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[^{89}Zr]bevacizumab PET/CT imaging of vestibular schwannomas for the prediction of bevacizumab treatment effect in patients with symptomatic *NF2*-related schwannomatosis: a study protocol for a phase II single centre, prospective, feasibility trial

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ABSTRACT

Introduction Treatment with bevacizumab achieves both tumour stabilisation or regression and preservation or improvement of hearing. However, the efficacy of bevacizumab varies between patients and within patients. Side effects due to bevacizumab treatment are also common. It would be of value to predict therapeutic response prior to initiating therapy to prevent unnecessary exposure in patients unlikely to benefit.

Methods and analysis We aim to recruit 25 patients with *NF2*-related schwannomatosis (NF2) with bilateral vestibular schwannomas. Patients will receive an intravenous injection of 37 MBq [^{89}Zr]bevacizumab followed by positron emission tomography (PET)/CT imaging 4 days later. After clinical evaluation at baseline, patients undergo bevacizumab treatment and are followed up at 3 and 6 months. The primary objective is to examine associations between pretreatment [^{89}Zr]bevacizumab uptake on PET/CT and changes in multiple hearing outcomes and radiological characteristics of the target tumour following treatment. Secondary outcome measures include vestibular functioning, patient reported outcome measures, cranial nerve functionality, peripheral neurology, non-target schwannoma response and renal function. Given the explorative nature of the study, associations between PET-derived metrics and clinical and radiological outcomes will be examined without formal hypothesis testing, using generalised estimating equations to account for within-patient correlation. Pairwise associations will be summarised in an association matrix with multiplicity addressed using an all-resolutions inference approach, and findings will be considered hypothesis generating.

Ethics and dissemination This study was submitted via the Clinical Trials Information System reviewed and approved by the Medical Research Ethics Committee Leiden–The Hague–Delft Delft. The study findings will be disseminated through publication in peer-reviewed scientific journals and by presentation at national and international conferences.

Trial registration number The trial is registered at ClinicalTrials.gov Protocol Registration and Results System under the registration ID: NCT05685836.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The prospective study design is embedded in standard-of-care bevacizumab to reduce trial burden on the study population.
⇒ A wide range of outcome measurements (hearing response, radiologic response, vestibular function, cranial nerve functionality, peripheral neurology and patient-reported outcome measures) is included relevant to objective and subjective patient care.
⇒ Treating clinicians are blinded to the [^{89}Zr]bevacizumab positron emission tomography (PET)/CT findings during follow-up, minimising management and assessment bias.
⇒ The current study protocol involves a relatively high radiation exposure, with doses based on literature using older-generation PET scanners.
⇒ The study includes a single-centre, feasibility cohort of 10–25 participants. If this feasibility study yields positive results, a validation study will therefore need to be conducted in a larger cohort using a multicentre prospective approach.

INTRODUCTION

NF2-related schwannomatosis (NF2) is an autosomal dominant tumour predisposition

syndrome caused by mutations in the *NF2* tumour suppressor gene on chromosome 22.[1 2] The incidence of NF2 is low, with an estimate of 1 in 25 000 to 87 410 individuals.[3 4] The pathognomonic hallmark of NF2 is the presence of bilateral vestibular schwannomas, which almost all affected individuals develop before the age of 30 years old.[2] In addition, the majority of patients develop intramedullary spinal ependymomas, intracranial and spinal meningiomas, and schwannomas on other central and peripheral nerves.[5 6] Clinical severity of the disease varies widely, as patients with a germline alteration in *NF2* typically present during adolescence and develop multiple tumours throughout life, while those with less severe genotypes or mosaicism for *NF2* may present at an older age and with a milder disease.[4 7 8]

