to the brain in a cohort of 20 patients. This established feasibility and safety, and a 98% capture rate of embolic debris and a reduction in the number of lesions on DW-MRI. However, all patients still had lesions, with the majority concentrated in the posterior circulation territory[15].

We suspect that both solid and gaseous emboli cause SCI. However, our TCD data continuously demonstrates an overwhelming occurrence of gaseous MES at stent-deployment in TEVAR patients with and without filters, that amounts to a greater contribution of total MES than cumulative solid MES throughout TEVAR. Particulate embolism appeared to numerically correlate with the size of infarct, whilst gaseous emboli numerically correlated with the number of infarcts. These findings warrant our attention into investigating cerebral air embolism (CAE) as a cause of SCI and into CO2-flushed stent-grafts as a stand-alone intervention first, particularly as it is cheap, safe and easily implemented.

Whilst the different ultrasonic reflective properties of solid and gaseous emboli provide the basis for discriminating between the two, we are aware of skepticism regarding the sensitivity and specificity of TCD embolic differentiation software during an embolic shower.[26] We have sufficient recorded TCD data to demonstrate that the 'shower' of emboli seen at stent-graft deployment with resultant SCI on DW-MRI with saline flushing is reduced when stent-grafts are flushed with CO2, even when cerebral embolic protection devices are used to capture solid emboli. Reducing the contribution of gaseous embolic events will pave the way for future studies to tackle the residual problem of solid emboli, which will likely require the use of invasive devices, rather than a simple bench-top flushing procedure.

Objectives

This pilot trial aims to assess the feasibility of a full-scale RCT investigating the neuroprotective benefit against SCI with the use of CO2-flushed aortic stent-grafts. The results of this research will be used to gather further information regarding the neurological risks associated with TEVAR and the clinical significance of SCI, where a paucity of literature currently exists. It will also facilitate a more comprehensive and individualised consent process, allowing patients to make more informed decisions. We hope to inform the cardiovascular community about a potential prevention strategy against SCI. Stroke, dementia and neurocognitive decline are enormous burdens on healthcare resources, and any reduction in the incidence of these complications will

have a positive effect on health economics, which is vital in the current financial climate.

Methods and analysis

Study design

Type of study: Multicentre pilot RCT (see Figure 2 for trial flowchart).
Duration: Estimated duration is 36 months for patient recruitment, from June 2021 to June 2024.
Participants: All elective patients undergoing TEVAR for aortic pathology.
Target total sample size: 120 (60 in each intervention arm).

Enrolment

Patients suitable for TEVAR as decided upon by a vascular multi-disciplinary meeting will be invited to participate and enrolled after informed written consent. Participants will be recruited by the research team at each site before surgery before their procedure (Box 1).

Randomisation and interventions

Participants will be randomly assigned to TEVAR-CO2 or TEVAR-S group (Box 1) providing they fulfil the entry criteria at screening (Box 2). Participants will be randomized 1:1 via computerized randomization tool via the INTERCEPT Redcap database with stratification by zone of TEVAR. The latter has been chosen because more proximal landing zones in the aortic arch for stent-graft placement are closer to the cerebral vessels and represent a greater risk factor for stroke (Zone 0>1>2>3> 4). Stratification by zones will ensure the groups are similar with respect to this potential confounding factor. Randomisation will occur on the day of surgery. The surgical team delivering the intervention in theatre will be unblinded but are not involved in assessing the outcomes of the study. Participants and outcome assessors will be blinded to group allocation. For sheathed devices, there is a side-port for flushing with saline and/or CO_2. For unsheathed devices (e.g. CTAG, Gore), bench top-models have shown that using a dry seal, can allow sufficient flushing of the stent with CO2 and saline.

Box 1. Intervention and control treatment

TEVAR-S group

- **ALL** Stent-grafts used in a patient randomised to TEVAR-S are prepared according to their IFU including flushing of the device through the side flush port and with 60mls physiological saline solution.

TEVAR-CO2 group

- **ALL** Stent-grafts used in a patient randomised to TEVAR-CO2 are prepared according to their respective IFU. Flushing of the stent-graft will be performed first by flushing 100% CO_2 at 2l/min, 4 bar from a pressurized cylinder with 1.4inch tubing connected to the side flush port for 1 minutes followed by 60mls of physiological saline

Box 2. Inclusion and exclusion criteria

Inclusion criteria

- All patients suitable for TEVAR for any thoracic aortic pathology in zones 0-4

Exclusion criteria

- Stroke within the last 12 months
- Pregnancy
- <18yrs
- Unwilling or unable to provide informed consent
- Contraindications to MRI e.g. PPM, cerebral aneurysm clips, cochlear implant

Withdrawal criteria

- Any patient has the right to withdraw from the study at any point; their treatment and management will not be altered in any way.

