

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-067605
Article Type:	Protocol
Date Submitted by the Author:	05-Sep-2022
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 ; King's College London Cardiovascular Division, Surgery Abisi, Said; Guy's and St Thomas' Hospitals NHS Trust Lyons, Oliver; Canterbury District Health Board Gibbs, Richard; Imperial College London
Keywords:	Vascular surgery < SURGERY, Stroke medicine < INTERNAL MEDICINE, GERIATRIC MEDICINE, VASCULAR MEDICINE

SCHOLARONE™
Manuscripts

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

Authors:

Stephen Crockett- Stephen.crockett@nhs.net.
Lydia Hanna (corresponding author)- Lydia.hanna@Nhs.net
Abhinav Singh- abhinav.singh@nhs.net
Stephen Gunning- stephen.gunning@nhs.net
Richard Nicholas- richard.nicholas3@nhs.net
Colin Bicknell- colin.bicknell@nhs.net
Mohamad Hamady- mohamad.hamady@nhs.net
Dennis Gable- dennis.gable@bswhealth.org
Morad Sallam- morad.sallam@gstt.nhs.uk
Bijan Modarai- bijan.modarai@kcl.ac.uk
Said Abisi- said.abisi@gstt.nhs.uk
Oliver Lyons- oliver.lyons@cdhb.health.nz
Richard Gibbs- Richard.gibbs@nhs.net

Affiliations:

Oliver Lyons- University of Otago, Vascular Endovascular & Transplant Surgery, Canterbury District Health Board, New Zealand.

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 (CO₂) 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 CO₂ 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-CO₂ or TEVAR-Saline group, stratified according to TEVAR landing zone.

1
2
3 Participants will undergo pre-operative neurocognitive tests and quality of life
4 assessments, which will be repeated at 6 weeks and 6 months. Inpatient neurological
5 testing will be performed on day 1, 3 and 7 to screen for clinical stroke or delirium.
6 DW-MRI will be undertaken within 72 hours post-operatively and at 6 months to look
7 for evidence and persistence of SCI. We aim to recruit 120 participants (60 per group)
8 based on our sample size calculation.
9

10 ***Ethics and dissemination (including registration details)***

11
12
13 There is ethical approval for recruitment in UK (ClinicalTrials.gov Identifier
14 NCT03886675), and New Zealand (21/STH/192).
15
16

17 **Article summary**

18 ***Strength & Limitations of this study***

19 Limitations:

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

22 Strengths:

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

33 **Patient and Public involvement**

34
35 Patients will be involved throughout this trial, with initial informed consent to be
36 randomised into one of the two arms for preparing the stent-grafts, the blood test, MRI
37 scans, transcranial doppler studies and neurocognitive testing throughout the trial.
38
39

40 **Introduction**

41
42
43 There has been a significant increase in the number of thoracic endovascular aortic
44 repairs (TEVARs) performed in the last decade. TEVAR is offered as preventative
45 treatment to prevent rupture and death from aneurysmal aortic disease, aortic
46 dissection and traumatic aortic injury. It has been adopted as the standard method for
47 thoracic aortic repair as the avoidance of thoracotomy and aortic cross-clamping
48 means morbidity is reduced and hospital stay is significantly decreased [1]. Although
49 TEVAR has successfully reduced peri-procedural morbidity and mortality, stroke
50 remains a significant risk. Several studies have identified risk factors contributing to
51 neurological injury [2, 3] and further work is needed to investigate these risk factors to
52 predict more accurately the patients at higher risk of neurological injury.
53
54
55
56
57
58
59
60

1
2
3
4
5 There is a reported 3%^[4] to 6.1%^[5] risk of stroke with TEVAR. Our own observational
6 study has detected a 13% stroke rate in patients undergoing TEVAR^[6]. Furthermore,
7 68% of the patients developed covert brain injury as evidenced by new areas of brain
8 infarction (BI) seen on diffusion weighted MRI following TEVAR^[6]. Covert brain injury
9 occurs in aortic surgical and cardiovascular catheter-based interventions ^[6, 7] and
10 because these lesions do not manifest as clinical stroke with motor, sensory or speech
11 deficits, they are termed 'silent' cerebral infarction (SCI). The American Heart and
12 Stroke Association^[8] and the Neurological Academic Research Group (NeuroARC)^[9]
13 now recognise the evolving definition of 'stroke' into a tissue-based diagnosis even in
14 the absence of clinical symptoms. Incidentally identified SCI is a predictor of future
15 development of clinically overt stroke^[10], dementia^[11] and depression^[12]. There is also
16 a direct clinical consequence of SCI with cognitive deficits demonstrated by neuro-
17 psychometric testing^[11] and in our own study, 88% of patients with SCI suffered with
18 neurocognitive decline^[6]. Indeed, several studies have shown that radiologically
19 detected cerebral infarcts tend to occur in those parts of the brain responsible for
20 memory, mood and cognition. These procedurally related lesions are therefore not
21 'silent' but have clinically significant consequences.
22
23
24
25

26
27 Aetiological mechanisms of SCI in TEVAR remain uncharacterised, although several
28 neuroimaging studies have detected evidence of SCI within a few days post-
29 procedure, suggesting that peri-procedural cerebral embolisation may be a cause^[7, 13].
30 Further support for this hypothesis comes from continuous TCD monitoring of the
31 cerebral vessels for microembolic signals (MES) during TEVAR whereby high-risk
32 phases for cerebral embolization have been shown to occur at specific time points
33 during TEVAR^[6, 14]. Stent-graft deployment is the phase most associated with
34 embolisation, followed by wire manipulation in the aortic arch^[6].
35
36

37
38 Through the use of embolic differentiation software, we have deduced that >90% of
39 MES throughout TEVAR are gaseous in nature, with 81% of gaseous MES apparent
40 at stent-graft deployment. Once deployment is complete, TCD monitoring typically
41 detects no further embolic activity. We also found a positive association between
42 number of gaseous MES and number of new DW-MRI BI ^[15]. This suggests that
43 cerebral air embolization may be a significant cause of SCI in TEVAR and provides us
44 with a basis on which to target preventative strategies.
45
46

47
48 Stent-grafts are manufactured in room air conditions and retain air. According to
49 instructions for use (IFU), saline flushing is recommended to de-air the system.
50 Emerging experimental studies have shown a substantial amount of air release from
51 all commercially available grafts with bubbles ranging from 0.34-0.79ml, despite saline
52 flushing (see Figure 1) ^[16, 17]. This is a cause for concern given that cerebral arterioles
53 are 40-250µm in diameter^[18]. Large bubbles would be expected to cause downstream
54 ischaemia and neuronal injury, while smaller bubbles may incite endothelial damage
55 and activation of inflammatory and clotting cascades that may then cause secondary
56 ischaemia^[19]. These small bubbles have been implicated in causing post-operative
57 cognitive delirium (POCD)^[20].
58
59
60

1
2
3 Carbon-dioxide (CO₂) is 1.5 times denser than air and can fill an enclosed space and
4 displace air. It is 25 times more soluble in blood than air and does not lead to bubble
5 formation^[21]. CO₂ has been used extensively in cardiac surgery and shown to
6 significantly reduce intracardiac air^[22] and POCD^[23]. CO₂ can also significantly
7 reduce the average amount of released air from an TEVAR stent in an experimental
8 setting (0.79 vs 0.51 mL, p=0.005)^[17], and has been used clinically in a small series of
9 TEVAR patients where the authors describe a 3% clinical stroke rate. However, none
10 of these patients underwent any formal cognitive or neuroimaging assessment and
11 there was no control group, which has prompted the INTERCEPT trial ^[24, 25].
12
13
14

15 We know that more proximal zones are associated with higher stroke rates. What
16 remains unknown is whether CO₂ flushing is enough to prevent neurological brain
17 injury in these riskier zones, or whether solid embolisation from the manipulation of
18 instruments close to atherosclerotic aortic valves and carotid vessels in more proximal
19 zones is the main risk factor for neurological injury. This information will be used to aid
20 refinement of the inclusion/exclusion criteria for the full-scale RCT and will be used to
21 refine the sample-size calculation for use in the final trial.
22
23
24

25 We carried out a pilot study of 20 TEVAR patients who underwent CO₂ flushing and
26 used TCD to detect cerebral embolization rates and DW-MRI to assess for SCI. Intra-
27 operatively, there were no MES detected at stent graft deployment. The SCI rate was
28 25% and there was no clinical stroke in any of the patients (in comparison to 81% SCI
29 and 13% stroke rate in patients with saline flushing)^[6]. Although encouraging, we
30 recognize the need for level 1 evidence in the form of a robust randomised controlled
31 trial to answer the question 'is there a neuroprotective benefit against SCI and POCD
32 with the use of CO₂ flushed aortic stent-grafts.'
33
34
35

36 A review of registries on 28/01/2019 (www.clinicaltrials.gov and www.isrctn.com)
37 found but no similar studies in TEVAR.
38
39
40

41 Research influence:

42 We have produced the largest case series to date regarding SCI in TEVAR and
43 continue to highlight the magnitude of the problem by our ongoing study of
44 neuroimaging, TCD, neurological and neurocognitive data on these patients. These
45 data initially led us to believe that solid embolization of particulate atherosclerotic
46 matter dislodged from the thoracic aorta was responsible for SCI. Accordingly, we
47 trialed the use of a cerebral embolic protection device designed to capture particulate
48 matter 'en-route' to the brain in a cohort of 20 patients. This established feasibility and
49 safety, and a 98% capture rate of embolic debris and a reduction in the number of
50 lesions on DW-MRI. However, all patients still had lesions, with the majority
51 concentrated in the posterior circulation territory ^[15].
52
53
54

55 We suspect that both solid and gaseous emboli cause SCI. However, our TCD data
56 continuously demonstrates an overwhelming occurrence of gaseous MES at stent-
57 deployment in TEVAR patients with and without filters, that amounts to a greater
58 contribution of total MES than cumulative solid MES throughout TEVAR. Particulate
59 embolism appeared to numerically correlate with the size of infarct, whilst gaseous
60

1
2
3 emboli numerically correlated with the number of infarcts. These findings warrant our
4 attention into investigating cerebral air embolism (CAE) as a cause of SCI and into
5 CO2 flushed stent-grafts as a stand-alone intervention first, particularly as it is cheap,
6 safe and easily implemented.
7
8
9

10 Whilst the different ultrasonic reflective properties of solid and gaseous emboli provide
11 the basis for discriminating between the two, we are aware of skepticism regarding
12 the sensitivity and specificity of TCD embolic differentiation software during an embolic
13 shower.^[26] We have sufficient recorded TCD data to demonstrate that the 'shower' of
14 emboli seen at stent-graft deployment with resultant SCI on DW-MRI with saline
15 flushing is reduced when stent-grafts are flushed with CO2, even when cerebral
16 embolic protection devices are used to capture solid emboli. Reducing the contribution
17 of gaseous embolic events will pave the way for future studies to tackle the residual
18 problem of solid emboli, which will likely require the use of invasive devices, rather
19 than a simple bench-top flushing procedure.
20
21
22

23 The results of our study will be used to gather further information regarding the
24 neurological risks associated with TEVAR and the clinical significance of SCI, where
25 a paucity of literature currently exists. It will also facilitate a more comprehensive and
26 individualised consent process, allowing patients to make more informed decisions.
27 We hope to inform the cardiovascular community about a potential prevention strategy
28 against SCI. Stroke, dementia and neurocognitive decline are enormous burdens on
29 healthcare resources, and any reduction in the incidence of these complications will
30 have a positive effect on health economics, which is vital in the current financial
31 climate.
32
33
34

35 (please see attached documents for images)
36
37

38 **Figure 1.** A) Air bubble release during stent-graft deployment from the proximal end of the stent-graft
39 as it opens in a benchtop experiment carried out by our group
40 B) Air bubble release during stent-graft deployment from the distal end of the stent-graft as it opens in
41 a benchtop experiment carried out by our group.
42
43
44

45 **Methods & analysis**

46
47 *Type of study:* Multi-centre pilot randomised controlled superiority trial (see Figure 2
48 for flow chart for RCT).

49 *Duration:* Estimated duration is 36 months for patient recruitment.

50 *Number and type of subjects:* All elective patients undergoing TEVAR for aortic
51 pathology.
52

53 *Target total sample size:* 120, (60 in each intervention arm).
54
55

56 **Enrolment**

57 Patients suitable for TEVAR as decided upon by a vascular multi-disciplinary meeting
58 will be invited to participate and enrolled after informed written consent. Participants
59 will be recruited by the research team at each site before surgery before their
60 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 CO₂. 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% CO₂ 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

- 1
- 2
- 3
- 4
- 5 • 6-week, 6 month and 1 year follow-up:
- 6 a) NIHSS and mRS
- 7 b) 4AT
- 8 c) MOCA and neurocognitive battery as above
- 9 d) SF-36 and EQ5D5L
- 10
- 11
- 12

13 4. *Secondary outcome: Serial **biomarker** blood tests e.g. S100B*

14 A sample of the patient's blood will be taken along with routine blood tests
15 preoperatively, at the end of procedure and 24hrs later. We will study the
16 upregulation of proinflammatory mediators in response to TEVAR between the
17 two groups. Serial measurement of biomarkers will look at inflammatory
18 pathway upregulation, modification of low-density lipoprotein (LDL) moieties
19 inducing the modification of LDL into oxidised LDL and consumption of
20 protection antibodies that work on maintaining homeostasis against danger
21 associated molecular patterns (DAMPs)[44]. S100B is regarded as a marker of
22 brain damage. Reduced serum levels have been detected in patients who
23 underwent carbon-dioxide field flooding in mitral valve operations with
24 cardiopulmonary bypass where there is a risk of CAE [45]. Further analysis will
25 be done via a proteomic inflammatory panel analysis [46]. We will also study the
26 extent of neurological injury using S100B and markers of cell death: TNF
27 receptor 1 (TNFR-1), TRAIL receptor 2 (TRAILR-2) and Fas [47, 48].

