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Title: Study protocol for COvid-19 Vascular sERvice (COVER) study: The impact of the COVID-19 pandemic on the provision, practice and outcomes of vascular surgery

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ABSTRACT

Background: The novel Coronavirus Disease 2019 (COVID-19) pandemic is having a profound impact on global healthcare. Shortages in staff, operating theatre space and intensive care beds has led to a significant reduction in the provision of surgical care. Even vascular surgery, often insulated from resource scarcity due to its status as an urgent specialty, has limited capacity due to the pandemic. Furthermore, many vascular surgical patients are elderly with multiple comorbidities putting them at increased risk of COVID-19 and its complications. There is an urgent need to investigate the impact on patients presenting to vascular surgeons during the COVID-19 pandemic.

Methods and Analysis: The COvid-19 Vascular sERvice (COVER) study has been designed to investigate the worldwide impact of the COVID-19 pandemic on vascular surgery, at both service provision and individual patient level. COVER is running as a collaborative study through the Vascular and Endovascular Research Network (VERN) with the support of numerous national (Vascular Society of Great Britain and Ireland, British Society of Endovascular Therapy, British Society of Interventional Radiology, Rouleaux Club) and an evolving number of international organisations (Vascupedia, SingVasc, Audible Bleeding (USA), Australian and New Zealand Vascular Trials Network (ANZVTN)). The study has 3 'Tiers': Tier 1 is a survey of vascular surgeons to capture longitudinal changes to the provision of vascular services within their hospital; Tier 2 captures data on vascular and endovascular procedures performed during the pandemic; and Tier 3 will capture any deviations to patient management strategies from pre-pandemic best practice. Data submission and collection will be electronic using online survey tools (Tier 1: SurveyMonkey® for service provision data) and encrypted data capture forms (Tiers 2 and 3: REDCap® for patient level data). Tier 1 data will undergo real-time serial analysis to determine longitudinal changes in practice, with country-specific analyses also performed. The analysis of Tier 2 and Tier 3 data will occur on completion of the study as per the pre-specified statistical analysis plan.

Ethical Approval: Ethical approval from the UK Health Research Authority has been obtained for Tiers 2 and 3 (20/NW/0196 Liverpool Central). Participating centres in the UK will be required to seek local research and development approval. Non-UK centres will need to obtain a research

ethics committee or institutional review board approvals in accordance with national and/or local requirements.

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INTRODUCTION:

The novel coronavirus disease 2019 (COVID-19) pandemic is having an unprecedented effect on the provision of healthcare services worldwide. The delivery of surgical care to patients during this time is suffering as resources dwindle and hospital services are overwhelmed (1, 2). It is essential to document the effect of this pandemic on the provision of vascular surgical services and the outcomes for vascular patients to guide future guidelines and provide foresight for potential problems beyond the pandemic.

Vascular patients are, for the majority, considered high risk for respiratory compromise and subsequent mortality if they contract COVID-19 (3, 4) They are often frail, elderly, comorbid, and have less respiratory and physiological reserve than many others who contract the SARS-CoV2 virus (5). A significant proportion of vascular surgical practice involves performing prophylactic operations to reduce the risk of a future cardiovascular event, for example carotid endarterectomy to prevent stroke or abdominal aortic aneurysm repair to prevent rupture. In addition, urgent or emergency surgical intervention to prevent the loss of limb or life, often through an endovascular and/or open revascularisation procedure, are commonplace.

Given the complex nature of vascular operations and the equally complex and co-morbid patient population, the COVID-19 pandemic presents a particularly challenging situation for the vascular surgeon. There is a delicate balance between the risk of a patient contracting or surviving COVID-19, the availability of critical care and anaesthetic support needed to perform high-risk vascular interventions, and the risk of limb loss, other significant morbidity or mortality for the patient from their presenting condition if treatment is unduly delayed.