Primary objectives: Evaluation of pilot RCT processes

Conduct an evaluation of the processes described in this pilot RCT, to inform the feasibility and design of a full-scale RCT. Evaluation outcome measures includes:

1. Recruitment (number eligible and willing to be randomised, identify challenges to randomisation).
2. Retention in follow-up assessments.
3. Study design for the full RCT (appropriateness of inclusion/exclusion criteria, study outcomes) and identification of important stratification variables.
4. Sample size refinement for a future full-scale RCT.

Secondary objectives: Neurological outcomes

1. *Primary neurological outcome: Incidence of DW-MRI SCI*

MRI scans will be performed at each site where the patient is recruited from. DW-MRI will be performed within 72hrs postoperatively to look for new lesions using a 3-Tesla Discovery MR750w system (GE healthcare, UK) or equivalent system, and at 6-months routine outpatient appointment to look for residual disease. We have previously published the MRI protocol[15] that we will use and these sequences may have to be modified where only a 1.5T scanner is available and discussions with the local MR department will be undertaken to ensure image accuracy. Chronic small vessel ischemia will be classified using the Fazekas Scale[27]. Pre-op MRI will not be carried out, with a Fazekas score carried out on their post-op MRI to give an estimation of their chronic small vessel disease. This decision was made due to previous experience of loss of patients for follow-up scans, and the focus of the MRIs being on acute lesions, which will be easily identifiable using the MRI sequences chosen. MRIs will be compared for number, laterality and vascular territory (anterior or posterior circulation, or border zone territory) of lesions. Maximum diameter and surface area of lesions will also be recorded and lesion surface area as measured on the slice of

largest lesion diameter. Lesions are considered as separate if there is no continuity between them on the same slice and adjacent slices.

2. *Secondary neurological outcome: Detection of periprocedural cerebral solid and gaseous emboli*

Continuous bilateral TCD insonation of the middle cerebral artery (MCA) will be used to detect rates of intraoperative solid and gaseous cerebral MES throughout all stages of TEVAR. For logistical reasons, this will likely be carried out at London centres only. Accepted criteria for emboli detection will be used[28]. MES will be differentiated between solid and gas through software using multi-frequency TCD instrumentation which insonates simultaneously between 2.0MHz and 2.5MHz (EmboDop DWL, Compumedics Ltd, Germany). Manual offline analysis of the number of solid and gaseous emboli will be performed by trained assessors independent of each other. As it is impossible to characterise a solid or gas embolus manually during an 'embolic shower', the automated observations of the TCD equipment will be used.

3. *Secondary neurological outcomes: Neurological assessment, delirium, neurocognitive and quality of life testing*

<u>Pre-operatively all patients will undergo:</u>

a) Neurological assessment and outcome measurement with the National Institutes of Health Stroke (NIHSS) [29] and disability assessment on modified Rankin scale (mRS) [30-32].
b) Baseline delirium test with the 4AT [33].
c) Screening test for cognitive impairment with Montreal Cognitive Assessment (MOCA) [34]
d) Detailed neurocognitive assessment with a battery of validated tests categorized into visual memory, executive function, attention and decision-making. These have been devised after review of the literature, they are tests which we have used in our previous studies [35] and have been pragmatically chosen in collaboration with a clinical psychologist
    a. (i). Rey Auditory Verbal Learning [36]
       (ii). 'FAS'- Verbal fluency test (paper-based test) [37]
       (iii). Grooved Pegboard Test (instrumentation based test to assess manual dexterity) [38]
       (iv). Trail making test TMT [39] (paper-based test to assess attention and switching)
       (v). Hospital Anxiety and Depression Scale (HADS) [40] to detect any psychological influence on the test results (paper-based)
    b. (vi). National Adult Reading Test (NART)[41] to test premorbid intelligence levels
e) Quality of life assessment with SF-36 [42] and EQ5D5L[43].