28 Levels of biomarkers will be correlated with DW-MRI SCI, neurological and
29 neurocognitive assessments. For pragmatic reasons including transportation
30 this test will only be conducted in participants recruited at London hospitals.

31 5. *Secondary outcome: **Risk factor assessment***

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

38
39
40
41
42
43 **Sample Size:** Observational data indicate that the incidence of SCI from TEVAR is
44 81%^[6]. Based on our CO₂-pilot study that reduced SCI to 25%, a 50% reduction in
45 SCI is possible. Taking a pragmatic and realistic approach to recruitment we aim for
46 an effect size of 40% reduction in incidence of SCI. Considering a 10% MRI dropout
47 rate from our observational study, a total of 76 (38 per group) would be sufficient to
48 detect an effect size. However, given that randomisation will be by zone of TEVAR, of
49 which there are 5, and we expect a 20% MRI drop-out rate, we are aiming to recruit
50 120 cases (60 in each arm). This number has been chosen to ensure 10-12 patients
51 in each of 5 arch landing zones in each of the two intervention groups, to allow us to
52 quantify brain injury by zone between the two interventions in addition to establishing
53 an overall measure of effect between the two interventions.

54
55
56
57 **Statistical analysis**

58 Statistical analysis will be by intention to treat. Standard descriptive statistics will be
59 used throughout (mean, range, standard deviation, and median, IQR), with
60

1
2
3 comparative statistics for normally and non-normally distributed data with $p < 0.05$
4 considered as significant. Cronbach's alpha will be used to assess inter-rater reliability
5 of MRI and TCD data. Subgroup analysis will be used to examine SCI and TCD MES
6 rates with respect to PLZ, atheroma grade and stent-graft type.
7

8 9 **Ethics and dissemination**

10
11 The study coordination centre has obtained approval from the London Fulham
12 Research Ethics Committee and Southern Health and Disability Ethics Committee
13 (NZ) and UK's Health Regulator Authority (HRA). The study will be conducted in
14 accordance with declaration of Helsinki.
15
16

17 ClinicalTrials.gov Identifier NCT03886675

18
19 Based on Protocol version 4 (18/1/2022)
20
21
22

23 **Funding statement**

24
25 This work was supported by J.P Moulton Charitable Foundation, grant number
26 (P79851) as well as HRUK (Heart Research UK, RG2684/19/22) and the Maurice &
27 Phyllis Paykel Trust (New Zealand).
28
29

30 **Competing interests statement**

31
32 There are no competing interests in this study
33
34

35 **Data statement**

36
37 The results of this study will be kept on an anonymized Redcap database, and will be
38 published in full on completion of the study. Data requests can be made to
39 corresponding author.
40
41

42 **Monitoring**

43
44 The data monitoring committee will be made up of SC & LH. They will carry out interim
45 analysis on an ad hoc basis, with no specific stopping guidelines. Any adverse events
46 will be recorded in the trial management folder, and serious adverse events will be
47 reviewed by the CI, with involvement of the local ethics committee if indicated. There
48 will be no planned audits, but any audits will be undertaken by Imperial R&D if
49 required.
50
51

52 **Acknowledgements**

53
54 We would like to acknowledge the research nurses, R&D department, radiology, and
55 theatre staff at all centres involved for their continued hard work in carrying out this
56 trial.
57
58

59 3833 words
60

Author contributions

Stephen Crockett- data collection, and write up; Stephen.crockett@nhs.net.
 Lydia Hanna (corresponding author)- design, ethical approval, funding application, PI for the study; Lydia.hanna@nhs.net
 Abhinav Singh- development of MRI protocol; abhinav.singh@nhs.net
 Stephen Gunning- development of neurocognitive testing battery; stephen.gunning@nhs.net
 Richard Nicholas- study design; richard.nicholas3@nhs.net
 Colin Bicknell- study design; colin.bicknell@nhs.net
 Mohamad Hamady- study design; mohamad.hamady@nhs.net
 Dennis Gable- study design; dennis.gable@bswhealth.org
 Morad Sallam- PI for St Thomas's Hospital, data collection; morad.sallam@gstt.nhs.uk
 Bijan Modarai- study design and data collection; bijan.modarai@kcl.ac.uk
 Said Abisi- data collection; said.abisi@gstt.nhs.uk
 Oliver Lyons- PI for CDHB (New Zealand), data collection; oliver.lyons@cdhb.health.nz
 Richard Gibbs- chief investigator for the study and led the study design, ethical approval and funding application; Richard.gibbs@nhs.net

References

1. Lee, H.C., et al., *Endovascular Repair versus Open Repair for Isolated Descending Thoracic Aortic Aneurysm*. Yonsei Med J, 2015. **56**(4): p. 904-12.
2. Feezor, R.J., et al., *Risk factors for perioperative stroke during thoracic endovascular aortic repairs (TEVAR)*. J Endovasc Ther, 2007. **14**(4): p. 568-73.
3. Delafontaine, J.L., et al., *Outcome Comparison of TEVAR with and without Left Subclavian Artery Revascularization from Analysis of Nationwide Inpatient Sample Database*. Ann Vasc Surg, 2019. **58**: p. 174-179.
4. Chaikof, E.L., et al., *Endovascular repair for diverse pathologies of the thoracic aorta: an initial decade of experience*. J Am Coll Surg, 2009. **208**(5): p. 802-16; discussion 816-8.
5. Ehlert, B.A., et al., *Impact of operative indication and surgical complexity on outcomes after thoracic endovascular aortic repair at National Surgical Quality Improvement Program Centers*. J Vasc Surg, 2011. **54**(6): p. 1629-36.
6. Perera, A.H., et al., *Cerebral embolization, silent cerebral infarction and neurocognitive decline after thoracic endovascular aortic repair*. Br J Surg, 2018. **105**(4): p. 366-378.
7. Fanning, J.P., et al., *Neurological Injury in Intermediate-Risk Transcatheter Aortic Valve Implantation*. J Am Heart Assoc, 2016. **5**(11).
8. Sacco, R.L., et al., *An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association*. Stroke, 2013. **44**(7): p. 2064-89.

9. Lansky, A.J., et al., *Proposed Standardized Neurological Endpoints for Cardiovascular Clinical Trials: An Academic Research Consortium Initiative*. J Am Coll Cardiol, 2017. **69**(6): p. 679-691.
10. Gutsche, J.T., et al., *Risk factors for perioperative stroke after thoracic endovascular aortic repair*. Ann Thorac Surg, 2007. **84**(4): p. 1195-200; discussion 1200.
11. Kobayashi, S., et al., *Subcortical silent brain infarction as a risk factor for clinical stroke*. Stroke, 1997. **28**(10): p. 1932-9.
12. Vermeer, S.E., et al., *Silent brain infarcts and the risk of dementia and cognitive decline*. N Engl J Med, 2003. **348**(13): p. 1215-22.
13. Kahlert, P., et al., *Silent cerebral ischemia after thoracic endovascular aortic repair: a neuroimaging study*. Ann Thorac Surg, 2014. **98**(1): p. 53-8.
14. Bismuth, J., et al., *Transcranial Doppler findings during thoracic endovascular aortic repair*. J Vasc Surg, 2011. **54**(2): p. 364-9.
15. Grover, G., et al., *Cerebral embolic protection in thoracic endovascular aortic repair*. J Vasc Surg, 2018. **68**(6): p. 1656-1666.
16. Inci, K., et al., *Air bubbles are released by thoracic endograft deployment: An in vitro experimental study*. SAGE Open Med, 2016. **4**: p. 2050312116682130.
17. Rohlfes, F., et al., *Air Embolism During TEVAR: Carbon Dioxide Flushing Decreases the Amount of Gas Released from Thoracic Stent-Grafts During Deployment*. J Endovasc Ther, 2017. **24**(1): p. 84-88.
18. Pappano, A.J. and W.G. Wier, *Cardiovascular physiology*. 2019.
19. Mitchell, S. and D. Gorman, *The pathophysiology of cerebral arterial gas embolism*. J Extra Corpor Technol, 2002. **34**(1): p. 18-23.
20. Borger, M.A., et al., *Neuropsychologic impairment after coronary bypass surgery: effect of gaseous microemboli during perfusionist interventions*. J Thorac Cardiovasc Surg, 2001. **121**(4): p. 743-9.
21. Martens, S., et al., *Carbon dioxide field flooding reduces neurologic impairment after open heart surgery*. Ann Thorac Surg, 2008. **85**(2): p. 543-7.
22. Svenarud, P., M. Persson, and J. van der Linden, *Effect of CO2 insufflation on the number and behavior of air microemboli in open-heart surgery: a randomized clinical trial*. Circulation, 2004. **109**(9): p. 1127-32.
23. Chaudhuri, K., et al., *Carbon dioxide insufflation in open-chamber cardiac surgery: a double-blind, randomized clinical trial of neurocognitive effects*. J Thorac Cardiovasc Surg, 2012. **144**(3): p. 646-653.e1.
24. Kölbel, T., et al., *Carbon Dioxide Flushing Technique to Prevent Cerebral Arterial Air Embolism and Stroke During TEVAR*. J Endovasc Ther, 2016. **23**(2): p. 393-5.
25. Lyons, O. and J. Schmidli, *Preventing Stroke Due to Intervention in the Aortic Arch*. European Journal of Vascular and Endovascular Surgery, 2020. **61**.
26. Markus, H.S. and M. Punter, *Can transcranial Doppler discriminate between solid and gaseous microemboli? Assessment of a dual-frequency transducer system*. Stroke, 2005. **36**(8): p. 1731-4.
27. Fazekas, F., et al., *MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging*. AJR Am J Roentgenol, 1987. **149**(2): p. 351-6.
28. *Basic identification criteria of Doppler microembolic signals. Consensus Committee of the Ninth International Cerebral Hemodynamic Symposium*. Stroke, 1995. **26**(6): p. 1123.
29. National Institute of Neurological, D. and Stroke, *NIH stroke scale*. 2011: [Bethesda, Md.?] : National Institute of Neurological Disorders and Stroke, Dept. of Health and Human Services, USA, [2011?].

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
30. Rankin, J., *Cerebral vascular accidents in patients over the age of 60. II. Prognosis*. Scott Med J, 1957. **2**(5): p. 200-15.
 31. Bonita, R. and R. Beaglehole. *Modification of Rankin Scale: Recovery of motor function after stroke*. 1988.
 32. van Swieten, J.C., et al., *Interobserver agreement for the assessment of handicap in stroke patients*. Stroke, 1988. **19**(5): p. 604-7.
 33. Saller, T., A.M.J. MacLulich, and R. Perneczky, *The 4AT - an instrument for delirium detection for older patients in the post-anaesthesia care unit*. Anaesthesia, 2020. **75**(3): p. 410.
 34. Nasreddine, Z.S., et al., *The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment*. J Am Geriatr Soc, 2005. **53**(4): p. 695-9.
 35. Perera, A.H., et al., *Robotic Arch Catheter Placement Reduces Cerebral Embolization During Thoracic Endovascular Aortic Repair (TEVAR)*. Eur J Vasc Endovasc Surg, 2017. **53**(3): p. 362-369.
 36. Bean, J., *Rey Auditory Verbal Learning Test, Rey AVLT*, in *Encyclopedia of Clinical Neuropsychology*, J.S. Kreutzer, J. DeLuca, and B. Caplan, Editors. 2011, Springer New York: New York, NY. p. 2174-2175.
 37. Patterson, J., *F-A-S Test*, in *Encyclopedia of Clinical Neuropsychology*, J.S. Kreutzer, J. DeLuca, and B. Caplan, Editors. 2011, Springer New York: New York, NY. p. 1024-1026.
 38. Merker, B. and K. Podell, *Grooved Pegboard Test*, in *Encyclopedia of Clinical Neuropsychology*, J.S. Kreutzer, J. DeLuca, and B. Caplan, Editors. 2011, Springer New York: New York, NY. p. 1176-1178.
 39. Llinàs-Reglà, J., et al., *The Trail Making Test*. Assessment, 2017. **24**(2): p. 183-196.
 40. Zigmond, A.S. and R.P. Snaith, *The hospital anxiety and depression scale*. Acta Psychiatr Scand, 1983. **67**(6): p. 361-70.
 41. Venegas, J. and E. Clark, *National Adult Reading Test*, in *Encyclopedia of Clinical Neuropsychology*, J.S. Kreutzer, J. DeLuca, and B. Caplan, Editors. 2011, Springer New York: New York, NY. p. 1705-1705.
 42. Ware, J.E., R.H. Brook, and A. Davies-Avery, *Conceptualization and measurement of health for adults in the health insurance study: model of health and methodology*. 1980.
 43. *EuroQol--a new facility for the measurement of health-related quality of life*. Health Policy, 1990. **16**(3): p. 199-208.
 44. Khan, T.Z., et al., *Oxidised LDL and Anti-Oxidised LDL Antibodies Are Reduced by Lipoprotein Apheresis in a Randomised Controlled Trial on Patients with Refractory Angina and Elevated Lipoprotein(a)*. Antioxidants (Basel), 2021. **10**(1).
 45. Ishimaru, S., *Endografting of the aortic arch*. J Endovasc Ther, 2004. **11 Suppl 2**: p. Ii62-71.
 46. *Accelerated proteomics together*. 28/07/20]; Available from: <https://www.olink.com/products/inflammation>). .
 47. Hartley, A., D. Haskard, and R. Khamis, *Markers of Apoptosis Predict Cardiovascular Outcomes and Point to 'Response to Injury' as a Common Pathway Leading to Diabetes and Cardiovascular Events*. EBioMedicine, 2018. **28**: p. 19-20.
 48. Gorla, R., et al., *Systemic inflammatory response syndromes in the era of interventional cardiology*. Vascul Pharmacol, 2018.

