Abdominal aortic aneurysms

The quest for meaningful biomarkers and opportunities to improve surgical care

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CHAPTER 9

Design and protocol of a comprehensive multicentre biobank for abdominal aortic aneurysms

Submitted

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ABSTRACT

Introduction

The pathophysiology and natural course of abdominal aortic aneurysms (AAAs) are insufficiently understood. In order to improve our understanding, it is imperative to carry out longitudinal research which combines biomarkers with data and imaging markers, all measured over multiple time points. Therefore, a multicentre biobank, databank and imagebank has been established in the Netherlands: the '*Pearl Abdominal Aortic Aneurysm*' (AAA bank).

Methods and analysis

The AAA bank is a prospective multicentre observational bio-, data- and imagebank of patients with an AAA. It is embedded within the framework of the Dutch String of Pearls Institute (PSI) which facilitates uniform biobanking in all university medical centres (UMCs) in the Netherlands. The AAA bank has been initiated by the two UMCs of Amsterdam UMC and by Leiden University Medical Center. Included patients with AAA will be followed during AAA follow-up. At every patient contact, clinical data is collected for standardised storage in the databank. Three types of biomaterials are collected at baseline and during follow-up: blood (including DNA and RNA), urine and AAA tissue if open surgical repair is performed. Imaging data that are obtained as part of clinical care are stored in the imagebank. All data and biomaterials are processed and stored in a standardised manner. AAA growth will be based on multiple measurements and will therefore be analysed with a repeated measures analysis. Potential associations between AAA growth and risk factors that are also measured on multiple time points can be assessed with a multivariate mixed-effects model, while potential associations between AAA rupture and risk factors can be tested with a conditional dynamic prediction model with landmarking.

Ethics and dissemination

The AAA bank is approved by the Medical ethics Board of the Amsterdam UMC (University of Amsterdam).

Registration

This study was retrospectively registered on October 25, 2017 on www.clinicaltrials.gov (NCT03320408).

INTRODUCTION

An abdominal aortic aneurysm (AAA) is a focal dilatation of the abdominal aorta that affects mostly elderly men. The prevalence of AAA in the general population is 1.3-2.2% in 65-year old men.[1, 2] An AAA is an asymptomatic disorder which is associated with a high risk of mortality in case of rupture.[3] Management of patients with an AAA is aimed at preventing rupture, either by surveillance for small AAAs or by prophylactic AAA repair if the rupture risk is deemed high, in general at a diameter of more than 5.5 cm. A large body of research has been dedicated to determining the optimal surgical treatment for AAA, focusing on either the threshold diameter for repair, the method of repair, or the outcome and follow-up after treatment. Although many studies have tried to unravel AAA pathophysiology, this aspect is still insufficiently understood. Most of the current knowledge originates from histopathological studies that reflect the end stage of AAA disease. Early determinants and drivers of AAA formation are largely unidentified due to the unavailability of AAA tissue from an early stage of the disease. Therefore, the known determinants of AAA development are limited to general risk factors such as male sex, ageing, smoking or connective tissue diseases.[4, 5]

Recent studies focused on biomarker research to find early disease markers and potential targets for pharmacological treatment. Promising circulating biomarkers included markers of matrix turnover (matrix metalloproteinases), markers of inflammation (interleukins and C-reactive protein) and markers of lipid metabolism (lipoproteins).[6-8] Unfortunately, to date, none of these biomarkers have found their way to clinical practice. This is mostly due to their low prognostic value for AAA progression, and because many studies have not corrected for factors as smoking or comorbidities.[7] The same applies to new imaging biomarkers such as ^{18}F-fluoro-deoxy-glucose (^{18}F-FDG), or biomechanical markers such as peak wall stress and wall shear stress.[9-11]

To better understand AAA pathophysiology and its natural course, it is imperative to combine studies with biomarkers, imaging markers, and longitudinal data. To that end, a multicentre databank, biobank and imagebank has been established in the Netherlands: the '*Pearl Abdominal Aortic Aneurysm*, hereafter referred to as the AAA bank. The aim of this project is to facilitate future studies on AAA. It is part of the Dutch String of Pearls Institute (PSI), which facilitates uniform biobanking in all eight university medical centres (UMCs) in the Netherlands.[12] The systematic collection of clinical data, biomaterials and imaging data will enable a diverse range of studies on patients with AAA. The AAA bank will especially focus on patients with a small AAA to collect longitudinal data early on in the development of AAA.

The first proposed study that will be carried out with the collected biomaterials is the 'Predicting aneurysm growth and rupture with longitudinal biomarkers' (PARIS) study.