A major curtailment of vascular practice has already occurred, with many vascular institutions postponing all but the most urgent surgery, choosing and endovascular surgical option where feasible, delaying routine clinic appointments, and using telephone consultations much more frequently(6). Given the unparalleled nature of the situation, there is an urgent need to quantify the impact of COVID-19 on the provision of vascular surgical services, the adjustments made to vascular practice, and the consequence to patient care.

The COvid-19 Vascular sERvice (COVER) Study is a three-tiered study designed to capture global data on vascular practice(s) during the pandemic including how practice evolves over time, the effect on outcomes for patients presenting with, and/or receiving treatment for, vascular surgical conditions during the pandemic and in the subsequent months of global recovery.

METHODS:

Overview of COVER

COVER will be run as a worldwide collaborative research project. It will be led by the UK-based Vascular and Endovascular Research Network (VERN). VERN is an established vascular trainee research collaborative, which has previously designed and delivered several projects across the UK and internationally(7, 8). The project is formally supported by the Vascular Society of Great Britain and Ireland (VSGBI), the British Society for Endovascular Therapy, the Rouleaux Club (the UK body representing Vascular Surgery Trainees), the British Society of Interventional Radiology (BSIR) and BSIR trainees (BSIRT). A number of international collaborators are also working with VERN (Vascupedia, SingVasc, Australian and New Zealand Vascular Trials Network (ANZVTN), Audible Bleeding (USA)) to deliver this globally.

The overall study objective is to understand and evaluate the impact of the COVID-19 pandemic on global vascular practice and on outcomes for patients presenting with vascular problems or receiving treatment for vascular conditions. The study has 3 'Tiers': Tier 1 is a survey of vascular surgeons to capture longitudinal changes to the provision of vascular services within their hospital; Tier 2 captures data on vascular and endovascular procedures performed during the pandemic; and Tier 3 will capture any deviations to patient management strategies from pre-pandemic best practice.

Centres and individuals will be invited to participate in the COVER study which will be advertised via VERN social media channels as well as via regional VERN representatives (doctors, nurses and other healthcare professionals) and through our collaborative networks mailing lists. Engagement with each tier of the project by each collaborator is anticipated and outlined below.

Centre eligibility

All hospitals and networks which provide cover for elective and emergency vascular patients.

Tier 1 - Changes to unit-level clinical processes

Primary objective

To objectively capture the changes made to the structure and delivery of vascular surgery at unit level throughout the COVID-19 pandemic and compare it to the guidance provided by national and

157 international societies (e.g. VSGBI, the Society for Vascular Surgery, the European Society for Vascular
158 Surgery or the Society of Vascular surgery (SVS,USA)).

159 **Methods**

160 The Tier 1 "service evaluation study" will be circulated to all interested centres and data collected via an
161 online survey platform (SurveyMonkey®). This will be conducted upon each centre registering to
162 participate in the overall study bundle. This survey will be repeated at regular intervals to document
163 ongoing changes to unit practice in response to changing circumstances. The intervals between the
164 survey repeats will depend upon the progress of the pandemic. Collaborators will be updated regularly
165 regarding survey outcomes. Responses will reflect unit practice as a whole and should therefore be a
166 unified unit level response approved by the centre lead.

167 **Outcomes**

168 Primary outcome:
169 To document changes to structure and processes within vascular service, including:

170 - Operations/interventions offered/not offered
171 - Thresholds for offering admission/intervention
172 - Seniority and/or number of specialists performing caseload
173 - Management of screening / surveillance programmes (AAA, post-EVAR, bypass graft
174 surveillance, stent surveillance)
175 - Imaging availability
176 - Interventional radiology support and availability
177 - Conduct of multi-disciplinary team meetings
178 - Changes to trainee (resident/registrar) and consultant/attending rotas
179 - Outpatient clinic availability and format
180 - Use of vascular team members to cross-cover other specialties or clinical areas
181 - The availability of personal protective equipment (PPE)

182

183 This information will be fed back to the relevant bodies (VSGBI, ESVS, SVS etc.) to allow real-time
184 feedback on practicalities of updated guidelines. The information will also be circulated via social media.
185

Tier 2 – Vascular and Endovascular procedural data capture

Primary objective

This tier of the project is aimed at capturing data on all vascular and endovascular interventions being undertaken throughout the COVID-19 pandemic. It is anticipated that the type and nature of vascular procedures performed will change due to pressures on the wider healthcare service, with rationing of resources, operating theatre and bed availability (including critical care), and anaesthetic support.