Figure 1A



Figure 1B

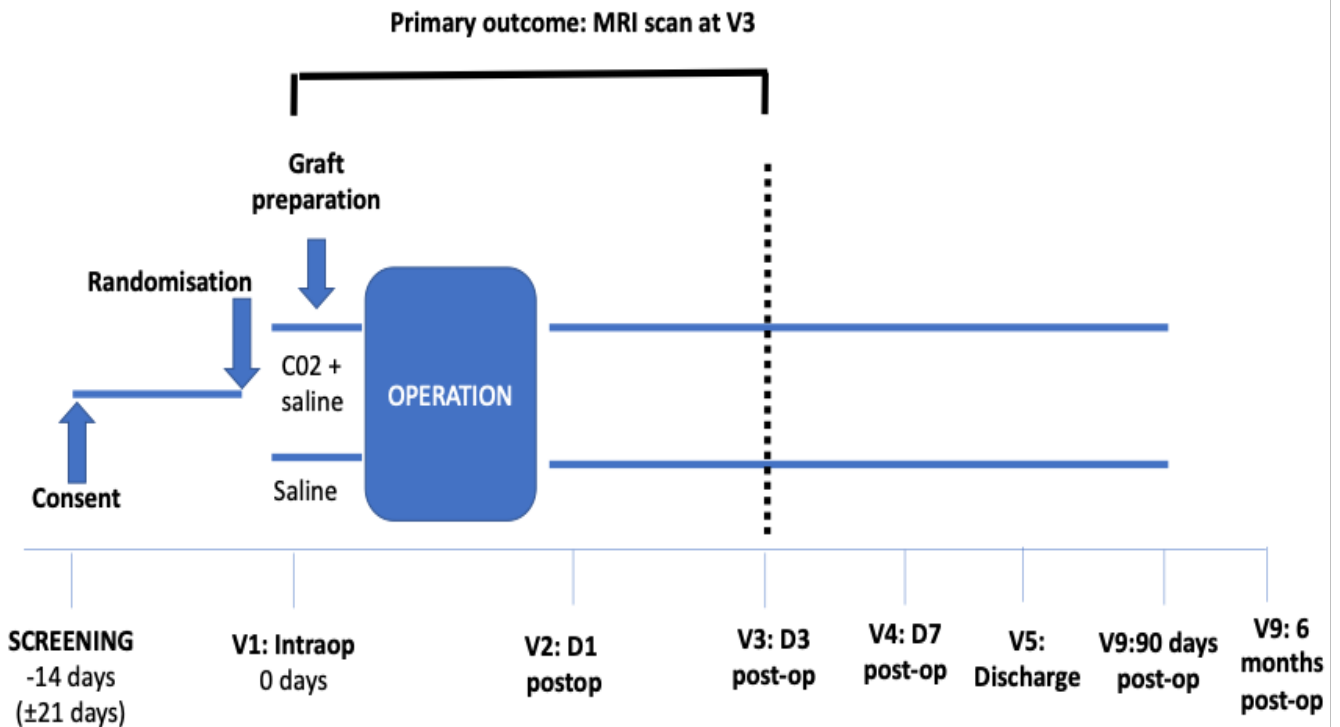


ew only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 2

INTERCEPT TRIAL STRUCTURE



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 SPIRIT reporting 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

1	Roles and	#5b	Name and contact information for the trial sponsor	12
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	12
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate authority	
12			over any of these activities	
13				
14				
15				
16	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	n/a
17	responsibilities:		centre, steering committee, endpoint adjudication committee,	
18	committees		data management team, and other individuals or groups	
19			overseeing the trial, if applicable (see Item 21a for data	
20			monitoring committee)	
21				
22				
23				
24	Introduction			
25				
26				
27	Background and	#6a	Description of research question and justification for undertaking	3-5
28	rationale		the trial, including summary of relevant studies (published and	
29			unpublished) examining benefits and harms for each intervention	
30				
31				
32	Background and	#6b	Explanation for choice of comparators	3-5
33	rationale: choice of			
34	comparators			
35				
36				
37	Objectives	#7	Specific objectives or hypotheses	9
38				
39				
40	Trial design	#8	Description of trial design including type of trial (eg, parallel	8-9
41			group, crossover, factorial, single group), allocation ratio, and	
42			framework (eg, superiority, equivalence, non-inferiority,	
43			exploratory)	
44				
45				
46				
47	Methods:			
48	Participants,			
49	interventions, and			
50	outcomes			
51				
52				
53	Study setting	#9	Description of study settings (eg, community clinic, academic	7-9
54			hospital) and list of countries where data will be collected.	
55			Reference to where list of study sites can be obtained	
56				
57				
58				
59				
60				

1	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
2				
3				
4				
5				
6	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
7	description			
8				
9				
10	Interventions:	#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
11	modifications			
12				
13				
14				
15	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
16	adherence			
17				
18				
19				
20	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
21	concomitant care			
22				
23				
24	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
25				
26				
27				
28				
29				
30				
31				
32				
33				
34	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
35				
36				
37				
38				
39				
40	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
41				
42				
43				
44				
45	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	2
46				
47				
48				

Methods: Assignment of interventions (for controlled trials)

54	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
55				
56				
57				
58				
59				

provided in a separate document that is unavailable to those who enrol participants or assign interventions

1			
2			
3			
4	Allocation	#16b	Mechanism of implementing the allocation sequence (eg, central 8
5	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
6			describing any steps to conceal the sequence until interventions
7	mechanism		are assigned
8			
9			
10			
11	Allocation:	#16c	Who will generate the allocation sequence, who will enrol 8
12	implementation		participants, and who will assign participants to interventions
13			
14			
15	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial 8
16			participants, care providers, outcome assessors, data analysts),
17			and how
18			
19			
20	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible, 8
21	emergency unblinding		and procedure for revealing a participant's allocated intervention
22			during the trial
23			
24			
25	Methods: Data		
26	collection,		
27	management, and		
28	analysis		
29			
30			
31			
32	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and 9-10
33			other trial data, including any related processes to promote data
34			quality (eg, duplicate measurements, training of assessors) and a
35			description of study instruments (eg, questionnaires, laboratory
36			tests) along with their reliability and validity, if known.
37			Reference to where data collection forms can be found, if not in
38			the protocol
39			
40			
41			
42			
43	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up, 9-10
44	retention		including list of any outcome data to be collected for participants
45			who discontinue or deviate from intervention protocols
46			
47			
48			
49	Data management	#19	Plans for data entry, coding, security, and storage, including any 10
50			related processes to promote data quality (eg, double data entry;
51			range checks for data values). Reference to where details of data
52			management procedures can be found, if not in the protocol
53			
54			
55	Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary 9-10
56			outcomes. Reference to where other details of the statistical
57			analysis plan can be found, if not in the protocol
58			
59			
60			

1	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted	
2	analyses		analyses)	
3				
4	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	
5	population and missing		adherence (eg, as randomised analysis), and any statistical	
6	data		methods to handle missing data (eg, multiple imputation)	
7				
8				
9				
10	Methods: Monitoring			
11				
12	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary of	10
13	formal committee		its role and reporting structure; statement of whether it is	
14			independent from the sponsor and competing interests; and	
15			reference to where further details about its charter can be found,	
16			if not in the protocol. Alternatively, an explanation of why a	
17			DMC is not needed	
18				
19				
20				
21				
22	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	10
23	interim analysis		including who will have access to these interim results and make	
24			the final decision to terminate the trial	
25				
26				
27	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited	10
28			and spontaneously reported adverse events and other unintended	
29			effects of trial interventions or trial conduct	
30				
31				
32				
33	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and	10
34			whether the process will be independent from investigators and	
35			the sponsor	
36				
37				
38	Ethics and			
39	dissemination			
40				
41				
42	Research ethics	#24	Plans for seeking research ethics committee / institutional review	
43	approval		board (REC / IRB) approval	
44				
45				
46	Protocol amendments	#25	Plans for communicating important protocol modifications (eg,	
47			changes to eligibility criteria, outcomes, analyses) to relevant	
48			parties (eg, investigators, REC / IRBs, trial participants, trial	
49			registries, journals, regulators)	
50				
51				
52				
53	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial	
54			participants or authorised surrogates, and how (see Item 32)	
55				
56				
57				
58				
59				
60				

1	Consent or assent:	#26b	Additional consent provisions for collection and use of
2	ancillary studies		participant data and biological specimens in ancillary studies, if
3			applicable
4			
5			
6	Confidentiality	#27	How personal information about potential and enrolled
7			participants will be collected, shared, and maintained in order to
8			protect confidentiality before, during, and after the trial
9			
10			
11	Declaration of interests	#28	Financial and other competing interests for principal investigators
12			for the overall trial and each study site
13			
14			
15	Data access	#29	Statement of who will have access to the final trial dataset, and
16			disclosure of contractual agreements that limit such access for
17			investigators
18			
19			
20	Ancillary and post trial	#30	Provisions, if any, for ancillary and post-trial care, and for
21	care		compensation to those who suffer harm from trial participation
22			
23			
24	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial results
25	trial results		to participants, healthcare professionals, the public, and other
26			relevant groups (eg, via publication, reporting in results
27			databases, or other data sharing arrangements), including any
28			publication restrictions
29			
30			
31			
32			
33	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of
34	authorship		professional writers
35			
36			
37	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,
38	reproducible research		participant-level dataset, and statistical code
39			
40			
41	Appendices		
42			
43	Informed consent	#32	Model consent form and other related documentation given to
44	materials		participants and authorised surrogates
45			
46			
47	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of
48			biological specimens for genetic or molecular analysis in the
49			current trial and for future use in ancillary studies, if applicable
50			
51			

52 None The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons
53 Attribution License CC-BY-NC. This checklist can be completed online using <https://www.goodreports.org/>, a
54 tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
55
56
57
58
59



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

1		assessing outcomes) and how	
2	11b	If relevant, description of the similarity of interventions	p.2-4
3	Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes
4		12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses
5			n/a
6	Results		
7	Participant flow (a	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and
8	diagram is strongly		were analysed for the primary outcome
9	recommended)	13b	For each group, losses and exclusions after randomisation, together with reasons
10			p.7-8
11	Recruitment	14a	Dates defining the periods of recruitment and follow-up
12		14b	Why the trial ended or was stopped
13			n/a
14	Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
15	Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was
16			by original assigned groups
17	Outcomes and	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its
18	estimation		precision (such as 95% confidence interval)
19		17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
20			n/a
21	Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing
22			pre-specified from exploratory
23			n/a
24	Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)
25			n/a
26	Discussion		
27	Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses
28	Generalisability	21	Generalisability (external validity, applicability) of the trial findings
29	Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
30			n/a
31	Other information		
32	Registration	23	Registration number and name of trial registry
33	Protocol	24	Where the full trial protocol can be accessed, if available
34			n/a
35	Funding	25	Sources of funding and other support (such as supply of drugs), role of funders
36			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:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-067605.R1
Article Type:	Protocol
Date Submitted by the Author:	04-Jan-2023
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

SCHOLARONE™
Manuscripts

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'

Corresponding author:

Miss Lydia Hanna

Address: Imperial College Healthcare Trust. St Mary's Hospital. Praed Street W2
1NY London, UK.

Lydia.hanna@nhs.net.

07747 002704

Co-Authors:

Stephen Crockett- Stephen.crockett@nhs.net.

Imperial College Healthcare Trust. St Mary's Hospital. Praed Street W2 1NY London,
UK.

Lydia Hanna (corresponding author)- Lydia.hanna@Nhs.net, Imperial College
Healthcare Trust. St Mary's Hospital. Praed Street W2 1NY London, UK.

Abhinav Singh- abhinav.singh@nhs.net

Imperial College Healthcare Trust. Charing Cross Hospital, Fulham Palace Rd,
London W6 8RF, London, UK.

Stephen Gunning- stephen.gunning@nhs.net

Imperial College Healthcare Trust. Charing Cross Hospital, Fulham Palace Rd,
London W6 8RF, London, UK.

Richard Nicholas- richard.nicholas3@nhs.net

Imperial College Healthcare Trust. Charing Cross Hospital, Fulham Palace Rd,
London W6 8RF, London, UK

Colin Bicknell- colin.bicknell@nhs.net

Imperial College Healthcare Trust. St Mary's Hospital. Praed Street W2 1NY London,
UK.

Mohamad Hamady- mohamad.hamady@nhs.net

Imperial College Healthcare Trust. St Mary's Hospital. Praed Street W2 1NY London,
UK.