The PARIS study aims to determine the association between AAA progression and the evolution of serum levels of proteases and cytokines.

The scientific aims of the AAA bank are (1) to gain insight in the pathophysiology and natural history of AAA; (2) to gain more knowledge about the rupture risk of AAA; and (3) to evaluate and improve treatment of patients with an AAA. Future studies with data from the AAA bank must adhere to these scientific aims.

METHODS AND ANALYSIS

Study design

The AAA bank is a prospective multicentre observational biobank, databank and imagebank of patients with AAA in The Netherlands (ClinicalTrials.gov: NCT03320408, see table 1 for the World Health Organization (WHO) Trial Registration Data Set). The active protocol at the time of writing is version 3, 22 December 2017. The AAA bank is embedded within the framework of PSI, which is co-financed by the Dutch government and the Netherlands Federation of University Medical centres (NFU).[12] PSI was established in 2007 and aims to facilitate standardised nationwide biobanks and clinical databases.[13] At the time of writing, 17 different patient cohorts (*Pearls*) for different diseases have been initiated within the PSI framework. Examples include the Diabetes Pearl, the Pearl Neurodegenerative Diseases, the Stroke Pearl, and the Dutch Pancreas biobank.[14-17] All these biobanks adhere to an internal regulatory framework, which prescribes legal and ethical rules concerning the conduct of all Pearl-related activities.[13]

The AAA bank has been initiated by the two UMCs from Amsterdam University Medical Centers (University of Amsterdam and Vrije Universiteit Amsterdam) and by Leiden University Medical Center (LUMC). In accordance with the goals of PSI and NFU, the AAA bank aims to expand to the other Dutch UMCs. The AAA bank is currently an ongoing project, with active recruitment and collection of data and biomaterials. The first patient was recruited on October 4, 2017.

Study population

All capable adults with AAA in participating university medical centres are eligible for inclusion in the AAA bank. This also includes patients who previously have undergone AAA repair. Patients who are incapable due to a ruptured AAA (RAAA) can also be included, using a special recruitment process, which will be described below. All included patients will be followed for as long as they visit their treating vascular surgeon.

Table 1. WHO trial registration data set

Primary registry and trial identifying number	ClinicalTrials.gov: NCT03320408
Date of registration in primary registry	25 October 2017
Secondary identifying numbers	NL59991.018.17, PARIS study, biobank Pearl AAA
Sources of monetary of material support	AMC Foundation for monetary support.
Primary sponsor	Academic Medical Center – University of Amsterdam
Secondary sponsor(s)	none
Contact for public queries	Els Kuiters, e.kuiters@amc.uva.nl, +31205667832, Meibergdreef 9, 1105AZ, Amsterdam, the Netherlands.
Contact for scientific queries	Principal investigator: prof. R. Balm, r.balm@amc.nl, +3120-5667832, Meibergdreef 9, 1105AZ, Amsterdam, The Netherlands. Els Kuiters, e.kuiters@amc.uva.nl, +31205667832, Meibergdreef 9, 1105AZ, Amsterdam, the Netherlands.
Public title	PARIS study & biobank Pearl AAA
Scientific title	Predicting aneurysm growth and rupture with longitudinal biomarkers (PARIS study) & biobank Pearl AAA
Countries of recruitment	The Netherlands
Health condition(s)	Abdominal aortic aneurysm
Intervention(s)	None
Key inclusion and exclusion criteria	Inclusion criteria: adult with an AAA, or who has been previously treated for an AAA. Adequate comprehension of the Dutch language to provide written informed consent. Exclusion criteria: Decisionally impaired patients. The exception are patients who are decisionally impaired due to the effects of an acute AAA for whom a separate recruitment and consent procedure exists.
Study type	Observational longitudinal patient registry and biobank
Date of first enrolment	4 October 2017
Sample size	Planned: 750 Currently enrolled: 87
Recruitment status	Recruiting; participants are currently being recruited and enrolled
Primary outcome(s)	Outcome: AAA growth. Time frame: up to 10 years of follow-up Outcome. AAA rupture. Time frame: up to 10 years of follow-up Outcome: all-cause mortality. Time frame: up to 10 years of follow-up Outcome: evolution of serum levels of proteases and cytokines. Time frame: a maximum of 1 measurement annually up to 10 years of follow-up Outcome: proteases and cytokine levels in AAA tissue. Time frame: if open AAA repair is performed and AAA tissue is collected. This is a one-time measurement.
Key secondary outcome(s)	Outcome: incidence and type of complications after AAA repair. Time frame: up to 10 years of follow-up after AAA repair
Ethics review	Status: approved Date of approval: 25 August 2017 Name and contact details of ethics committees: Medical Ethics Board of Amsterdam UMC (University of Amsterdam). mecamc@amc.uva.nl, +31205667389, Trinity building C, fourth floor, Pietersbergweg 17, 1105BM Amsterdam, the Netherlands. Biobank Ethics Board of Amsterdam UMC (University of Amsterdam), biobanktoetsing@amc.uva.nl, +31205666730, Meibergdreef 9, 1105AZ, Amsterdam, the Netherlands.
Completion date	Expected: 4 October 2032
Summary results	No results yet.
IPD sharing statement	Plan to share IPD: Yes Plan description: IPD sharing for research will be allowed in a data sharing procedure. Scientific requests need to fall under the scope of the scientific aims as formulated in this manuscript. Researchers willing to requests IPD can initiate this procedure by contacting the researchers. Data will be released depending on the scientific quality of the submitted request.