Management of vestibular schwannomas related to NF2 is challenging.[9] While vestibular schwannomas are benign in origin and typically indolent or slowly progressive, hearing loss, vertigo and/or imbalance, and tinnitus are reported by the majority of patients. In addition to vestibular schwannomas, other schwannomas and cranial nerve deficits may occur. Compared with its unilateral variant, NF2-associated vestibular schwannomas lead to reduced life expectancy and more substantial morbidity due to an earlier onset, higher tumour growth rate, higher incidence of multifocal tumours and poorer outcomes with standard therapies.[10–12] Therapeutic intervention is often recommended for large or progressive tumours, worsening symptoms or impending complications such as brainstem compression. For the treatment of vestibular schwannomas, modern treatment paradigms include surgery, microsurgery and radiation therapy.[1 9 13] However, in NF2, surgical approaches are associated with a higher tumour recurrence rate and loss of serviceable hearing is reported in half of the cases.[14] Radiotherapy offers good tumour control in almost all NF2 patients, but hearing is preserved in only 45% of the cases and other cranial nerve deficits are common.[14 15] In NF2, a tumour susceptibility syndrome, radiotherapy poses an additional risk for malignant transformation of benign tumours and the development of new primary tumours in irradiated surrounding tissues.[16 17]

A relatively recent treatment option is pharmacotherapy with bevacizumab, a monoclonal antibody that inhibits vascular endothelial growth factor (VEGF) overexpressed in schwannomas.[18–20] Blockage of VEGF with bevacizumab achieves both tumour stabilisation or regression and preservation or even improvement of hearing.[19–23] Improvements in quality of life (QoL), subjective hearing, tinnitus and imbalance have also been reported.[24–26] However, the efficacy of bevacizumab varies between patients and responsiveness of schwannomas can differ within the same patient. Side effects due to bevacizumab treatment, such as hypertension, proteinuria and several blood disorders, have been reported in almost a quarter of patients.[21 27 28]

Given the variability in treatment response to bevacizumab, it would be of value to predict therapeutic response prior to initiating therapy. A non-invasive approach would help prevent unnecessary exposure to potential toxicities, as well as reduce the substantial financial burden in patients unlikely to benefit.[29 30] Positron emission tomography (PET) with Zirconium-89 (^{89}Zr)-labelled bevacizumab can be used to visualise and quantify VEGF-targeting. It might be a promising method for non-invasive upfront patient selection to identify those who may benefit from bevacizumab treatment.[31–35]

In this protocol, we present the methods of a phase II, non-randomised, single centre, single-blinded, prospective, feasibility trial evaluating the use of [^{89}Zr]bevacizumab PET/CT as a quantitative imaging biomarker to predict treatment of bevacizumab for NF2.

METHODS AND ANALYSIS

Trial design

In this phase II, non-randomised, single centre, single-blinded, prospective, feasibility trial, the association between the pretreatment uptake of [^{89}Zr]bevacizumab on PET/CT imaging and the effect of bevacizumab treatment on the vestibular schwannoma of interest is investigated. Patients receive an intravenous injection of 37 MBq [^{89}Zr]bevacizumab (5 mg protein dose) followed by [^{89}Zr]bevacizumab PET/CT imaging 4 days later.[36 37] After careful clinical evaluation at baseline, patients undergo per protocol bevacizumab treatment for NF2 and are followed up at 3 and 6 months.

This study represents the first theragnostic investigation of its kind to explore the use of [^{89}Zr]bevacizumab as a potential predictive biomarker for treatment response in NF2. Before a confirmatory clinical trial can be designed, several technical, clinical and methodological aspects must first be carefully evaluated. In particular, it must be determined whether the tracer binds to the intended molecular target in vestibular schwannomas and whether sufficient contrast can be achieved between tumour tissue and the surrounding normal tissue. Additionally, it is necessary to assess whether the signal-to-noise ratio is adequate to allow reliable interpretation of the images.

Beyond these imaging characteristics, the practical feasibility of the imaging protocol within the clinical workflow must also be considered. This includes evaluating whether patients tolerate the procedure well and whether they demonstrate adequate compliance with the imaging protocol. Furthermore, it is important to determine whether tracer uptake can be quantified reliably using PET-derived metrics. Finally, the study must establish whether integrating this imaging approach into a larger prospective clinical trial would be realistic and practically achievable.

Participants

Patients with NF2 who are planned for bevacizumab therapy will be recruited. Individuals will be approached by their treating physician (usually an otorhinolaryngologist, neurosurgeon or medical oncologist) during visits

at the monthly multidisciplinary NF2 outpatient clinic or after multidisciplinary consultation at the NF2 expertise centre of the Leiden University Medical Center (LUMC), Leiden, the Netherlands. The decision to participate in the trial is made by the patient after evaluation of the potential risks and benefits. Bevacizumab treatment will be initiated if clinically indicated, regardless of whether the patient chooses to participate in the trial. Informed consent will be obtained after sufficient, but at least 24 hours, reflection time has been provided.