Methods

This will be undertaken for a 3-month period in the first instance. This time period is subject to change depending on how the pandemic progresses.

Patient enrolment

Patients will be identified prospectively at the time of surgery. To ensure comprehensive data capture, patients may also be identified retrospectively following an emergency procedure for example. All patients receiving a vascular procedure are eligible for enrolment, including COVID-19 positive (+ve), COVID-19 suspected and COVID-19 negative (-ve).

Outcomes

Primary outcome:

To document all vascular surgery and interventional procedures performed throughout the COVID-19 pandemic across participating vascular centres.

Specifically:

- Types of procedure performed
- Time taken from presentation to intervention
- Mode of referral (primary vs. secondary care)
- Site of surgery: hub or spoke hospital
- Imaging modalities used and timings
- UK National Confidential Enquiry into Patient Outcome and Death (NCEPOD) classification
- Operative technique(s) and device(s) used
- Mode(s) of anaesthesia

- Time to discharge
- Whether suspected or confirmed COVID-19 +ve at time of surgery, COVID-19 +ve after surgery, or COVID-19 -ve
- Documentation of changes to usual practice (type of procedure, type of anaesthetic, post-procedural destination)

Secondary outcomes:

Outcomes following intervention. These will be reviewed at 30 days, 6 and 12 months following intervention.

- Re-admission
- Re-intervention
- All-cause mortality
- Disease-specific mortality
- Morbidity
- If COVID-19 +ve: respiratory outcome, admission to intensive care unit.

Tier 3 – Changes to acute vascular care management

Primary objective

Tier 3 is designed to capture modification to the management of **all referred** urgent vascular cases during the COVID-19 pandemic and identify deviations from pre-pandemic best practice, standards and/or guidelines for acute/urgent cases due to healthcare pressures or resource limitations. This will focus on (but not be limited to) chronic limb-threatening ischaemia, symptomatic carotid disease, acute aortic syndromes and aortic aneurysmal disease.

Methods

This will take place over a minimum of one month and will invite vascular specialists to complete an anonymised proforma for every patient with any of the conditions listed above referred to the vascular service. Timings may change based on the duration of the pandemic.

Patient enrolment

Patients will be identified prospectively at the time of referral to the vascular team. To ensure comprehensive data capture, patients may also be identified retrospectively. All patients referred to vascular services are eligible for enrolment, including COVID-19 +ve, COVID-19 suspected and COVID-19 -ve.

Outcomes

Primary outcome:

To document any deviation from "best vascular practice" and the impact on patient care, specifically focusing on:

- Chronic Limb Threatening Ischaemia (CLTI) (9):
  - Decision to discharge, admit or refer to an emergency ('hot') clinic
  - Decision for endovascular- or open surgical revascularisation first strategy
  - Decision for best medical therapy, palliation or primary amputation
- Symptomatic carotid disease:
  - Patients managed with best medical therapy (BMT)
  - Modifications to the indication and decision for carotid endarterectomy (CEA)
  - Delays to treatment due to lack of resources, including operating theatre, anaesthetic support or bed availability
- Abdominal Aortic Aneurysm (AAA):
  - Use of endovascular repair +/- local anaesthesia
  - Changes to criteria for intervention
  - Decisions for palliation, i.e. 'turn down'
- Acute Aortic Syndrome (AAS):
  - Decision to manage in non-critical care beds
  - Changes to imaging protocol at unit level
  - Decision to defer intervention

Secondary Outcomes:

- To collect longitudinal data to identify condition-specific outcomes for these patients at 6 and 12 months (as a minimum).
- Example condition-specific outcome measures to include:
  - CLTI: limb salvage, amputation free survival, all-cause mortality
  - Carotid disease: ipsilateral stroke rate, any stroke rate, all-cause mortality