Dennis Gable- dennis.gable@bswhealth.org

Baylor Scott & White Health, Plano, Texas, USA

Morad Sallam- morad.sallam@gstt.nhs.uk

Guy's and St Thomas' NHS Foundation Trust, Westminster Bridge Road, London
SE1 7EH

Bijan Modarai- bijan.modarai@kcl.ac.uk

1
2
3 Guy's and St Thomas' NHS Foundation Trust, Westminster Bridge Road, London
4 SE1 7EH
5

6 Said Abisi- said.abisi@gstt.nhs.uk

7
8 Guy's and St Thomas' NHS Foundation Trust, Westminster Bridge Road, London
9 SE1 7EH
10

11 Oliver Lyons- oliver.lyons@cdhb.health.nz

12 Canterbury District Health Board, Canterbury, New Zealand
13

14 Richard Gibbs- Richard.gibbs@nhs.net

15 Imperial College Healthcare Trust. St Mary's Hospital. Praed Street W2 1NY London,
16 UK.
17
18

19 **Keywords**

20
21 Thoracic aortic endovascular repair; cerebral infarction; stroke; cognitive decline
22
23

24 **Abstract word count**

25
26 528 words
27

28 **Word Count**

29
30 3672 words
31
32

33 **Number of references**

34
35 48
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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'

Authors

Stephen Crockett- Stephen.crockett@nhs.net.
Lydia Hanna (corresponding author)- Lydia.hanna@Nhs.net
Abhinav Singh- abhinav.singh@nhs.net
Stephen Gunning- stephen.gunning@nhs.net
Richard Nicholas- richard.nicholas3@nhs.net
Colin Bicknell- colin.bicknell@nhs.net
Mohamad Hamady- mohamad.hamady@nhs.net
Dennis Gable- dennis.gable@bswhealth.org
Morad Sallam- morad.sallam@gstt.nhs.uk
Bijan Modarai- bijan.modarai@kcl.ac.uk
Said Abisi- said.abisi@gstt.nhs.uk
Oliver Lyons- oliver.lyons@cdhb.health.nz
Richard Gibbs- Richard.gibbs@nhs.net

Affiliations:

Oliver Lyons- University of Otago, Vascular Endovascular & Transplant Surgery, Canterbury
District Health Board, New Zealand.

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 (CO₂) 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 CO₂ 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-CO₂ or TEVAR-Saline group, stratified according to TEVAR landing zone.

1
2
3 Participants will undergo pre-operative neurocognitive tests and quality of life
4 assessments, which will be repeated at 6 weeks and 6 months. Inpatient neurological
5 testing will be performed on day 1, 3 and 7 to screen for clinical stroke or delirium.
6 DW-MRI will be undertaken within 72 hours post-operatively and at 6 months to look
7 for evidence and persistence of SCI. We aim to recruit 120 participants (60 per group)
8 based on our sample size calculation.
9

10 11 **Ethics and Dissemination**

12 The study coordination centre has obtained approval from the London Fulham
13 Research Ethics Committee (19/LO/0836) and Southern Health and Disability Ethics
14 Committee (NZ) and UK's Health Regulator Authority (HRA). Consent for entering into
15 the study will be taken using standardised consent forms by the local study team, led
16 by a local PI. The results of the trial will be published in an open access journal.
17
18
19

20 21 **Article summary**

22 23 *Strength & Limitations of this study*

- 24 • Unprecedented levels of neurocognitive data, neuroimaging and follow up for
25 patients undergoing TEVAR to determine the clinical impact of cerebral
26 infarction complicating thoracic aortic endovascular repair.
- 27 • Multicentre RCT providing generalizable results.
- 28 • A cheap and readily available intervention is being studied, and results could
29 be rapidly implemented.
- 30 • The results of our study will be used to gather further information regarding the
31 neurological risk associated with TEVAR and the clinical significance of SCI,
32 where a paucity of literature exists.
- 33 • Incomplete blinding as the surgeons carrying out the procedure cannot be
34 blinded to stent graft flushing.
35
36
37
38
39
40

41 42 **Introduction**

43 There has been a significant increase in the number of thoracic endovascular aortic
44 repairs (TEVARs) performed in the last decade. TEVAR is offered as a treatment to
45 prevent rupture and death from aneurysmal aortic disease, aortic dissection and
46 traumatic aortic injury. It has been adopted as the standard method for thoracic aortic
47 repair as the avoidance of thoracotomy and aortic cross-clamping means morbidity is
48 reduced and hospital stay is significantly decreased [1]. Although TEVAR has
49 successfully reduced peri-procedural morbidity and mortality, stroke remains a
50 significant risk. Several studies have identified risk factors contributing to neurological
51 injury [2, 3] and further work is needed to investigate these risk factors to predict more
52 accurately the patients at higher risk of neurological injury.
53
54
55

56 There is a reported 3%^[4] to 8%^[5] risk of stroke with TEVAR. Our own observational
57 study detected a 13% stroke rate in patients undergoing complex TEVAR^[6].
58 Furthermore, 68% of these patients developed covert brain injury as evidenced by
59
60

1
2
3 new areas of brain infarction (BI) seen on diffusion weighted MRI following the
4 intervention.^[6] Covert brain injury occurs in aortic surgical and cardiovascular catheter-
5 based interventions ^[6, 7] and because these lesions do not manifest as clinical stroke
6 with motor, sensory or speech deficits, they have been erroneously termed 'silent'
7 cerebral infarction (SCI). The American Heart and Stroke Association^[8] and the
8 Neurological Academic Research Group (NeuroARC)^[9] now recognise the evolving
9 definition of 'stroke' into a tissue-based diagnosis even in the absence of clinical
10 symptoms. Incidentally identified SCI is a predictor of future development of clinically
11 overt stroke^[10], dementia^[11] and depression^[12]. There is also a direct clinical
12 consequence of SCI with cognitive deficits demonstrated by neuro-psychometric
13 testing^[11] and in our own study, 88% of patients with SCI suffered with neurocognitive
14 decline^[6]. Indeed, several studies have shown that radiologically detected cerebral
15 infarcts tend to occur in those parts of the brain responsible for memory, mood and
16 cognition. These procedurally related lesions are therefore not 'silent' but have
17 clinically significant consequences.
18
19
20
21

22 Aetiological mechanisms of SCI in TEVAR remain uncharacterised, although several
23 neuroimaging studies have detected evidence of SCI within a few days post-
24 procedure, suggesting that peri-procedural cerebral embolisation may be a cause^{[7,}
25 ^{13]}. Further support for this hypothesis comes from continuous TCD monitoring of the
26 cerebral vessels for microembolic signals (MES) during TEVAR whereby high-risk
27 phases for cerebral embolization have been shown to occur at specific time points
28 during TEVAR^[6, 14]. Stent-graft deployment is the phase most associated with
29 embolisation , followed by wire manipulation in the aortic arch^[6].
30
31
32
33

34 Through the use of embolic differentiation software, we have deduced that >90% of
35 MES throughout TEVAR are gaseous in nature, with 81% of gaseous MES apparent
36 at stent-graft deployment. Once deployment is complete, TCD monitoring typically
37 detects no further embolic activity. We also found a positive association between
38 number of gaseous MES and number of new DW-MRI BI ^[15]. This suggests that
39 cerebral air embolization may be a significant cause of SCI in TEVAR and provides us
40 with a basis on which to target preventative strategies.
41
42
43

44 Stent-grafts are manufactured in room air conditions and retain air. According to
45 instructions for use (IFU), saline flushing is recommended to de-air the system.
46 Emerging experimental studies have shown a substantial amount of air release from
47 all commercially available grafts with bubbles ranging from 0.34-0.79ml, despite saline
48 flushing (see Figure 1) ^[16, 17]. This is a cause for concern given that cerebral arterioles
49 are 40-250µm in diameter^[18]. Large bubbles would be expected to cause downstream
50 ischaemia and neuronal injury, while smaller bubbles may incite endothelial damage
51 and activation of inflammatory and clotting cascades that may then cause secondary
52 ischaemia^[19]. These small bubbles have been implicated in causing post-operative
53 cognitive delirium (POCD)^[20].
54
55
56

57 Carbon-dioxide (CO₂) is 1.5 times denser than air and can fill an enclosed space and
58 displace air. It is 25 times more soluble in blood than air and does not lead to bubble
59 formation^[21]. CO₂ has been used extensively in cardiac surgery and shown to
60

1
2
3 significantly reduce intracardiac air^[22] and POCD^[23]. CO₂ can also significantly
4 reduce the average amount of released air from an TEVAR stent in an experimental
5 setting (0.79 vs 0.51 mL, p=0.005)^[17], and has been used clinically in a small series of
6 TEVAR patients where the authors describe a 3% clinical stroke rate. However, none
7 of these patients underwent any formal cognitive or neuroimaging assessment and
8 there was no control group, which has prompted the INTERCEPT trial ^[24, 25].

11
12 We know that more proximal zones are associated with higher stroke rates. What
13 remains unknown is whether CO₂ flushing is enough to prevent neurological brain
14 injury in these riskier zones, or whether solid embolisation from the manipulation of
15 instruments close to atherosclerotic aortic valves and carotid vessels in more proximal
16 zones is the main risk factor for neurological injury. This information will be used to aid
17 refinement of the inclusion/exclusion criteria for the full-scale RCT and will be used to
18 refine the sample-size calculation for use in the final trial.

21
22 We carried out a pilot study of 20 TEVAR patients who underwent CO₂ flushing and
23 used TCD to detect cerebral embolization rates and DW-MRI to assess for SCI. Intra-
24 operatively, there were no MES detected at stent graft deployment. The SCI rate was
25 25% and there was no clinical stroke in any of the patients (in comparison to 81% SCI
26 and 13% stroke rate in similar patients undergoing TEVAR with standard saline
27 flushing)^[6]. Although encouraging, we recognize the need for level 1 evidence in the
28 form of a robust randomised controlled trial to answer the question 'is there a
29 neuroprotective benefit against SCI and POCD with the use of CO₂ flushed aortic
30 stent-grafts.'

33
34 A review of registries on 28/01/2019 (www.clinicaltrials.gov and www.isrctn.com)
35 found but no similar studies in TEVAR.

37 38 Research influence:

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

51
52 We suspect that both solid and gaseous emboli cause SCI. However, our TCD data
53 continuously demonstrates an overwhelming occurrence of gaseous MES at stent-
54 deployment in TEVAR patients with and without filters, that amounts to a greater
55 contribution of total MES than cumulative solid MES throughout TEVAR. Particulate
56 embolism appeared to numerically correlate with the size of infarct, whilst gaseous
57 emboli numerically correlated with the number of infarcts. These findings warrant our
58 attention into investigating cerebral air embolism (CAE) as a cause of SCI and into
59
60

1
2
3 CO2 flushed stent-grafts as a stand-alone intervention first, particularly as it is cheap,
4 safe and easily implemented.
5
6

7
8 Whilst the different ultrasonic reflective properties of solid and gaseous emboli provide
9 the basis for discriminating between the two, we are aware of skepticism regarding
10 the sensitivity and specificity of TCD embolic differentiation software during an embolic
11 shower.^[26] We have sufficient recorded TCD data to demonstrate that the 'shower' of
12 emboli seen at stent-graft deployment with resultant SCI on DW-MRI with saline
13 flushing is reduced when stent-grafts are flushed with CO2, even when cerebral
14 embolic protection devices are used to capture solid emboli. Reducing the contribution
15 of gaseous embolic events will pave the way for future studies to tackle the residual
16 problem of solid emboli, which will likely require the use of invasive devices, rather
17 than a simple bench-top flushing procedure.
18
19

20
21 The results of our study will be used to gather further information regarding the
22 neurological risks associated with TEVAR and the clinical significance of SCI, where
23 a paucity of literature currently exists. It will also facilitate a more comprehensive and
24 individualised consent process, allowing patients to make more informed decisions.
25 We hope to inform the cardiovascular community about a potential prevention strategy
26 against SCI. Stroke, dementia and neurocognitive decline are enormous burdens on
27 healthcare resources, and any reduction in the incidence of these complications will
28 have a positive effect on health economics, which is vital in the current financial
29 climate.
30
31

32
33 (please see attached documents for images)
34
35

36 **Figure 1.** A) Air bubble release during stent-graft deployment from the proximal end of the stent-graft
37 as it opens in a benchtop experiment carried out by our group
38 B) Air bubble release during stent-graft deployment from the distal end of the stent-graft as it opens in
39 a benchtop experiment carried out by our group.
40
41

42 **Methods & analysis**

43
44 *Type of study:* Multi-centre pilot randomised controlled superiority trial (see Figure 2
45 for flow chart for RCT).

46
47 *Duration:* Estimated duration is 36 months for patient recruitment, from June 2021 to
48 June 2024

49
50 *Number and type of subjects:* All elective patients undergoing TEVAR for aortic
51 pathology.

52
53 *Target total sample size:* 120, (60 in each intervention arm).

54 **Patient and Public involvement**

55
56 None
57
58

59 **Enrolment**

60

1
2
3 Patients suitable for TEVAR as decided upon by a vascular multi-disciplinary meeting
4 will be invited to participate and enrolled after informed written consent. Participants
5 will be recruited by the research team at each site before surgery before their
6 procedure (Box 1).
7

8 9 **Randomisation and Interventions**

10 Participants will be randomly assigned to TEVAR-CO₂ or TEVAR-S group (Box 1)
11 providing they fulfil the entry criteria at screening (Box 2). Participants will be
12 randomized 1:1 via computerized randomization tool via the INTERCEPT Redcap
13 database with stratification by zone of TEVAR. The latter has been chosen because
14 more proximal landing zones in the aortic arch for stent-graft placement are closer to
15 the cerebral vessels and represent a greater risk factor for stroke (Zone 0>1>2>3> 4).
16 Stratification by zones will ensure the groups are similar with respect to this potential
17 confounding factor. Randomisation will occur on the day of surgery. The surgical team
18 delivering the intervention in theatre will be unblinded but are not involved in assessing
19 the outcomes of the study. Participants and outcome assessors will be blinded to
20 group allocation. For sheathed devices, there is a side-port for flushing with saline
21 and/or CO₂. For unsheathed devices (e.g. CTAG, Gore), bench top-models have
22 shown that using a dry seal, can allow sufficient flushing of the stent with CO₂ and
23 saline.
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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% CO₂ 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

- 1
- 2
- 3
- 4
- 5 • 6-week, 6 month and 1 year follow-up:
- 6 a) NIHSS and mRS
- 7 b) 4AT
- 8 c) MOCA and neurocognitive battery as above
- 9 d) SF-36 and EQ5D5L
- 10
- 11
- 12

13 4. *Secondary outcome: Serial **biomarker** blood tests e.g. S100B*

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

31
32
33
34 The samples will be centrifuged and stored at -80°C. Using Enzyme Linked
35 Immunosorbent Assay (ELISA), we will then analyse for S100B amongst a
36 number of other biomarkers at the National Heart and Lung Institute by SC.