Inclusion and exclusion criteria

In order to be eligible for the study, a subject must meet all of the following criteria:

- Aged 18 years or older.
- Confirmed diagnosis of NF2 by the updated diagnostic criteria for NF2.[6]
- Be eligible for bevacizumab treatment.
- Show measurable disease, defined as at least one vestibular schwannoma with a volume>0.4 cm^3 that can be measured using contrast-enhanced T1-weighted cranial MRI; Provide written informed consent.

Exclusion criteria are the following:

- Contra-indications for PET/CT or MRI.
- Known allergies to [^{89}Zr]bevacizumab.
- Concurrent treatment with everolimus.
- Severe comorbidities that may interfere with bevacizumab treatment.

Sample size

This study has an exploratory nature. It is the first theragnostic study of its kind to investigate the use of [^{89}Zr]bevacizumab as a potential predictive biomarker to upfront predict treatment response to bevacizumab in patients with NF2.

Therefore, the sample size is not determined by a formal power calculation. At our centre, approximately 150 patients with NF2 are under active surveillance. Based on historical treatment patterns, it is anticipated that up to 25 of these patients will receive bevacizumab during the study period. As this is a feasibility trial, no control group will be included.

Seeing the rarity of NF2, large patient series of individuals treated with bevacizumab remain scarce. A multicentre prospective study will be required to adequately evaluate the predictive value of [^{89}Zr]bevacizumab PET/CT.

Randomisation and blinding

Randomisation is not performed prior to or during the trial. Treating physicians are blinded to the outcomes of the PET/CT scan.

Study design

After determining eligibility for the trial, participants will undergo standard-of-care treatment with bevacizumab, with the addition of a pretreatment [^{89}Zr]bevacizumab PET/CT scan (figure 1).[36 37] As per protocol in the Netherlands, 7.5 mg/kg bevacizumab is intravenously

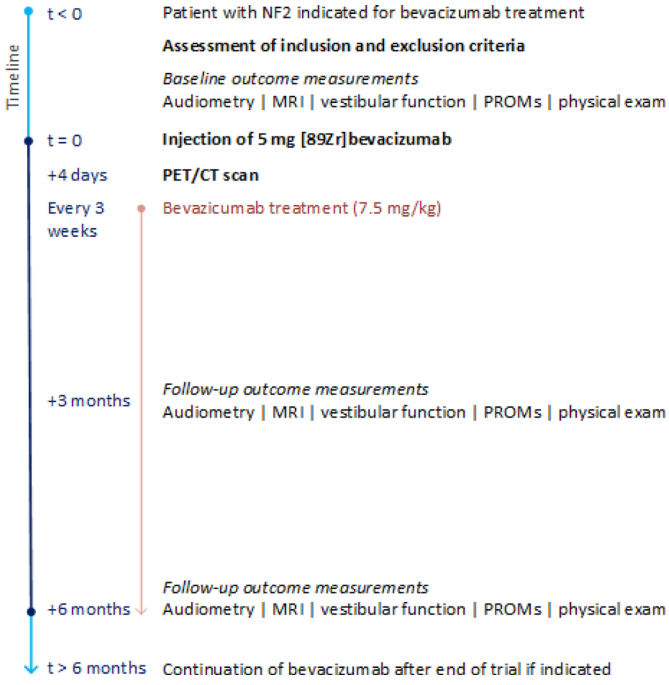

Figure 1 Study protocol flow chart. Routine bevacizumab care is supplemented by study-specific procedures (in bold). Time points (baseline, month 3, month 6) mark assessment windows. NF2, NF2-related schwannomatosis; PET, positron emission tomography; PROMs, patient-reported outcome measures.

administered every 3 weeks for 6 months or until a clinically relevant event occurs, monitored by the treating oncologist and/or NF2 multidisciplinary team.

Clinical assessments (audiometry, MRI, vestibular tests and neurological examination) are performed and patient-reported outcome measures (PROMs) are collected at three distinct timepoints: at baseline preceding start of bevacizumab treatment, 3 months into treatment and 6 months into treatment. Bevacizumab may be discontinued or adjusted in dosage at any time during the study at the discretion of the treating physician or based on patient preference.