<u>Within 48 hours of patients return to level 1 care (or prior to discharge if discharged from ITU):</u>

a) NIHSS and mRs
b) 4AT
c) MOCA

<u>6-week and 6 month follow-ups:</u>

a) NIHSS and mRS
b) 4AT
c) MOCA and neurocognitive battery as above
d) SF-36 and EQ5D5L

4. *Secondary neurological outcome: Serial biomarker blood tests (e.g. S100B)*
A sample of the patient's blood will be taken along with routine blood tests preoperatively, at the end of procedure and 24hrs later. We will study the upregulation of proinflammatory mediators in response to TEVAR between the two groups. Serial measurement of biomarkers will look at inflammatory pathway upregulation, modification of low-density lipoprotein (LDL) moieties inducing the modification of LDL into oxidised LDL and consumption of protection antibodies that work on maintaining homeostasis against danger associated molecular patterns (DAMPS)[44]. S100B is regarded as a marker of brain damage. Reduced serum levels have been detected in patients who underwent carbon-dioxide field flooding in mitral valve operations with cardiopulmonary bypass where there is a risk of CAE [45]. Further analysis will be done via a proteomic inflammatory panel analysis [46]. We will also study the extent of neurological injury using S100B and markers of cell death: TNF receptor 1 (TNFR-1), TRAIL receptor 2 (TRAILR-2) and Fas [47, 48].
Levels of biomarkers will be correlated with DW-MRI SCI, neurological and neurocognitive assessments. For pragmatic reasons including transportation this test will only be conducted in participants recruited at London hospitals.

The samples will be centrifuged and stored at -80°c. Using Enzyme Linked Immunosorbent Assay (ELISA), we will then analyse for S100B amongst a number of other biomarkers at the National Heart and Lung Institute by SC.

5. *Secondary neurological outcome: Risk factor assessment*
Procedural risk factors such as conventional proximal landing zones for the stent (PLZ)[45], coverage of arch vessel origins and intraoperative factors such as but not limited to, number of digital subtraction angiography (DSA) runs and length of time of hypotension, stent type, length of procedure and post stent ballooning will be recorded for multivariate analysis to allow risk factor assessment.

Sample size

Observational data indicate that the incidence of SCI from TEVAR is 81%[6]. Based on our CO2-pilot study that reduced SCI to 25%, a 50% reduction in SCI is possible. Taking a pragmatic and realistic approach to recruitment, we aim for an effect size of 40% reduction in incidence of SCI. Considering a 10% MRI dropout rate from our observational study, a total of 76 (38 per group) would be sufficient to detect an effect size. However, given that randomisation will be by zone of TEVAR, of which there are 5, and we expect a 20% MRI drop-out rate, we are aiming to recruit 120 cases (60 in each arm). This number has been chosen to ensure 10-12 patients in each of 5 arch landing zones in each of the two intervention groups, to allow us to quantify brain injury by zone between the two interventions in addition to establishing an overall measure of effect between the two interventions.

Statistical analysis

Statistical analysis will be by intention to treat. Standard descriptive statistics will be used throughout (mean, range, standard deviation, and median, IQR), with comparative statistics for normally and non-normally distributed data with $p<0.05$ considered as significant. Cronbach's alpha will be used to assess inter-rater reliability of MRI and TCD data. Subgroup analysis will be used to examine SCI and TCD MES rates with respect to PLZ, atheroma grade and stent-graft type.

The data monitoring committee will be made up of SC & LH. They will carry out interim analysis on an ad hoc basis, with no specific stopping guidelines. Any adverse events will be recorded in the trial management folder, and serious adverse events will be reviewed by the CI, with involvement of the local ethics committee if indicated. There will be no planned audits, but any audits will be undertaken by Imperial R&D if required.

Patient and public involvement

None.

Ethics and dissemination

The study coordination centre has obtained approval from the London Fulham Research Ethics Committee and Southern Health and Disability Ethics Committee (NZ) and UK's Health Regulator Authority (HRA). The study will be conducted in accordance with declaration of Helsinki. Any protocol modifications will be undertaken through the local ethics committee. Consent for entering into the study will be taken using standardised consent forms (see supplementary materials) by the local study team, led by a local PI. For St Mary's Hospital, St George's Hospital and St Thomas' Hospital, this includes consenting for blood sampling for biochemical marker analysis. Patients will be given an anonymised code upon entering the trial, which will be stored on a secure hard drive to maintain confidentiality throughout.

The study has received ethical approval for recruitment in the UK (Fulham REC, 19/LO/0836), New Zealand (21/STH/192) and the USA (IRB 019- 264, Ref 378630). The trial is registered at ClinicalTrials.gov (NCT03886675).

The authors have no financial or competing interest to declare. The final trial dataset will be accessible by the trial co-ordinators (SC & LH), as well as the CI (RG). Post-trial provisions and compensation are covered by the policy with Gallagher insurance company. The results of the trial will be submitted for publication in an open access journal.