37 5. *Secondary outcome: **Risk factor assessment***

38
39 Procedural risk factors such as conventional proximal landing zones for the
40 stent (PLZ)[45], coverage of arch vessel origins and intraoperative factors such
41 as but not limited to, number of digital subtraction angiography (DSA) runs and
42 length of time of hypotension, stent type, length of procedure and post stent
43 ballooning will be recorded for multivariate analysis to allow risk factor
44 assessment.
45
46
47

48 **Sample Size:** Observational data indicate that the incidence of SCI from TEVAR is
49 81%^[6]. Based on our CO₂-pilot study that reduced SCI to 25%, a 50% reduction in
50 SCI is possible. Taking a pragmatic and realistic approach to recruitment we aim for
51 an effect size of 40% reduction in incidence of SCI. Considering a 10% MRI dropout
52 rate from our observational study, a total of 76 (38 per group) would be sufficient to
53 detect an effect size. However, given that randomisation will be by zone of TEVAR, of
54 which there are 5, and we expect a 20% MRI drop-out rate, we are aiming to recruit
55 120 cases (60 in each arm). This number has been chosen to ensure 10-12 patients
56 in each of 5 arch landing zones in each of the two intervention groups, to allow us to
57 quantify brain injury by zone between the two interventions in addition to establishing
58 an overall measure of effect between the two interventions.
59
60

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)

Funding statement

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 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.

References

1. Lee, H.C., et al., *Endovascular Repair versus Open Repair for Isolated Descending Thoracic Aortic Aneurysm*. Yonsei Med J, 2015. **56**(4): p. 904-12.
2. Feezor, R.J., et al., *Risk factors for perioperative stroke during thoracic endovascular aortic repairs (TEVAR)*. J Endovasc Ther, 2007. **14**(4): p. 568-73.
3. Delafontaine, J.L., et al., *Outcome Comparison of TEVAR with and without Left Subclavian Artery Revascularization from Analysis of Nationwide Inpatient Sample Database*. Ann Vasc Surg, 2019. **58**: p. 174-179.

4. Chaikof, E.L., et al., *Endovascular repair for diverse pathologies of the thoracic aorta: an initial decade of experience*. J Am Coll Surg, 2009. **208**(5): p. 802-16; discussion 816-8.
5. Ehlert, B.A., et al., *Impact of operative indication and surgical complexity on outcomes after thoracic endovascular aortic repair at National Surgical Quality Improvement Program Centers*. J Vasc Surg, 2011. **54**(6): p. 1629-36.
6. Perera, A.H., et al., *Cerebral embolization, silent cerebral infarction and neurocognitive decline after thoracic endovascular aortic repair*. Br J Surg, 2018. **105**(4): p. 366-378.
7. Fanning, J.P., et al., *Neurological Injury in Intermediate-Risk Transcatheter Aortic Valve Implantation*. J Am Heart Assoc, 2016. **5**(11).
8. Sacco, R.L., et al., *An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association*. Stroke, 2013. **44**(7): p. 2064-89.
9. Lansky, A.J., et al., *Proposed Standardized Neurological Endpoints for Cardiovascular Clinical Trials: An Academic Research Consortium Initiative*. J Am Coll Cardiol, 2017. **69**(6): p. 679-691.
10. Gutsche, J.T., et al., *Risk factors for perioperative stroke after thoracic endovascular aortic repair*. Ann Thorac Surg, 2007. **84**(4): p. 1195-200; discussion 1200.
11. Kobayashi, S., et al., *Subcortical silent brain infarction as a risk factor for clinical stroke*. Stroke, 1997. **28**(10): p. 1932-9.
12. Vermeer, S.E., et al., *Silent brain infarcts and the risk of dementia and cognitive decline*. N Engl J Med, 2003. **348**(13): p. 1215-22.
13. Kahlert, P., et al., *Silent cerebral ischemia after thoracic endovascular aortic repair: a neuroimaging study*. Ann Thorac Surg, 2014. **98**(1): p. 53-8.
14. Bismuth, J., et al., *Transcranial Doppler findings during thoracic endovascular aortic repair*. J Vasc Surg, 2011. **54**(2): p. 364-9.
15. Grover, G., et al., *Cerebral embolic protection in thoracic endovascular aortic repair*. J Vasc Surg, 2018. **68**(6): p. 1656-1666.
16. Inci, K., et al., *Air bubbles are released by thoracic endograft deployment: An in vitro experimental study*. SAGE Open Med, 2016. **4**: p. 2050312116682130.
17. Rohlfes, F., et al., *Air Embolism During TEVAR: Carbon Dioxide Flushing Decreases the Amount of Gas Released from Thoracic Stent-Grafts During Deployment*. J Endovasc Ther, 2017. **24**(1): p. 84-88.
18. Pappano, A.J. and W.G. Wier, *Cardiovascular physiology*. 2019.
19. Mitchell, S. and D. Gorman, *The pathophysiology of cerebral arterial gas embolism*. J Extra Corpor Technol, 2002. **34**(1): p. 18-23.
20. Borger, M.A., et al., *Neuropsychologic impairment after coronary bypass surgery: effect of gaseous microemboli during perfusionist interventions*. J Thorac Cardiovasc Surg, 2001. **121**(4): p. 743-9.
21. Martens, S., et al., *Carbon dioxide field flooding reduces neurologic impairment after open heart surgery*. Ann Thorac Surg, 2008. **85**(2): p. 543-7.
22. Svenarud, P., M. Persson, and J. van der Linden, *Effect of CO2 insufflation on the number and behavior of air microemboli in open-heart surgery: a randomized clinical trial*. Circulation, 2004. **109**(9): p. 1127-32.
23. Chaudhuri, K., et al., *Carbon dioxide insufflation in open-chamber cardiac surgery: a double-blind, randomized clinical trial of neurocognitive effects*. J Thorac Cardiovasc Surg, 2012. **144**(3): p. 646-653.e1.
24. Kölbel, T., et al., *Carbon Dioxide Flushing Technique to Prevent Cerebral Arterial Air Embolism and Stroke During TEVAR*. J Endovasc Ther, 2016. **23**(2): p. 393-5.

- 1
- 2
- 3
- 4 25. Lyons, O. and J. Schmidli, *Preventing Stroke Due to Intervention in the Aortic Arch*. European Journal of Vascular and Endovascular Surgery, 2020. **61**.
- 5
- 6 26. Markus, H.S. and M. Punter, *Can transcranial Doppler discriminate between solid and gaseous microemboli? Assessment of a dual-frequency transducer system*. Stroke, 2005. **36**(8): p. 1731-4.
- 7
- 8
- 9 27. Fazekas, F., et al., *MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging*. AJR Am J Roentgenol, 1987. **149**(2): p. 351-6.
- 10
- 11 28. *Basic identification criteria of Doppler microembolic signals. Consensus Committee of the Ninth International Cerebral Hemodynamic Symposium*. Stroke, 1995. **26**(6): p. 1123.
- 12
- 13
- 14
- 15 29. National Institute of Neurological, D. and Stroke, *NIH stroke scale*. 2011: [Bethesda, Md.?] : National Institute of Neurological Disorders and Stroke, Dept. of Health and Human Services, USA, [2011?].
- 16
- 17 30. Rankin, J., *Cerebral vascular accidents in patients over the age of 60. II. Prognosis*. Scott Med J, 1957. **2**(5): p. 200-15.
- 18
- 19 31. Bonita, R. and R. Beaglehole. *Modification of Rankin Scale: Recovery of motor function after stroke*. 1988.
- 20
- 21 32. van Swieten, J.C., et al., *Interobserver agreement for the assessment of handicap in stroke patients*. Stroke, 1988. **19**(5): p. 604-7.
- 22
- 23 33. Saller, T., A.M.J. MacLulich, and R. Pernecky, *The 4AT - an instrument for delirium detection for older patients in the post-anaesthesia care unit*. Anaesthesia, 2020. **75**(3): p. 410.
- 24
- 25 34. Nasreddine, Z.S., et al., *The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment*. J Am Geriatr Soc, 2005. **53**(4): p. 695-9.
- 26
- 27 35. Perera, A.H., et al., *Robotic Arch Catheter Placement Reduces Cerebral Embolization During Thoracic Endovascular Aortic Repair (TEVAR)*. Eur J Vasc Endovasc Surg, 2017. **53**(3): p. 362-369.
- 28
- 29 36. Bean, J., *Rey Auditory Verbal Learning Test, Rey AVLT*, in *Encyclopedia of Clinical Neuropsychology*, J.S. Kreutzer, J. DeLuca, and B. Caplan, Editors. 2011, Springer New York: New York, NY. p. 2174-2175.
- 30
- 31 37. Patterson, J., *F-A-S Test*, in *Encyclopedia of Clinical Neuropsychology*, J.S. Kreutzer, J. DeLuca, and B. Caplan, Editors. 2011, Springer New York: New York, NY. p. 1024-1026.
- 32
- 33 38. Merker, B. and K. Podell, *Grooved Pegboard Test*, in *Encyclopedia of Clinical Neuropsychology*, J.S. Kreutzer, J. DeLuca, and B. Caplan, Editors. 2011, Springer New York: New York, NY. p. 1176-1178.
- 34
- 35 39. Llinàs-Reglà, J., et al., *The Trail Making Test. Assessment*, 2017. **24**(2): p. 183-196.
- 36
- 37 40. Zigmond, A.S. and R.P. Snaith, *The hospital anxiety and depression scale*. Acta Psychiatr Scand, 1983. **67**(6): p. 361-70.
- 38
- 39 41. Venegas, J. and E. Clark, *National Adult Reading Test*, in *Encyclopedia of Clinical Neuropsychology*, J.S. Kreutzer, J. DeLuca, and B. Caplan, Editors. 2011, Springer New York: New York, NY. p. 1705-1705.
- 40
- 41 42. Ware, J.E., R.H. Brook, and A. Davies-Avery, *Conceptualization and measurement of health for adults in the health insurance study: model of health and methodology*. 1980.
- 42
- 43 43. *EuroQol--a new facility for the measurement of health-related quality of life*. Health Policy, 1990. **16**(3): p. 199-208.
- 44
- 45 44. Khan, T.Z., et al., *Oxidised LDL and Anti-Oxidised LDL Antibodies Are Reduced by Lipoprotein Apheresis in a Randomised Controlled Trial on Patients with Refractory Angina and Elevated Lipoprotein(a)*. Antioxidants (Basel), 2021. **10**(1).
- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

- 1
2
3 45. Ishimaru, S., *Endografting of the aortic arch*. J Endovasc Ther, 2004. **11 Suppl 2**: p.
4 li62-71.
5
6 46. *Accelerated proteomics together*. 28/07/20]; Available from:
7 <https://www.olink.com/products/inflammation>). .
8 47. Hartley, A., D. Haskard, and R. Khamis, *Markers of Apoptosis Predict*
9 *Cardiovascular Outcomes and Point to 'Response to Injury' as a Common Pathway*
10 *Leading to Diabetes and Cardiovascular Events*. EBioMedicine, 2018. **28**: p. 19-20.
11 48. Gorla, R., et al., *Systemic inflammatory response syndromes in the era of*
12 *interventional cardiology*. Vascul Pharmacol, 2018.
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 1A



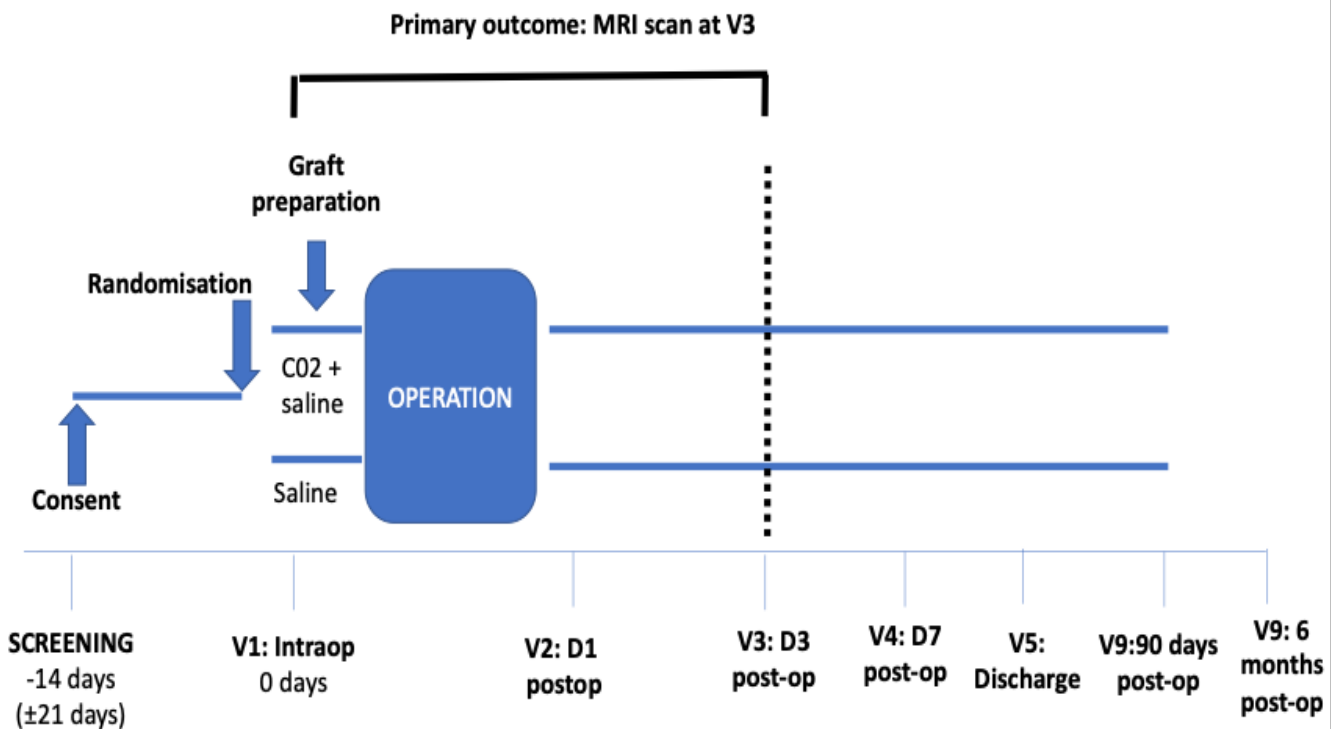
Figure 1B



ew only

Figure 2

INTERCEPT TRIAL STRUCTURE



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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