As part of routine clinical care, blood and urine samples are collected before starting bevacizumab therapy and periodically repeated throughout the treatment. All contra-indications for [^{89}Zr]bevacizumab PET/CT are similar to those for standard-of-care bevacizumab; no additional blood or urine samples, therefore, have to be taken for the purpose of the study. Vital signs are evaluated before bevacizumab administration at each hospital admission. During treatment, toxicity is systematically evaluated at every outpatient visit.

[^{89}Zr]bevacizumab administration

For pretreatment imaging, bevacizumab-N-succinyldesferal-zirconium-89, otherwise known as [^{89}Zr]bevacizumab, is used. Both the labelling process and quality controls have been described previously.[38–40] The radiolabeling of bevacizumab with [^{89}Zr] is performed in accordance with good manufacturing practice (GMP)

at the GMP facility of the department of radiology and nuclear medicine of the Amsterdam University Medical Center (Amsterdam UMC), Amsterdam, the Netherlands.

After production, [^{89}Zr]bevacizumab will be directly transported and prepared for administration. At the radio pharmacy at our institute, a 20 mL syringe containing 37 MBq [^{89}Zr]bevacizumab will be prepared and dispensed, bearing a label with identification required by local law, the protocol number, drug identification and dosage. Next, administration takes place as a 10 min intravenous infusion under qualified medical supervision. Afterwards, the infusion line is flushed twice with normal saline and the patient is closely monitored for 1 hour after injection to detect any infusion-related anaphylactic reaction. This single pretreatment dose of 5.0 mg bevacizumab is not expected to have any therapeutic effect, as treatment with bevacizumab is intravenously administered at a dosage of 5.0 mg/kg and above.

PET/CT acquisition and analysis

Using the digital Vereos PET/CT system (Philips Healthcare, Best, the Netherlands), imaging of the patient's head will be performed in one bed position with an acquisition time of 960 s per bed position, as it has been shown to provide the best signal-to-noise ratio for small lesion detection.[41–43] The abdominal area is also scanned to assess renal tracer activity of [^{89}Zr]bevacizumab, at 300 s per bed position across two bed positions. It is hypothesised that increased renal tracer activity of [^{89}Zr]bevacizumab may predict treatment-related complications (urinary protein excretion>30 mg/dL) of bevacizumab treatment.[21] PET images are reconstructed using European Association of Nuclear Medicine Research-compliant protocols to achieve harmonisation across studies, hospitals and PET systems. Next, PET images are fused with a low-dose CT (35 mAs, 120 kV) that will be acquired prior to the PET for attenuation correction and lesion localisation purposes.

Quantitative image analysis will be performed, under the supervision of a nuclear medicine physician with 25 years of clinical experience, using MIM Software (MIM Encore V.7.4.2 or higher, MIM Software; Cleveland, Ohio, USA). Regions of interest are interpreted by semiquantitative analysis, using three-dimensional volumes of interest drawn around the lesions as accurately determined by MRI. Background uptake is quantified using a blood pool from the abdominal aorta. Outcomes of interest are decay-corrected mean body-weighted standardised uptake value (SUV_{mean}),[44 45] peak SUV (SUV_{peak}),[46] tumour-to-blood standard uptake ratio[47] and tumour enhancement.

MRI acquisition and analysis

For anatomical coregistration of vestibular schwannomas, MRI will be performed on a 3 Tesla scanner focused on the cerebellopontine angle and posterior fossa. As part of routine clinical care, the protocol includes thin-slice gadolinium-enhanced T1-weighted imaging, thin-slice heavily T2-weighted imaging and T2 turbo spin-echo brain imaging.[48 49] Additional research sequences comprise diffusion-weighted imaging, susceptibility-weighted imaging and dynamic contrast-enhanced imaging. All vestibular schwannomas on MRI are manually delineated by a head-and-neck radiologist with over 20 years of clinical experience. Outcome measures on MRI include extrameatal tumour volume (cm^3), largest linear tumour dimensions in three planes (anterior–posterior; medial–lateral; cranial–caudal), tumour growth rate (at 3 and 6 months), diffusion restriction, tumour enhancement, T2 hyperintensities and absence or presence of microbleeds.[50–52]

Outcome measures

The primary outcome of interest is the association between different measures of pretreatment [^{89}Zr]bevacizumab uptake on PET/CT imaging and changes in multiple hearing outcomes and radiological characteristics of the target tumour to bevacizumab treatment. Secondary outcome measures include vestibular functioning, PROMs, cranial nerve functionality, peripheral neurology, non-target schwannoma response and renal function.