Protocol version

Based on protocol version 7 (Feb 6, 2023).

Funding

This work was supported by J.P Moulton Charitable Foundation, grant number (P79851) as well as HRUK (Heart Research UK, RG2684/19/22) and the Maurice & Phyllis Paykel Trust (New Zealand).

Competing interests

We declare no competing interests.

Data availability statement

The results of this study will be kept on an anonymized Redcap database and will be published in full on completion of the study. Data requests can be made to corresponding author.

Acknowledgements

We would like to acknowledge the research nurses, R&D department, radiology, and theatre staff at all centres involved for their continued hard work in carrying out this trial.

Contributors

Stephen Crockett has been involved in the set-up, data collection, and write up for this project. Lydia Hanna designed the trial, gained ethical approval, gained funding for the trial. Abhinav Singh developed the MRI protocol, and will be the blinded assessor of the MRIs for the trial. Stephen Gunning has developed the neurocognitive battery with LH, and helped in neurocognitive training for staff. Richard Nicholas, Colin Bicknell, Mohammad Hamady were involved in the study design. Denis Gable was involved in study design and is PI for Baylor Scott & White (Texas). Morrad Sallam is the PI for St Thomas' Hospital. Bijan Modarai has been involved in the study design, and data collection alongside Said Abisi. Oliver Lyons is the PI for CDHB (New Zealand). Richard Gibbs is the chief investigator for the study and led the study design, ethical approval and funding application.

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FIGURE LEGENDS

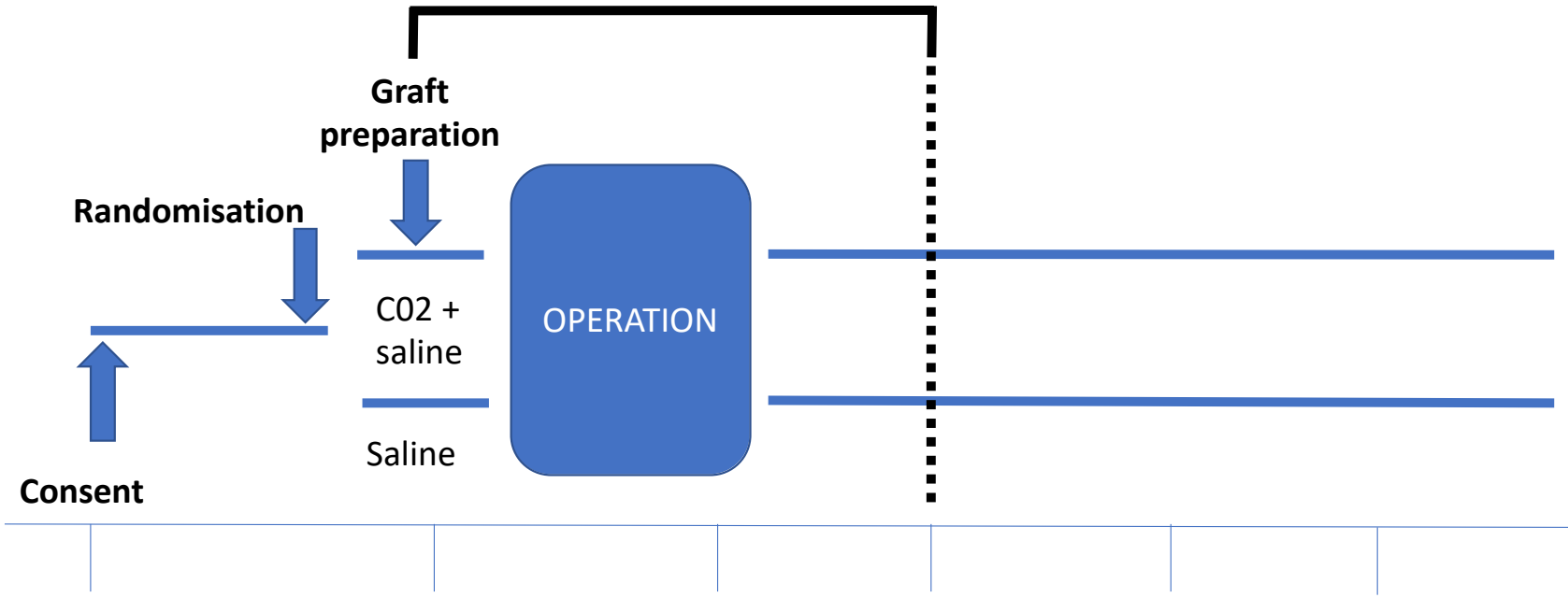
Figure 1. (A) Air bubble release during stent-graft deployment from the proximal end of the stent-graft as it opens in a benchtop experiment carried out by our group; (B) Air bubble release during stent-graft deployment from the distal end of the stent-graft as it opens in a benchtop experiment carried out by our group.