AAA = abdominal aortic aneurysm

Recruitment procedure

Eligible patients are recruited at the inpatient or outpatient clinic of the department of Vascular Surgery of the participating hospitals by research physicians and/or data managers. Participants who agree to participate give written informed consent during their visit to the inpatient or outpatient clinic. When patients arrive in an emergency setting with a ruptured or symptomatic AAA, oral consent is required from either the patient or a legal representative. This oral consent has to be confirmed in writing at a later stage – either by the patient, or by a representative in case of a fatal outcome. In the event that no written informed consent can be obtained, all data and biomaterials collected for the AAA bank will be destroyed.

Study procedures

The study procedures of the AAA bank are embedded within regular AAA treatment. Clinical data and biomaterials are collected during visits that are already part of clinical treatment, to limit participant burden and improve participant retention. No research visits will be planned for the AAA bank. In addition, only imaging data that is obtained as part of clinical care will be stored in the AAA bank.

In line with regular AAA management, four distinct study phases have been identified: inclusion phase, surveillance phase, surgical phase, and postoperative phase (Figure 1; blue boxes). Within each phase, multiple visits can take place – especially in the surveillance or postoperative phase. These phases can theoretically continue indefinitely, depending on the course of the AAA. With regard to the 'surveillance phase', the Dutch AAA guideline advises that patients visit a vascular surgeon at intervals of two years, one year, or three months, depending on the AAA diameter.[18] Patients can move from the 'surveillance phase' to the 'surgical phase' and subsequently to the 'postoperative phase' (Figure 1).

Clinical data – PRISMA

At every patient contact, clinical data are collected for storage in the databank of the AAA bank by research physicians and/or data managers. All data items have been incorporated in electronic Data Capture Systems (eDCSs). These eDCSs are integrated in an information model called Parelsnoer Repository for Information Specification, Modelling and Architecture (PRISMA, Table 2). The PRISMA model for the AAA bank was constructed with assistance of an experienced information architect of PSI. The eDCSs cover data items ranging from baseline characteristics such as comorbidity to surgical characteristics and postoperative complications. Postoperative complications are registered in codes of the Dutch National Surgical Complications Registry (LHCR), which was established by a committee of the Association of Surgeons of the Netherlands (NVvH).

Data are registered via local data capture platforms, such as Castor EDC[19] (Ciwit, the Netherlands, which is hosted by True[20] in the Netherlands), and are centrally stored

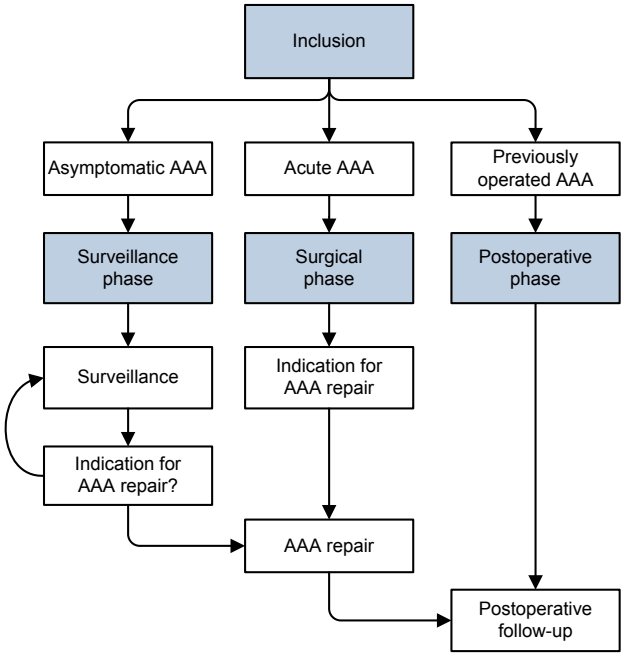

Figure 1. Flow chart of study phases

in Project Manager Internet Server (ProMISe)[21], a web-based relational database management system (Advanced Data Management, the Netherlands). These systems are compliant with Good Clinical Practice and are ISO27001 certified. All patients are being registered under a study number that is electronically assigned by a designated tool. This study number is used during data collection and data processing.