For peer review only



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 SPIRIT reporting 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

1	Roles and	#5a	Names, affiliations, and roles of protocol contributors	12
2	responsibilities:			
3	contributorship			
4				
5				
6	Roles and	#5b	Name and contact information for the trial sponsor	12
7	responsibilities:			
8	sponsor contact			
9	information			
10				
11				
12				
13	Roles and	#5c	Role of study sponsor and funders, if any, in study	12
14	responsibilities:		design; collection, management, analysis, and	
15	sponsor and funder		interpretation of data; writing of the report; and the	
16			decision to submit the report for publication, including	
17			whether they will have ultimate authority over any of	
18			these activities	
19				
20				
21				
22				
23	Roles and	#5d	Composition, roles, and responsibilities of the	n/a
24	responsibilities:		coordinating centre, steering committee, endpoint	
25	committees		adjudication committee, data management team, and	
26			other individuals or groups overseeing the trial, if	
27			applicable (see Item 21a for data monitoring	
28			committee)	
29				
30				
31				
32				
33	Introduction			
34				
35	Background and	#6a	Description of research question and justification for	3-5
36	rationale		undertaking the trial, including summary of relevant	
37			studies (published and unpublished) examining	
38			benefits and harms for each intervention	
39				
40				
41				
42	Background and	#6b	Explanation for choice of comparators	3-5
43	rationale: choice of			
44	comparators			
45				
46				
47	Objectives	#7	Specific objectives or hypotheses	9
48				
49	Trial design	#8	Description of trial design including type of trial (eg,	8-9
50			parallel group, crossover, factorial, single group),	
51			allocation ratio, and framework (eg, superiority,	
52			equivalence, non-inferiority, exploratory)	
53				
54				
55				

56 **Methods:**
57 **Participants,**

interventions, and outcomes

1				
2				
3				
4	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
5				
6				
7				
8				
9				
10				
11	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
12				
13				
14				
15				
16				
17				
18	Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
19				
20				
21				
22				
23	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
24				
25				
26				
27				
28				
29				
30	Interventions: adherence	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	n/a
31				
32				
33				
34				
35	Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a
36				
37				
38				
39	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
40				
41				
42				
43				
44				
45				
46				
47				
48				
49				
50	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
51				
52				
53				
54				
55				
56				
57	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including	2
58				
59				
60				

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

1
2
3
4
5
6
7
8
9 Data collection plan: [#18b](#) Plans to promote participant retention and complete 9-10
10 retention
11 follow-up, including list of any outcome data to be
12 collected for participants who discontinue or deviate
13 from intervention protocols

14
15 Data management [#19](#) Plans for data entry, coding, security, and storage, 10
16 including any related processes to promote data
17 quality (eg, double data entry; range checks for data
18 values). Reference to where details of data
19 management procedures can be found, if not in the
20 protocol
21
22
23
24

25 Statistics: outcomes [#20a](#) Statistical methods for analysing primary and 9-10
26 secondary outcomes. Reference to where other
27 details of the statistical analysis plan can be found, if
28 not in the protocol
29
30

31
32 Statistics: additional [#20b](#) Methods for any additional analyses (eg, subgroup
33 analyses and adjusted analyses)
34

35
36 Statistics: analysis [#20c](#) Definition of analysis population relating to protocol
37 population and non-adherence (eg, as randomised analysis), and any
38 missing data statistical methods to handle missing data (eg,
39 multiple imputation)
40
41

42 **Methods:**

43 **Monitoring**

44
45
46 Data monitoring: [#21a](#) Composition of data monitoring committee (DMC); 10
47 formal committee summary of its role and reporting structure; statement
48 of whether it is independent from the sponsor and
49 competing interests; and reference to where further
50 details about its charter can be found, if not in the
51 protocol. Alternatively, an explanation of why a DMC
52 is not needed
53
54
55
56
57
58
59
60

1	Data monitoring:	#21b	Description of any interim analyses and stopping	10
2	interim analysis		guidelines, including who will have access to these	
3			interim results and make the final decision to	
4			terminate the trial	
5				
6				
7				
8	Harms	#22	Plans for collecting, assessing, reporting, and	10
9			managing solicited and spontaneously reported	
10			adverse events and other unintended effects of trial	
11			interventions or trial conduct	
12				
13				
14	Auditing	#23	Frequency and procedures for auditing trial conduct, if	10
15			any, and whether the process will be independent	
16			from investigators and the sponsor	
17				
18				
19				
20	Ethics and			
21	dissemination			
22				
23				
24	Research ethics	#24	Plans for seeking research ethics committee /	2
25	approval		institutional review board (REC / IRB) approval	
26				
27				
28	Protocol amendments	#25	Plans for communicating important protocol	2
29			modifications (eg, changes to eligibility criteria,	
30			outcomes, analyses) to relevant parties (eg,	
31			investigators, REC / IRBs, trial participants, trial	
32			registries, journals, regulators)	
33				
34				
35				
36	Consent or assent	#26a	Who will obtain informed consent or assent from	2
37			potential trial participants or authorised surrogates,	
38			and how (see Item 32)	
39				
40				
41	Consent or assent:	#26b	Additional consent provisions for collection and use of	2
42	ancillary studies		participant data and biological specimens in ancillary	
43			studies, if applicable	
44				
45				
46				
47	Confidentiality	#27	How personal information about potential and enrolled	2, 10
48			participants will be collected, shared, and maintained	
49			in order to protect confidentiality before, during, and	
50			after the trial	
51				
52				
53	Declaration of	#28	Financial and other competing interests for principal	10
54	interests		investigators for the overall trial and each study site	
55				
56				
57				
58				
59				
60				

1	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
2				
3				
4				
5				
6	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	2
7	trial care			
8				
9				
10				
11	Dissemination policy:	#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
12	trial results			
13				
14				
15				
16				
17				
18				
19				
20				
21	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of professional writers	11
22	authorship			
23				
24				
25	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2
26	reproducible research			
27				
28				
29	Appendices			
30				
31	Informed consent	#32	Model consent form and other related documentation given to participants and authorised surrogates	See consent v3 document
32	materials			
33				
34				
35				
36				
37	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
38				
39				
40				
41				
42				

None The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist can be completed online using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-067605.R2
Article Type:	Protocol
Date Submitted by the Author:	20-Feb-2023
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

SCHOLARONE™
Manuscripts

1
2
3 **Carbon dioxide flushing versus saline flushing of thoracic aortic stents:**
4 **protocol for a multicentre pilot randomised controlled trial**
5
6

7 **Authors:**

8 Stephen Crockett

9 stephen.crockett@nhs.net

10 Imperial College Healthcare Trust, St Mary's Hospital, Praed Street, London W2
11 1NY, UK
12
13

14 Lydia Hanna

15 lydia.hanna@nhs.net

16 Imperial College Healthcare Trust, St Mary's Hospital, Praed Street, London W2
17 1NY, UK
18
19

20 Abhinav Singh

21 abhinav.singh@nhs.net

22 Imperial College Healthcare Trust, Charing Cross Hospital, Fulham Palace Rd,
23 London W6 8RF, UK
24
25

26 Stephen Gunning

27 stephen.gunning@nhs.net

28 Imperial College Healthcare Trust, Charing Cross Hospital, Fulham Palace Rd,
29 London W6 8RF, UK
30
31

32 Richard Nicholas

33 richard.nicholas3@nhs.net

34 Imperial College Healthcare Trust, Charing Cross Hospital, Fulham Palace Rd,
35 London W6 8RF, UK
36
37

38 Colin Bicknell

39 colin.bicknell@nhs.net

40 Imperial College Healthcare Trust, St Mary's Hospital, Praed Street, London W2
41 1NY, UK
42
43

44 Mohamad Hamady

45 mohamad.hamady@nhs.net

46 Imperial College Healthcare Trust, St Mary's Hospital, Praed Street, London W2
47 1NY, UK
48
49

50 Dennis Gable

51 dennis.gable@bswhealth.org

52 Baylor Scott & White Health, Plano, Texas, USA
53
54

55 Morad Sallam

56 morad.sallam@gstt.nhs.uk

57 Guy's and St Thomas' NHS Foundation Trust, Westminster Bridge Road, London
58 SE1 7EH, UK
59
60

Bijan Modarai

1
2
3 bijan.modarai@kcl.ac.uk

4 Guy's and St Thomas' NHS Foundation Trust, Westminster Bridge Road, London
5 SE1 7EH, UK
6

7
8 Said Abisi

9 said.abisi@gstt.nhs.uk

10 Guy's and St Thomas' NHS Foundation Trust, Westminster Bridge Road, London
11 SE1 7EH, UK
12

13 Oliver Lyons

14 oliver.lyons@cdhb.health.nz

15 Vascular Endovascular & Transplant Surgery, University of Otago, and Canterbury
16 District Health Board, New Zealand
17
18

19 Richard Gibbs

20 richard.gibbs@nhs.net

21 Imperial College Healthcare Trust, St Mary's Hospital, Praed Street, London W2
22 1NY, UK
23
24

25
26 **Correspondence to:**

27
28 Lydia Hanna

29 Imperial College Healthcare Trust, St Mary's Hospital, Praed Street, London W2
30 1NY, UK.

31 lydia.hanna@nhs.net.
32
33

34
35 **Keywords**

36
37 Thoracic aortic endovascular repair; cerebral infarction; stroke; cognitive decline
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 (CO₂) 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 CO₂-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-CO₂ 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

1
2
3 repair (TEVAR) and the clinical significance of silent cerebral infarction, where
4 a paucity of literature exists.

- 5 • A cheap and readily available intervention is being studied.
- 6 • Unprecedented levels of neurocognitive, neuroimaging and follow up data will
7 be collected to determine the clinical impact of cerebral infarction complicating
8 TEVAR.
- 9 • Blinding is incomplete, as the surgeons carrying out the procedure cannot be
10 blinded to stent graft flushing.

11 12 13 14 15 **Introduction**

16
17 There has been a significant increase in the number of thoracic endovascular aortic
18 repairs (TEVARs) performed in the last decade. TEVAR is offered as preventative
19 treatment to prevent rupture and death from aneurysmal aortic disease, aortic
20 dissection and traumatic aortic injury. It has been adopted as the standard method for
21 thoracic aortic repair as the avoidance of thoracotomy and aortic cross-clamping
22 means morbidity is reduced and hospital stay is significantly decreased [1]. Although
23 TEVAR has successfully reduced peri-procedural morbidity and mortality, stroke
24 remains a significant risk. Several studies have identified risk factors contributing to
25 neurological injury [2, 3] and further work is needed to investigate these risk factors to
26 predict more accurately the patients at higher risk of neurological injury.

27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
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.

51
52
53
54
55
56
57
58
59
60
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].