Hearing response and radiologic response

Hearing response will be assessed using standard clinical audiometry, including Pure Tone Average (PTA) and Word Recognition Score (WRS).[53 54] The WRS will be determined both at the 50% speech-intelligibility point and at the maximum score. The PTA will be calculated as average hearing threshold at 0.5, 1, 2 and 3 kilohertz (kHz). If the threshold for 3 kHz is unavailable, an estimate of the threshold will be used by averaging the thresholds of 2 and 4 kHz. Hearing response will be evaluated at the end of treatment relative to hearing at baseline.

Radiologic response will be assessed using extrameatal tumour volume on MRI and will be evaluated at end of treatment compared with baseline.[49 55]

Vertigo

To evaluate vestibular function, the video head impulse test (v-HIT), the cervical vestibular evoked myogenic potential (cVEMP) test and caloric testing are used as in standard clinical practice.[56–59] The v-HIT is conducted using a commercially available monocular video oculography system (ICS Impulse, Otometrics/Natus; Taastrup, Denmark).[56] Caloric testing will be performed as the conventional open bithermal loop with warm and cold temperature water alternating in the right and left ear, analysed through a video-based system (Hortmann Vestlab 100, Otometrics/Natus; Taastrup, Denmark). cVEMPs are recorded as myogenic responses from the ipsilateral contracted sternocleidomastoid muscle, using standard evoked potential equipment.[60 61]

Patient-reported outcome measures

QoL questionnaires to be used are the Penn Acoustic Neuroma Quality-of-Life,[62] NF2 Impact on Quality-of-Life[10] and Health Utilities Index-3.[63] Participants are

also asked to fill out two questionnaires on dizziness, the Dizziness Handicap Inventory[64 65] and Oscillopsia Severity Questionnaire.[66] Furthermore, patients are asked to subjectively describe the occurrence and evolution of hearing loss, tinnitus and vestibular symptoms over the course of their study participation.

Cranial and peripheral neurology

Neurologic investigation additional to the vestibulocochlear nerve function tests comprises the trigeminal nerve function, the facial nerve function and peripheral neurology. Facial nerve function is graded using the House-Brackmann scale.[67] General neurological examination is performed by a treating physician during a patient visit at the outpatient clinic. If applicable, the localisation of peripheral schwannomas and presence of related symptoms are evaluated.

Renal function

Renal function (estimated Glomerular Filtration Rate (eGFR), mL/min) will be obtained from blood samples collected during regular check-ups with the treating oncologist. An eGFR of 90 mL/min or higher is seen as normal or high (class 1). Renal toxicity (class 2–5) is classified according to international clinical guidelines.[68]

Statistical analysis

Patient characteristics will be summarised descriptively.

Since this study is hypothesis generating, associations between PET-derived metrics and all clinical and radiological outcomes will be examined to identify signals that may justify further investigation in a subsequent, adequately powered study. No formal hypothesis testing for primary endpoints will be performed and observed associations will be interpreted as preliminary. The primary analytic focus will be on hearing outcomes and tumour volume, while associations with prespecified secondary endpoints will also be explored.

To account for possible within-patient correlation when multiple tumours are present, associations at the lesion level will be analysed using generalised estimating equations, clustered by patient. Pairwise associations will be summarised in an association matrix with corresponding p values. Multiplicity will be addressed across this matrix using an all-resolutions inference approach, which controls the family-wise error rate across different clusterings and thresholds.

For data presentation and visualisation, scatterplots and boxplots will be provided. Given the small sample size, multiplicity of comparisons and exploratory design, findings will be considered hypothesis-generating and used to inform endpoint selection analytic strategies for future confirmatory studies.