Biomaterials

Three types of biomaterials are collected: blood, urine and AAA tissue (Table 3). Blood and urine are collected repeatedly during the surveillance phase, up to a maximum of once per year to limit patient burden. Blood is saved as plasma, serum and whole blood for DNA and RNA. When open surgical repair of AAA is performed, aortic tissue is collected, snap frozen and stored at -80°C, and as formalin-fixed paraffin-embedded (FFPE) tissue. After surgery for AAA, blood and urine are collected up to one year postoperatively (Table 3). All procedures concerning biomaterials adhere to standard operating procedures outlined by PSI. Furthermore, all biomaterials are stored in designated PSI biobanks within each UMC. Thus, all biomaterials are stored in the UMC where they are collected.

Table 2. The PRISMA information model of the AAA bank

eDCS name	Inclusion			Follow-up[N]			Stream
	Asymptomatic AAA	Operation for acute AAA	Previously operated AAA	Surveillance phase	Surgical phase	Postoperative phase	
Patient information		1			M		
Informed consent		1			M		
Living situation		1			1		
Current aneurysm state		1			1		
First occurrence comorbidity		1			M		
Family history		0..n			M		
Social history		1			M		
Initial aneurysm characteristics		1					
Comorbidity status		1			1		
Medication		1			1		
Intoxications		1			1		
Physical examination		1		1	1		
Blood test results		1			1		
Surveillance	1			1			
Preoperative assessment			1		1		
AAA repair			1		1		
Postoperative admission			1		1		
Postoperative follow-up			1			1	
Biomaterials	1				1		
Cardiovascular events							dt
Other surgical procedures							dt
Malignancies							dt
AAA imaging	0..n						dt
Complications							dt
Imaging data	1				1		dt

eDCS: electronic Data Capture System;
1: indicates that an eDCS is registered once and is overwritten in case of future changes.
M: Means 'Modify', and indicates that the eDCS can be modified within the same observation period. N: Indicates that this eDCS can be registered multiple times (but at least once)
0..n: Indicates that this eDCS can be registered multiple times (but is not mandatory)
The eDCS from previous observation periods remain unchanged.
dt: the eDCS is saved as a time-stream with date-time format.

Table 3. Biomaterials collected for the AAA bank

Biomaterials	Inclusion	Surveillance phase	Surgical phase	Postoperative phase	Storage temperature
Blood - EDTA plasma	once	max. 1 / year	once	Once: 1 year postoperative	≤ -80°C
Blood - Serum	once	max. 1 / year	once	Once: 1 year postoperative	≤ -80°C
Blood - Citrate plasma	once	max. 1 / year	once	Once: 1 year postoperative	≤ -80°C
Blood - EDTA for DNA	once				4°C or ≤ -20°C
Blood - PAXgene for RNA	once				≤ -80°C
Urine	once	max. 1 / year	once	Once: 1 year postoperative	≤ -80°C
Aneurysm tissue - frozen			once		≤ -80°C
Aneurysm tissue - FFPE			once		room temperature

EDTA = Ethylenediaminetetraacetic acid, FFPE = Formalin-fixed paraffin-embedded

Imaging data

In order to facilitate future imaging studies, computed tomography (CT) and magnetic resonance imaging (MRI) data that are obtained as part of clinical care are also stored centrally. At the time of writing, the participating centres are harmonizing the CT protocols to acquire standardised images. Partners currently involved in the central storage of images are Translational Research IT (TRaIT, part of Dutch non-profit organisation Lygature) and Vancis, a Dutch service provider of IT services for research with a ISO27001 certificate.[22-24] The imaging data are stored centrally in an Extensible Neuroimaging Archive Toolkit (XNAT) server (Buckner Lab, Harvard University, United States of America).[25] This server is operated by TraIT and is hosted by Vancis.

Imaging data are stored as Digital Imaging and Communications in Medicine (DICOM) data. Before the data are sent to the central server, the study number is allocated to the imaging data to enable linking of imaging data with clinical data and biomaterials. All other identifiable data are removed from the DICOM data using Clinical Trial Processor (CTP, Radiological Society of North America, United States of America).[26]

Statistical analyses

The primary outcomes are AAA growth, AAA rupture and all-cause mortality. AAA growth will be based on multiple measurements and will therefore be analysed with a repeated measures analysis. Potential associations between AAA growth and risk factors that are also measured on multiple time points can be assessed with a multivariate mixed-effects

model, while potential associations between AAA rupture and risk factors can be tested with a conditional dynamic prediction model with landmarking.