1
2
3
4
5 Through the use of embolic differentiation software, we have deduced that >90% of
6 MES throughout TEVAR are gaseous in nature, with 81% of gaseous MES apparent
7 at stent-graft deployment. Once deployment is complete, TCD monitoring typically
8 detects no further embolic activity. We also found a positive association between
9 number of gaseous MES and number of new DW-MRI BI [15]. This suggests that
10 cerebral air embolization may be a significant cause of SCI in TEVAR and provides us
11 with a basis on which to target preventative strategies.
12
13

14
15 Stent-grafts are manufactured in room air conditions and retain air. According to
16 instructions for use (IFU), saline flushing is recommended to de-air the system.
17 Emerging experimental studies have shown a substantial amount of air release from
18 all commercially available grafts with bubbles ranging from 0.34-0.79ml, despite saline
19 flushing (see Figure 1) [16, 17]. This is a cause for concern given that cerebral arterioles
20 are 40-250µm in diameter[18]. Large bubbles would be expected to cause downstream
21 ischaemia and neuronal injury, while smaller bubbles may incite endothelial damage
22 and activation of inflammatory and clotting cascades that may then cause secondary
23 ischaemia[19]. These small bubbles have been implicated in causing post-operative
24 cognitive delirium (POCD)[20].
25
26

27
28 Carbon dioxide (CO₂) is 1.5 times denser than air and can fill an enclosed space and
29 displace air. It is 25 times more soluble in blood than air and does not lead to bubble
30 formation[21]. CO₂ has been used extensively in cardiac surgery and shown to
31 significantly reduce intracardiac air[22] and POCD[23]. CO₂ can also significantly reduce
32 the average amount of released air from an TEVAR stent in an experimental setting
33 (0.79 vs 0.51 mL, p=0.005)[17], and has been used clinically in a small series of TEVAR
34 patients where the authors describe a 3% clinical stroke rate. However, none of these
35 patients underwent any formal cognitive or neuroimaging assessment and there was
36 no control group, which has prompted the present study [24, 25].
37
38

39
40 We know that more proximal zones are associated with higher stroke rates. What
41 remains unknown is whether CO₂ flushing is enough to prevent neurological brain
42 injury in these riskier zones, or whether solid embolisation from the manipulation of
43 instruments close to atherosclerotic aortic valves and carotid vessels in more proximal
44 zones is the main risk factor for neurological injury. This information will be used to aid
45 refinement of the inclusion/exclusion criteria for the full-scale randomized controlled
46 trial (RCT) and will be used to refine the sample size calculation for use in the trial.
47
48

49
50 We carried out a pilot study of 20 TEVAR patients who underwent CO₂ flushing and
51 used TCD to detect cerebral embolization rates and DW-MRI to assess for SCI. Intra-
52 operatively, there were no MES detected at stent graft deployment. The SCI rate was
53 25% and there was no clinical stroke in any of the patients (in comparison to 81% SCI
54 and 13% stroke rate in patients with saline flushing)[6]. Although encouraging, we
55 recognize the need for level 1 evidence in the form of a robust randomised controlled
56 trial to answer the question 'is there a neuroprotective benefit against SCI and POCD
57 with the use of CO₂ flushed aortic stent-grafts.'
58
59
60

1
2
3
4
5 A review of registries on 28/01/2019 (www.clinicaltrials.gov and www.isrctn.com)
6 found but no similar studies in TEVAR.
7

8 **Research influence**

9
10 We have produced the largest case series to date regarding SCI in TEVAR and
11 continue to highlight the magnitude of the problem by our ongoing study of
12 neuroimaging, TCD, neurological and neurocognitive data on these patients. These
13 data initially led us to believe that solid embolization of particulate atherosclerotic
14 matter dislodged from the thoracic aorta was responsible for SCI. Accordingly, we
15 trialed the use of a cerebral embolic protection device designed to capture
16 particulate matter 'en-route' to the brain in a cohort of 20 patients. This established
17 feasibility and safety, and a 98% capture rate of embolic debris and a reduction in
18 the number of lesions on DW-MRI. However, all patients still had lesions, with the
19 majority concentrated in the posterior circulation territory^[15].
20
21
22

23 We suspect that both solid and gaseous emboli cause SCI. However, our TCD data
24 continuously demonstrates an overwhelming occurrence of gaseous MES at stent-
25 deployment in TEVAR patients with and without filters, that amounts to a greater
26 contribution of total MES than cumulative solid MES throughout TEVAR. Particulate
27 embolism appeared to numerically correlate with the size of infarct, whilst gaseous
28 emboli numerically correlated with the number of infarcts. These findings warrant our
29 attention into investigating cerebral air embolism (CAE) as a cause of SCI and into
30 CO₂-flushed stent-grafts as a stand-alone intervention first, particularly as it is cheap,
31 safe and easily implemented.
32
33
34

35 Whilst the different ultrasonic reflective properties of solid and gaseous emboli provide
36 the basis for discriminating between the two, we are aware of skepticism regarding
37 the sensitivity and specificity of TCD embolic differentiation software during an embolic
38 shower.^[26] We have sufficient recorded TCD data to demonstrate that the 'shower' of
39 emboli seen at stent-graft deployment with resultant SCI on DW-MRI with saline
40 flushing is reduced when stent-grafts are flushed with CO₂, even when cerebral
41 embolic protection devices are used to capture solid emboli. Reducing the contribution
42 of gaseous embolic events will pave the way for future studies to tackle the residual
43 problem of solid emboli, which will likely require the use of invasive devices, rather
44 than a simple bench-top flushing procedure.
45
46
47
48

49 **Objectives**

50 This pilot trial aims to assess the feasibility of a full-scale RCT investigating the
51 neuroprotective benefit against SCI with the use of CO₂-flushed aortic stent-grafts.
52 The results of this research will be used to gather further information regarding the
53 neurological risks associated with TEVAR and the clinical significance of SCI, where
54 a paucity of literature currently exists. It will also facilitate a more comprehensive and
55 individualised consent process, allowing patients to make more informed decisions.
56 We hope to inform the cardiovascular community about a potential prevention strategy
57 against SCI. Stroke, dementia and neurocognitive decline are enormous burdens on
58 healthcare resources, and any reduction in the incidence of these complications will
59
60

1
2
3 have a positive effect on health economics, which is vital in the current financial
4 climate.
5
6
7

8 **Methods and analysis**

10 **Study design**

11 *Type of study:* Multicentre pilot RCT (see Figure 2 for trial flowchart).

12 *Duration:* Estimated duration is 36 months for patient recruitment, from June 2021 to
13 June 2024.

14 *Participants:* All elective patients undergoing TEVAR for aortic pathology.

15 *Target total sample size:* 120 (60 in each intervention arm).
16
17
18

19 **Enrolment**

20 Patients suitable for TEVAR as decided upon by a vascular multi-disciplinary meeting
21 will be invited to participate and enrolled after informed written consent. Participants
22 will be recruited by the research team at each site before surgery before their
23 procedure (Box 1).
24
25

26 **Randomisation and interventions**

27 Participants will be randomly assigned to TEVAR-CO₂ or TEVAR-S group (Box 1)
28 providing they fulfil the entry criteria at screening (Box 2). Participants will be
29 randomized 1:1 via computerized randomization tool via the INTERCEPT Redcap
30 database with stratification by zone of TEVAR. The latter has been chosen because
31 more proximal landing zones in the aortic arch for stent-graft placement are closer to
32 the cerebral vessels and represent a greater risk factor for stroke (Zone 0>1>2>3> 4).
33 Stratification by zones will ensure the groups are similar with respect to this potential
34 confounding factor. Randomisation will occur on the day of surgery. The surgical team
35 delivering the intervention in theatre will be unblinded but are not involved in assessing
36 the outcomes of the study. Participants and outcome assessors will be blinded to
37 group allocation. For sheathed devices, there is a side-port for flushing with saline
38 and/or CO₂. For unsheathed devices (e.g. CTAG, Gore), bench top-models have
39 shown that using a dry seal, can allow sufficient flushing of the stent with CO₂ and
40 saline.
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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% CO₂ 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*

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].

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

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

6-week and 6 month follow-ups:

- 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.

References

1. Lee, H.C., et al., *Endovascular Repair versus Open Repair for Isolated Descending Thoracic Aortic Aneurysm*. Yonsei Med J, 2015. **56**(4): p. 904-12.
2. Feezor, R.J., et al., *Risk factors for perioperative stroke during thoracic endovascular aortic repairs (TEVAR)*. J Endovasc Ther, 2007. **14**(4): p. 568-73.
3. Delafontaine, J.L., et al., *Outcome Comparison of TEVAR with and without Left Subclavian Artery Revascularization from Analysis of Nationwide Inpatient Sample Database*. Ann Vasc Surg, 2019. **58**: p. 174-179.

- 1
- 2
- 3
4. Chaikof, E.L., et al., *Endovascular repair for diverse pathologies of the thoracic aorta: an initial decade of experience*. J Am Coll Surg, 2009. **208**(5): p. 802-16; discussion 816-8.
5. Ehlert, B.A., et al., *Impact of operative indication and surgical complexity on outcomes after thoracic endovascular aortic repair at National Surgical Quality Improvement Program Centers*. J Vasc Surg, 2011. **54**(6): p. 1629-36.
6. Perera, A.H., et al., *Cerebral embolization, silent cerebral infarction and neurocognitive decline after thoracic endovascular aortic repair*. Br J Surg, 2018. **105**(4): p. 366-378.
7. Fanning, J.P., et al., *Neurological Injury in Intermediate-Risk Transcatheter Aortic Valve Implantation*. J Am Heart Assoc, 2016. **5**(11).
8. Sacco, R.L., et al., *An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association*. Stroke, 2013. **44**(7): p. 2064-89.
9. Lansky, A.J., et al., *Proposed Standardized Neurological Endpoints for Cardiovascular Clinical Trials: An Academic Research Consortium Initiative*. J Am Coll Cardiol, 2017. **69**(6): p. 679-691.
10. Gutsche, J.T., et al., *Risk factors for perioperative stroke after thoracic endovascular aortic repair*. Ann Thorac Surg, 2007. **84**(4): p. 1195-200; discussion 1200.
11. Kobayashi, S., et al., *Subcortical silent brain infarction as a risk factor for clinical stroke*. Stroke, 1997. **28**(10): p. 1932-9.
12. Vermeer, S.E., et al., *Silent brain infarcts and the risk of dementia and cognitive decline*. N Engl J Med, 2003. **348**(13): p. 1215-22.
13. Kahlert, P., et al., *Silent cerebral ischemia after thoracic endovascular aortic repair: a neuroimaging study*. Ann Thorac Surg, 2014. **98**(1): p. 53-8.
14. Bismuth, J., et al., *Transcranial Doppler findings during thoracic endovascular aortic repair*. J Vasc Surg, 2011. **54**(2): p. 364-9.
15. Grover, G., et al., *Cerebral embolic protection in thoracic endovascular aortic repair*. J Vasc Surg, 2018. **68**(6): p. 1656-1666.
16. Inci, K., et al., *Air bubbles are released by thoracic endograft deployment: An in vitro experimental study*. SAGE Open Med, 2016. **4**: p. 2050312116682130.
17. Rohlfes, F., et al., *Air Embolism During TEVAR: Carbon Dioxide Flushing Decreases the Amount of Gas Released from Thoracic Stent-Grafts During Deployment*. J Endovasc Ther, 2017. **24**(1): p. 84-88.
18. Pappano, A.J. and W.G. Wier, *Cardiovascular physiology*. 2019.
19. Mitchell, S. and D. Gorman, *The pathophysiology of cerebral arterial gas embolism*. J Extra Corpor Technol, 2002. **34**(1): p. 18-23.
20. Borger, M.A., et al., *Neuropsychologic impairment after coronary bypass surgery: effect of gaseous microemboli during perfusionist interventions*. J Thorac Cardiovasc Surg, 2001. **121**(4): p. 743-9.
21. Martens, S., et al., *Carbon dioxide field flooding reduces neurologic impairment after open heart surgery*. Ann Thorac Surg, 2008. **85**(2): p. 543-7.
22. Svenarud, P., M. Persson, and J. van der Linden, *Effect of CO2 insufflation on the number and behavior of air microemboli in open-heart surgery: a randomized clinical trial*. Circulation, 2004. **109**(9): p. 1127-32.
23. Chaudhuri, K., et al., *Carbon dioxide insufflation in open-chamber cardiac surgery: a double-blind, randomized clinical trial of neurocognitive effects*. J Thorac Cardiovasc Surg, 2012. **144**(3): p. 646-653.e1.
24. Kölbel, T., et al., *Carbon Dioxide Flushing Technique to Prevent Cerebral Arterial Air Embolism and Stroke During TEVAR*. J Endovasc Ther, 2016. **23**(2): p. 393-5.

- 1
- 2
- 3
- 4 25. Lyons, O. and J. Schmidli, *Preventing Stroke Due to Intervention in the Aortic Arch*. European Journal of Vascular and Endovascular Surgery, 2020. **61**.
- 5
- 6 26. Markus, H.S. and M. Punter, *Can transcranial Doppler discriminate between solid and gaseous microemboli? Assessment of a dual-frequency transducer system*. Stroke, 2005. **36**(8): p. 1731-4.
- 7
- 8
- 9 27. Fazekas, F., et al., *MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging*. AJR Am J Roentgenol, 1987. **149**(2): p. 351-6.
- 10
- 11 28. *Basic identification criteria of Doppler microembolic signals. Consensus Committee of the Ninth International Cerebral Hemodynamic Symposium*. Stroke, 1995. **26**(6): p. 1123.
- 12
- 13
- 14
- 15 29. National Institute of Neurological, D. and Stroke, *NIH stroke scale*. 2011: [Bethesda, Md.?] : National Institute of Neurological Disorders and Stroke, Dept. of Health and Human Services, USA, [2011?].
- 16
- 17
- 18 30. Rankin, J., *Cerebral vascular accidents in patients over the age of 60. II. Prognosis*. Scott Med J, 1957. **2**(5): p. 200-15.
- 19
- 20 31. Bonita, R. and R. Beaglehole. *Modification of Rankin Scale: Recovery of motor function after stroke*. 1988.
- 21
- 22 32. van Swieten, J.C., et al., *Interobserver agreement for the assessment of handicap in stroke patients*. Stroke, 1988. **19**(5): p. 604-7.
- 23
- 24 33. Saller, T., A.M.J. MacLulich, and R. Pernecky, *The 4AT - an instrument for delirium detection for older patients in the post-anaesthesia care unit*. Anaesthesia, 2020. **75**(3): p. 410.
- 25
- 26 34. Nasreddine, Z.S., et al., *The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment*. J Am Geriatr Soc, 2005. **53**(4): p. 695-9.
- 27
- 28 35. Perera, A.H., et al., *Robotic Arch Catheter Placement Reduces Cerebral Embolization During Thoracic Endovascular Aortic Repair (TEVAR)*. Eur J Vasc Endovasc Surg, 2017. **53**(3): p. 362-369.
- 29
- 30 36. Bean, J., *Rey Auditory Verbal Learning Test, Rey AVLT*, in *Encyclopedia of Clinical Neuropsychology*, J.S. Kreutzer, J. DeLuca, and B. Caplan, Editors. 2011, Springer New York: New York, NY. p. 2174-2175.
- 31
- 32 37. Patterson, J., *F-A-S Test*, in *Encyclopedia of Clinical Neuropsychology*, J.S. Kreutzer, J. DeLuca, and B. Caplan, Editors. 2011, Springer New York: New York, NY. p. 1024-1026.
- 33
- 34 38. Merker, B. and K. Podell, *Grooved Pegboard Test*, in *Encyclopedia of Clinical Neuropsychology*, J.S. Kreutzer, J. DeLuca, and B. Caplan, Editors. 2011, Springer New York: New York, NY. p. 1176-1178.
- 35
- 36 39. Llinàs-Reglà, J., et al., *The Trail Making Test. Assessment*, 2017. **24**(2): p. 183-196.
- 37
- 38 40. Zigmond, A.S. and R.P. Snaith, *The hospital anxiety and depression scale*. Acta Psychiatr Scand, 1983. **67**(6): p. 361-70.
- 39
- 40 41. Venegas, J. and E. Clark, *National Adult Reading Test*, in *Encyclopedia of Clinical Neuropsychology*, J.S. Kreutzer, J. DeLuca, and B. Caplan, Editors. 2011, Springer New York: New York, NY. p. 1705-1705.
- 41
- 42 42. Ware, J.E., R.H. Brook, and A. Davies-Avery, *Conceptualization and measurement of health for adults in the health insurance study: model of health and methodology*. 1980.
- 43
- 44 43. *EuroQol--a new facility for the measurement of health-related quality of life*. Health Policy, 1990. **16**(3): p. 199-208.
- 45
- 46 44. Khan, T.Z., et al., *Oxidised LDL and Anti-Oxidised LDL Antibodies Are Reduced by Lipoprotein Apheresis in a Randomised Controlled Trial on Patients with Refractory Angina and Elevated Lipoprotein(a)*. Antioxidants (Basel), 2021. **10**(1).
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