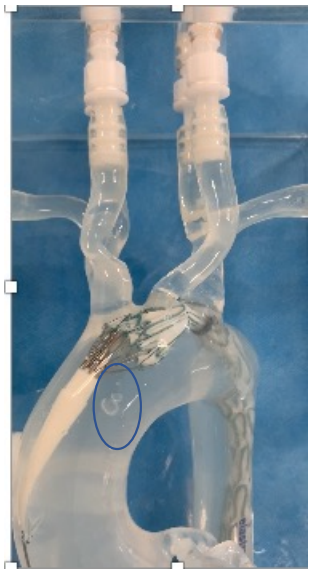
Figure 2. Patient flowchart for the pilot trial

Figure 1A

Figure 1B

INTERvention **with C**erebral **E**mbolic **P**rotection **in T**EVAR





Air bubble from stent

SCREENING/BASELINE
2-4 weeks before surgery

Delirium assessment
Stroke
Functional and quality of life assessment
Cognitive assessment

Day 0 Intraop

S100 blood test (pre & in recovery)
TCD monitoring

D1 Post-op

S100 blood test

<48h in Level 1

Delirium Assessment
Stroke Assessment

<72 hours post op (1-7 days)

DW-MRI

6 weeks Post-op

Delirium Assessment
Stroke Assessment
Functional and Quality of life assessment
Cognitive assessment

6 Months Post-op

Delirium Assessment
Stroke Assessment
Functional and Quality of life assessment
Cognitive assessment
DW-MRI

Imperial College London

Research Governance and Integrity Team

NHS Imperial College Healthcare NHS Trust

IRAS Number: 262145
Patient Identification Number for this trial:

CONSENT FORM

Title of Project:

INTERCEPTevar; 'Carbon-Dioxide Flushing versus Saline Flushing of Thoracic Aortic Stents: A Multi-centre Randomised Controlled Trial'

Chief Investigator: **Mr Richard Gibbs**

Please initial all boxes

1. I confirm that I have read and understand the information sheet dated **18/01/2022 version 2** for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from **Imperial College London** from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my GP being informed of my participation in the study. ☐

5. I agree to take part in the above study. ☐

6. I give / do not give **(delete as applicable)** consent for samples collected during this study to be used in future ethically approved studies. I give permission for my samples to be sent to other organisations, including these outside of the EEA (European Economic Area) ☐

Consent form date of issue: **18/01/2022**
Consent form version number: **3**
IRAS number: 262145

7. I give/do not give **(delete as applicable)** consent to being contacted to potentially taking part in other research studies. ☐

Name of Participant	Date	Signature
Name of Person taking consent.	Date	Signature

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	12
Funding	#4	Sources and types of financial, material, and other support	12

Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	12
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	12
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	12
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	n/a
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3-5
Objectives	#7	Specific objectives or hypotheses	9
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8-9
Methods: Participants,			

interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7-9
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	n/a
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including	2

		clinical and statistical assumptions supporting any sample size calculations	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	2
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	8
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate	9-10

		measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9-10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9-10
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10

Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	2
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	2
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	2
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	2, 10
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	10

Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	2
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	See consent v3 document
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	2 & 9 & consent form

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	p.1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	p.2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	p.2-4
	2b	Specific objectives or hypotheses	p.7
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	p.6
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	p.6
Participants	4a	Eligibility criteria for participants	p.6
	4b	Settings and locations where the data were collected	p.6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	P,.6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	p.7-8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	p.9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	p.10
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	p.6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	p.6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	p.6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	p.6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	p.2

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	p.2-4
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	p.7-8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	n/a
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	p.7-8
	13b	For each group, losses and exclusions after randomisation, together with reasons	p.7-8
Recruitment	14a	Dates defining the periods of recruitment and follow-up	p.6
	14b	Why the trial ended or was stopped	n/a
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	n/a
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	n/a
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	n/a
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	n/a
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	n/a
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	n/a
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	n/a
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	n/a
Other information			
Registration	23	Registration number and name of trial registry	p.10
Protocol	24	Where the full trial protocol can be accessed, if available	n./a
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	p.10

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.