Due to the expected multifactorial aspect of AAA growth, even weak correlations are of interest to detect. To that end, at least 750 patients are required to be able to detect a correlation coefficient of 0.16 with a power of 80%, and a significance level of .05.

Patient and public involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

ETHICS AND DISSEMINATION

The Medical Ethics Board and the Biobank Ethics Board of Amsterdam UMC (University of Amsterdam) have approved the AAA bank together with the PARIS study (Table 4) within the scope of the Dutch Medical Research Involving Human Subjects Act (WMO) under registration number NL59991.018.17. In general, biobanks in the Netherlands do not fall within the scope of the WMO. To be eligible for assessment under WMO, the formulation of a specific research question is required. However, specific research questions are often not present at the moment of biobank initiation.[27] Yet, the submission of the AAA bank together with the PARIS study (that contains a specific research question) enabled approval of the combined project within the scope of the WMO. This approval ensures that the AAA bank adheres to the highest legal and medical-ethical standards, and that participation of other future centres can be realised using the existing procedures of the WMO. Because of this design, all participating patients sign two informed consent forms – one for the biobank and one for the PARIS study (see appendix 1-6 for English versions of the forms). By consenting to the AAA bank and signing its consent form, patients not only consent to the collection and storage of their biomaterials and data, but also to future analyses of it for research about AAA. Any significant modification to the protocol which may impact patient safety, or the conduct, design or analysis of the study requires formal amendment to the protocol. These will need to be approved by the Medical Ethics Board and the Biobank ethics Board of Amsterdam UMC (University of Amsterdam).

To accommodate patients with different views on data collection, participants can refuse collection of DNA and the sharing of their data with foreign and/or commercial parties. All collected data and biomaterials will be stored for a maximum of 50 years. When a

Table 4. The PARIS study, the first proposed study that will be facilitated by the AAA bank

Aims	The aims of the PARIS study are the following: 1) to determine the association between AAA progression (growth or rupture) and the evolution of serum levels of both proteases and cytokines, 2) to determine the association between overall survival and the evolution of serum levels of proteases and cytokines, 3) to determine the association between serum levels of proteases and cytokines and level of proteases and cytokines in AAA tissue, and finally 4) to determine the incidence of, and characterise the type of complications after AAA repair.
Outcomes	The primary endpoints of the PARIS study are: AAA growth, AAA rupture, all-cause mortality, serum levels of cytokines and proteases, and cytokine and protease levels in AAA tissue. Secondary outcomes are the incidence and type of complications after AAA repair.
Sample Size	Because of the multifactorial aspect of AAA progression, we calculated a sample size that will be sufficient for detecting weak correlations between cytokine and protease levels and AAA growth. To detect a correlation coefficient of 0.16 with a power of 80%, and a significance level of .05, a sample size of 750 participants is required. Strategies to achieve sufficient participant enrolment include simple eligibility criteria, and the expressed intention to extend the number of participating centres.
Statistical analysis	The association between AAA growth and the evolution of serum levels of proteases and cytokines will be tested with a multivariate mixed-effects model. For the association between AAA rupture and the evolution of serum levels of proteases and cytokines, a conditional dynamic prediction model with landmarking will be used.

participant decides to withdraw from the AAA bank, all stored biomaterials and data will be destroyed or deleted. When reasonably possible, this is also done with materials that are sent out for a specific study.

Scientific board for future studies

Collected data and biomaterials of the AAA bank can only be used for future studies that fall within the scope of the scientific aims of the AAA bank, and that are approved by the scientific board. Researchers can submit a study proposal with the scientific board of the AAA bank. This board oversees all requests for data and consists of five members, with a minimum of one biostatistician (A.H. Zwinderman, Amsterdam UMC, University of Amsterdam, Department of Clinical Epidemiology) and either a legal expert or ethicist (provided by the String of Pearls Institute) among its members. The other three members are currently vascular surgeons from the initiating UMCs (DAL, WW, JFH). If a study proposal is approved by the scientific board, subsequent medical-ethical approval will be acquired if required by Dutch law or local guidelines. All study proposal require an agreed upon authorship policy prior to submitting a request for data. Furthermore, data is only released in accordance with standard PSI procedures.

Results of individual studies will be published in peer-reviewed scientific journals and will be presented at international conferences.

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