- 1
2
3 45. Ishimaru, S., *Endografting of the aortic arch*. J Endovasc Ther, 2004. **11 Suppl 2**: p.
4 li62-71.
5
6 46. *Accelerated proteomics together*. 28/07/20]; Available from:
7 <https://www.olink.com/products/inflammation>). .
8
9 47. Hartley, A., D. Haskard, and R. Khamis, *Markers of Apoptosis Predict*
10 *Cardiovascular Outcomes and Point to 'Response to Injury' as a Common Pathway*
11 *Leading to Diabetes and Cardiovascular Events*. EBioMedicine, 2018. **28**: p. 19-20.
12
13 48. Gorla, R., et al., *Systemic inflammatory response syndromes in the era of*
14 *interventional cardiology*. Vascul Pharmacol, 2018.
15
16
17

FIGURE LEGENDS

18
19
20 **Figure 1.** (A) Air bubble release during stent-graft deployment from the proximal end of the stent-graft
21 as it opens in a benchtop experiment carried out by our group; (B) Air bubble release during stent-
22 graft deployment from the distal end of the stent-graft as it opens in a benchtop experiment carried
23 out by our group.
24

25
26 **Figure 2.** Patient flowchart for the pilot trial
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 1A



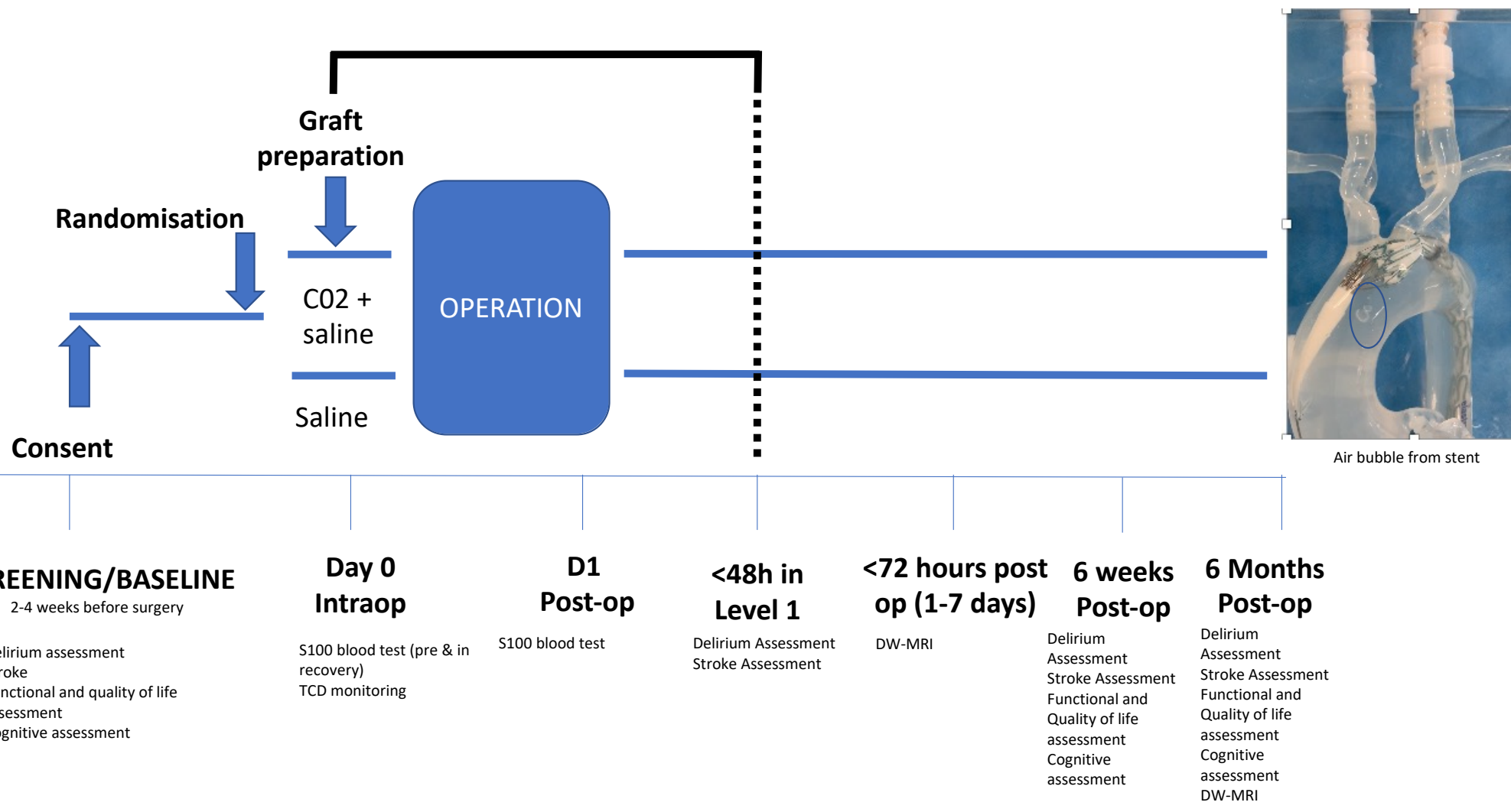
Figure 1B



ew only

INTERvention with Cerebral Embolic Protection in TEVAR

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47



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

For peer review only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 SPIRIT reporting 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

1	Roles and	#5a	Names, affiliations, and roles of protocol contributors	12
2	responsibilities:			
3	contributorship			
4				
5				
6	Roles and	#5b	Name and contact information for the trial sponsor	12
7	responsibilities:			
8	sponsor contact			
9	information			
10				
11				
12				
13	Roles and	#5c	Role of study sponsor and funders, if any, in study	12
14	responsibilities:		design; collection, management, analysis, and	
15	sponsor and funder		interpretation of data; writing of the report; and the	
16			decision to submit the report for publication, including	
17			whether they will have ultimate authority over any of	
18			these activities	
19				
20				
21				
22				
23	Roles and	#5d	Composition, roles, and responsibilities of the	n/a
24	responsibilities:		coordinating centre, steering committee, endpoint	
25	committees		adjudication committee, data management team, and	
26			other individuals or groups overseeing the trial, if	
27			applicable (see Item 21a for data monitoring	
28			committee)	
29				
30				
31				
32				
33	Introduction			
34				
35	Background and	#6a	Description of research question and justification for	3-5
36	rationale		undertaking the trial, including summary of relevant	
37			studies (published and unpublished) examining	
38			benefits and harms for each intervention	
39				
40				
41				
42	Background and	#6b	Explanation for choice of comparators	3-5
43	rationale: choice of			
44	comparators			
45				
46				
47	Objectives	#7	Specific objectives or hypotheses	9
48				
49	Trial design	#8	Description of trial design including type of trial (eg,	8-9
50			parallel group, crossover, factorial, single group),	
51			allocation ratio, and framework (eg, superiority,	
52			equivalence, non-inferiority, exploratory)	
53				
54				
55				

**Methods:
Participants,**

interventions, and outcomes

1			
2			
3			
4	Study setting	#9	Description of study settings (eg, community clinic, 7-9 academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
5			
6			
7			
8			
9			
10			
11	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If 8 applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
12			
13			
14			
15			
16			
17			
18	Interventions: description	#11a	Interventions for each group with sufficient detail to 8 allow replication, including how and when they will be administered
19			
20			
21			
22			
23	Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated n/a interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)
24			
25			
26			
27			
28			
29			
30	Interventions: adherence	#11c	Strategies to improve adherence to intervention n/a protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)
31			
32			
33			
34			
35	Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are n/a permitted or prohibited during the trial
36			
37			
38			
39	Outcomes	#12	Primary, secondary, and other outcomes, including 9 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
40			
41			
42			
43			
44			
45			
46			
47			
48			
49			
50	Participant timeline	#13	Time schedule of enrolment, interventions (including 9 any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
51			
52			
53			
54			
55			
56			
57	Sample size	#14	Estimated number of participants needed to achieve 2 study objectives and how it was determined, including
58			
59			
60			

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

1
2
3
4
5
6
7
8
9 Data collection plan: [#18b](#) Plans to promote participant retention and complete 9-10
10 retention
11 follow-up, including list of any outcome data to be
12 collected for participants who discontinue or deviate
13 from intervention protocols

14
15 Data management [#19](#) Plans for data entry, coding, security, and storage, 10
16 including any related processes to promote data
17 quality (eg, double data entry; range checks for data
18 values). Reference to where details of data
19 management procedures can be found, if not in the
20 protocol
21
22
23
24

25 Statistics: outcomes [#20a](#) Statistical methods for analysing primary and 9-10
26 secondary outcomes. Reference to where other
27 details of the statistical analysis plan can be found, if
28 not in the protocol
29
30

31
32 Statistics: additional [#20b](#) Methods for any additional analyses (eg, subgroup
33 analyses and adjusted analyses)
34

35
36 Statistics: analysis [#20c](#) Definition of analysis population relating to protocol
37 population and non-adherence (eg, as randomised analysis), and any
38 missing data statistical methods to handle missing data (eg,
39 multiple imputation)
40
41

42 **Methods:**

43 **Monitoring**

44
45
46 Data monitoring: [#21a](#) Composition of data monitoring committee (DMC); 10
47 formal committee summary of its role and reporting structure; statement
48 of whether it is independent from the sponsor and
49 competing interests; and reference to where further
50 details about its charter can be found, if not in the
51 protocol. Alternatively, an explanation of why a DMC
52 is not needed
53
54
55
56
57
58
59
60

1	Data monitoring:	#21b	Description of any interim analyses and stopping	10
2	interim analysis		guidelines, including who will have access to these	
3			interim results and make the final decision to	
4			terminate the trial	
5				
6				
7				
8	Harms	#22	Plans for collecting, assessing, reporting, and	10
9			managing solicited and spontaneously reported	
10			adverse events and other unintended effects of trial	
11			interventions or trial conduct	
12				
13				
14	Auditing	#23	Frequency and procedures for auditing trial conduct, if	10
15			any, and whether the process will be independent	
16			from investigators and the sponsor	
17				
18				
19				
20	Ethics and			
21	dissemination			
22				
23				
24	Research ethics	#24	Plans for seeking research ethics committee /	2
25	approval		institutional review board (REC / IRB) approval	
26				
27				
28	Protocol amendments	#25	Plans for communicating important protocol	2
29			modifications (eg, changes to eligibility criteria,	
30			outcomes, analyses) to relevant parties (eg,	
31			investigators, REC / IRBs, trial participants, trial	
32			registries, journals, regulators)	
33				
34				
35				
36	Consent or assent	#26a	Who will obtain informed consent or assent from	2
37			potential trial participants or authorised surrogates,	
38			and how (see Item 32)	
39				
40				
41	Consent or assent:	#26b	Additional consent provisions for collection and use of	2
42	ancillary studies		participant data and biological specimens in ancillary	
43			studies, if applicable	
44				
45				
46				
47	Confidentiality	#27	How personal information about potential and enrolled	2, 10
48			participants will be collected, shared, and maintained	
49			in order to protect confidentiality before, during, and	
50			after the trial	
51				
52				
53	Declaration of	#28	Financial and other competing interests for principal	10
54	interests		investigators for the overall trial and each study site	
55				
56				
57				
58				
59				
60				

1	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
2				
3				
4				
5				
6	Ancillary and post	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	2
7	trial care			
8				
9				
10				
11	Dissemination policy:	#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
12	trial results			
13				
14				
15				
16				
17				
18				
19				
20				
21	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of professional writers	11
22	authorship			
23				
24				
25	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	2
26	reproducible research			
27				
28				
29	Appendices			
30				
31	Informed consent	#32	Model consent form and other related documentation given to participants and authorised surrogates	See consent v3 document
32	materials			
33				
34				
35				
36				
37	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
38				
39				
40				
41				
42				
43				

None The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist can be completed online using <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)



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.