272 - AAA: aneurysm-related mortality, all-cause mortality
273 - AAS: complication rate including rupture, all-cause mortality
274 - Other vascular presentations such as via MDT, hot-foot clinic referrals.
275

276 **Tier 2 and Tier 3 data collection**

277 Tier 2 and Tier 3 data (all anonymised and non-identifiable) will be collected and stored through a secure
278 UK National Health Service server using the Research Electronic Data Capture (REDCap) web application.
279 Designated collaborators at each participating site will be provided with REDCap project server login
280 details, allowing them to securely submit data on to the REDCap system. REDCap has previously been
281 successfully used for a range of other international cohort studies, including those led by GlobalSurg and
282 the European Society of Coloproctology. The REDCap server is managed by the University of
283 Birmingham, UK, with support provided by the GlobalSurg team.
284

285 Anonymised data will be collected relating to COVID-19 status, comorbidities, physiological state,
286 treatment, operation or intervention, and outcome. A unique identifier will be assigned to each patient
287 record. All participating centres will keep a record of patient details relating to the unique identifier for
288 the collection of medium- and long-term outcome data and linking to the original participant record on
289 REDCap
290

291 **Analyses**

292 As this is a non-interventional study, analysis will be limited to presentation of numbers and
293 proportions, with comparisons made to national and international standards. Interim analyses will be
294 performed periodically to inform data collection and provide up to date information on the impact of
295 the pandemic. The first formal analysis for Tier 2 will be performed once 50 patients have been entered
296 onto the database, and the frequency of subsequent analyses will be determined by the findings of this.
297 Hospital-level data will not be released or published by the VERN team, but individual centres will have
298 full access to their own data.

299 **National and local approvals**

Ethical approval from the UK Health Research Authority has been obtained for Tiers 2 and 3, permitting the capture of patient outcomes at 6 and 12 months (20/NW/0196 Liverpool Central, IRAS: 282224). The study is registered with ISRCTN registry (80453162).

Participating centres in the UK will be required to seek local research and development approval. Non-UK centres will need to obtain a research ethics committee or institutional review board approval in accordance with national and/or local requirements. The principal investigator at each participating site is responsible for obtaining necessary local approvals. Study organisational sponsorship is through the R&D Department at University Hospitals, Coventry and Warwickshire NHS Trust, Coventry, UK.

Authorship

Collaborators from each site who contribute patients will be recognised on any resulting publications as PubMed-citable co-authors. The VERN model for collaborative authorship, that will be used for any disseminations arising from this project can be found here: https://vascular-research.net/authorship-policy/. An example of this can be found here: https://pubmed.ncbi.nlm.nih.gov/29452941).

DISCUSSION:

The COVER study has been designed as the first vascular trainee led, multi-national prospective study of Vascular Surgical practice during the COVID-19 pandemic. It has several key points that will make it increasingly relevant in the current climate. A high mortality has been reported in elective general surgery patients who are COVID positive(10), which is concerning for the vascular patient population who are at increased risk of succumbing to a COVID-19 infection owing to their older age, high levels of smoking and background respiratory conditions, and comorbidities including diabetes. These factors have all been linked to significantly reduced rates of survival in those that have contracted the SARS-CoV2 virus. Pre-existing conditions also mean that if our patients are admitted to hospital, they are less likely to be considered candidates for invasive ventilation due to the associated mortality reported(11). In addition, COVID-19 associated coagulopathy is emerging as a presenting complaint for COVID-19 infection and will impact on vascular been observed; however it is unclear if this is a reduction in self-