All collected data will be accessible for the coordinating investigator, the principal investigator and those involved in carrying out the analyses. Procedures for managing missing, unused or erroneous data are detailed in the patient's study report. Statistical analysis is performed in IBM SPSS Statistics (V.27.0 or higher).

Patient and public involvement

A multidisciplinary NF2 team at LUMC oversees trial design and delivery. Patient input was obtained via the Dutch Neurofibromatosis Association, whose representatives were asked to provide advisory input on the study rationale and feasibility, as well as support dissemination through association channels. Patients are asked to comment on the burden of the study through elaborate PROMs during the trial. A team of nuclear medicine and radiopharmaceutical specialists from the laboratories at LUMC and Amsterdam UMC is involved in the set-up of the trial and the writing process concerning the investigational product.

ETHICS AND DISSEMINATION

Ethics

The trial has been submitted through the Clinical Trial Information System (CTIS; number 2020-000156-35) and was reviewed and approved by the Medical Research Ethics Committee Leiden–The Hague–Delft (MERC LDD; number NL727743.058.20) for conduct in the Netherlands under the European Clinical Trial Regulation. Additionally, the Board of Directors and the research boards of the participating departments provided formal approval for the study.

The study will be carried out in accordance with the Declaration of Helsinki (October 2024), the Dutch Medical Research Involving Human Subjects Act (February 1998) and the International Conference on Harmonization Good Clinical Practice (November 2016), as well as any other laws and regulations applicable to clinical research in the Netherlands.

Patient safety

The risks of participation for subjects in the trial include risks associated with [^{89}Zr]bevacizumab and exposure to CT radiation. All risks associated with [^{89}Zr]bevacizumab PET/CT are similar to those for standard-of-care bevacizumab, thus no additional blood or urine samples have to be taken. During treatment, toxicity is systematically evaluated at every outpatient visit. Any adverse events are documented in the patient's medical record and communicated to the treating specialist. If a medical intervention is required, appropriate measures are taken and documented in the patient file. We use The Common Terminology Criteria for Adverse Events, V.5.0, to classify adverse events.[69] The sponsor will provide a safety report for the investigational medical product used in the trial via the CTIS.

Data safety

The processing of personal data will be carried out in accordance with the Dutch General Data Protection Regulation. No Data Safety Monitoring Board is

required, as the intervention in the study is not considered as high risk. Study data will be entered and stored in Castor, a secure electronic data capture system certified according to ISO 9001 and ISO 27001:2005 standards. All records will be retained for a minimum of 15 years after study completion. To guarantee confidentiality, patients will be assigned a unique study code linked to a password-protected identification list. Access to the coded database and identification list will be restricted to authorised study personnel, as documented in the site signature and delegation log. Study data will not be publicly accessible due to privacy restrictions, but may be shared anonymised on request to the corresponding author. Both the sponsor and the principal investigator will maintain a clinical trial master file that contains all essential documentation.

Dissemination

The investigator will submit a summary of the progress of the trial to the accredited MERC once a year. Within 1 year after termination of the trial, a summary of the study results will be submitted to the accredited MERC and CTIS. The protocol study is made available through open access publication. The findings of this study will be disseminated through publication in peer-reviewed scientific journals and by presentation at national and international conferences. All reports and presentations will be prepared in a manner that ensures anonymity and patient safety. The coordinating investigator will oversee the timing and content of publications.

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Contributors The conception and design of the study were developed by JPJD, PD-S, BMV, CAFB, JCJ, KSK, FHPvV, MP, DV, L-FDG-O, EFH and HAG. The drafting of the original protocol was done by JPJD, KSK, VSvD, MP, DV, L-FDG-O, EFH and HAG. The coordination of the study was carried out by JPJD, ALT and VSvD. Patient recruitment and collection of data were performed by JPJD, ALT, PD-S, BMV, CAFB, JCJ, RWK, JES, L-FDG-O, EFH and HAG. The statistical analysis plan was designed by JPJD, ALT, JCJ, JJG, L-FDG-O and EFH. The present manuscript was drafted by JPJD. The funding was obtained by KSK, L-FDG-O and EFH. All authors read, reviewed and agreed to the final manuscript prior to submission for publication. The guarantor is EFH.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods and analysis section for further details.

Patient consent for publication Informed consent will be obtained from all subjects involved in the study.

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