328 referrals to primary care due to fear of coming into hospital, or gatekeeping being performed by
329 referring teams.
330 There is a familiarity within vascular surgery with the consequences of delays in presentation for key
331 conditions such as acute aortic pathologies and CLTI, leading to fewer treatment options and poorer
332 prognosis. As the pandemic progresses and elective operating is curtailed or stopped completely, there
333 will be a growing list of patients who will require urgent surgery in the post-pandemic period once
334 'normal' service has resumed. This study will address the consequence of delaying surgery considered
335 urgent or essential, and an understanding of the vascular caseload volume that is accumulating during
336 the pandemic period that will need to be appropriately managed once the crisis has passed.
337 Through well-structured and purposeful collaborative working the VERN group developed and
338 submitted the COVER study for ethical approval. This has been granted promptly to facilitate COVID-19
339 related research within vascular surgery. Similarly, the global vascular community has responded
340 positively and over 150 centres have already participated in Tier 1 and registered interest for the other
341 tiers across the globe indicating the support and global appeal of the study.

342 VERN and the COVER study has a strong trainee focus with the opportunity for trainees to contribute
343 high quality data from their own centres. From previous work(14) we have been able to demonstrate
344 that trainees are highly motivated to participate in research when their efforts are recognised and
345 PubMed citable(14). This has been echoed by global collaborative studies such as those run by
346 GlobalSurg[(15) (https://globalsurg.org/), conducted under a single author name and listing all those
347 individuals who have contributed as co-authors.

348 The protocol has been designed with the support of the Vascular Society of Great Britain and Ireland,
349 who recognise the value and importance of accurate data collection during this period. The study data
350 collection tools have been developed in close co-operation with our colleagues in Europe, the USA and
351 Australia, to ensure questions are applicable and that possible answers reflect variations in practice
352 around the globe. It has also helped to ensure that information is collected in sufficient depth to
353 correlate with key outcomes at 6 and 12 months, without being onerous.

354 The study also benefits from the ongoing public dissemination of international vascular guidelines to
355 support clinicians managing the current COVID-19 crisis. This will enable comparison of real time
356 changes in practice against emerging and evolving guidelines. Furthermore, the availability of various
357 national registries, that have benchmarked 'normal' practice and 'expected' condition-specific outcomes
358 for key parameters against which there can be a detailed comparison of COVER study-reported practices

and outcomes. Data points relating to patient, technical and peri-operative variables will also be compared between countries and wider regions to explore how differences in populations and practice may impact on disease specific outcomes at 6 and 12 months.

Tier 1 has already collected valuable real-time data which has been used to inform those who create and disseminate national guidelines. Promoting inclusion amongst the global vascular trainee community will also play a role in professional development, research skills and achievements which would not otherwise be available.

Study limitations

COVER is a pragmatic real-world study. The nature of the current pandemic has meant that an appropriate sample size is difficult to calculate. Additionally, the dynamic nature of the COVID-19 pandemic means that numbers of cases, including those testing positive for or suspected to have infection with the SARS-CoV2 virus - hence a denominator for some calculations - are unknown. This insurmountable problem is not limited to this study and is currently frustrating efforts to determine appropriate strategies for lifting the lockdown in countries where the peak of the pandemic appears to have passed.

Many countries have scaled back elective practice and changed thresholds for operating on carotid stenosis and aortic aneurysms to varying degrees and along different timelines due to resource scarcities. This will have an impact on the volume of cases uploaded into Tier 2 and Tier 3 of the study, but the concurrent completion of Tier 1 should reflect this and has already provided live data from over 150 institutions in 45 countries across the globe. In the first instance, country-specific experiences have been shared to highlight practice changes around the globe with vascular colleagues. This information will also be used when analysing country-specific trends for surgery and referrals. This will allow inclusion of important variables such as type of hospital (private or government-run), loss of specialty firms with the redeployment of staff to support other specialties; the exact timing for milestones such as stopping screening programmes for aortic aneurysm, or moving to a practice of mainly best medical therapy for symptomatic carotid artery stenosis.

Conclusion

Success of the COVER study will provide the global vascular community with robust data on the impact of the COVID-19 pandemic on our patients and the future legacy of delayed surgery and adjusted decision making. It will support further collaboration between vascular trainees globally, bringing together and recognising efforts to collaborate with colleagues around the world.

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