Cost-effectiveness of MIS²ACE for thoracoabdominal aneurysm repair: protocol for health economic analysis of the PAPAARTIS clinical study

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Background and objectives

The PAPAartis trial was established to test the hypothesis that MIS²ACE can greatly reduce the incidence of ischaemic spinal cord injury (SCI) and mortality compared to standard open surgical or endovascular thoracoabdominal aneurysm repair alone for adult patients requiring thoracoabdominal aortic aneurysm repair (TAAA), Crawford type II or III(1). The health economic analysis will compare mean costs and QALY outcomes of MIS²ACE versus standard procedures.

Literature reviews

A systematic literature review was undertaken in October 2019 to identify publications including cost analyses or health economic analyses of procedures for repair of complex abdominal aortic aneurysms(2). The purpose of the review was to develop a framework for the health economic analyses and identify modelling approaches. 4 studies were identified. Populations and treatments were heterogeneous. One was a protocol paper without results, one was a Markov model, one was a decision tree and one was a within trial analysis (Table 1). The time horizon varied from 30 days to lifetime.

Table 1. Characteristics of the included studies (reproduced from (2))

Authors, price year	Country	Population	Treatment compared	Discount rate (%)	Model used	Time Horizon	Effectivness measure
Ciani 2017	UK	CAAA	f EI vs SI	Yes	Markov	10 years	QALY
Michel 2015	France	JRAAA or TAAAs	f/b EI vs SI	No	n/a	30 days	Clinical outcomes
Armstrong 2014	UK	JRAAAs or TAAAs	f/b EI vs SI y f EI vs M	n/a	n/a	n/a	n/a
Vaislic 2009	USA	Type II & III TAAAs	EI vs SI	No	Decision tree	30 day, 1yr and lifetime	Clinical outcomes

CAAA = Complex abdominal aortic aneurysm. TAAAs = Thoracoabdominal aortic aneurysms. JRAAAs = Juxtarenal abdominal aortic aneurysms. f / b EI = Fenestrated / branched endovascular intervention. EI = Endovascular intervention. SI = Open surgical intervention. QALY = Quality-adjusted life year. M medical treatment only. IC = incremental cost. N/a reported a protocol for a study but no results

In terms of clinical outcomes, all studies reported 30 day mortality. 2 studies considered spinal cord injury outcomes, one included the risk of permanent kidney damage and hemodialysis, and one study considered the risk of re-interventions beyond 30 days (Table 2).

Table 2. Clinical outcomes and complications reported (reproduced from (2))

	Cianí et al.		Michel et al.		Vaisilic et al.	
	EI	SI	EI	SI	EI	SI
30 day mortality	2.6%	14%	6.7%	5.4%	7.9%	14.9%
1 yr mortality	n/a		n/a		31.6%	21.5%
Paraplegia or SCI	n/a		4.1%	1%	10.5%	15.7%
Permanent Hemodialysis	n/a		5.6%	17.2%	n/a	
<30 day re-interventions	7%	3%	9.1%	5.6%	n/a	
>30 day re-interventions	0.088/py	0	n/a		n/a	

EI = Endovascular intervention. SI = Surgical intervention. n/a = not reported. Py person year. Armstrong does not report any clinical complications in his study. SCI = Spinal cord injury.

3 of the 4 studies reported resource use in natural units (as well as in monetary values), as recommended by methods guidelines (3) (Table 3). All these 3 studies reported intensive care and hospital stay. 2 reported operating time and blood units, and one reported radioscopy time and use of contrast. One reported transfer to a rehabilitation centre after the hospital stay.

Table 3. Hospital resources consumed, units (reproduced from (2))

	Michel et al.		Cianí et al.		Armstrong et al.	
	SI	EI	EI	SI	EI	SI
ICU stays (days)	4	3.6	2.53	3.41	3.6	18.3
Operating time (min)			289.72	251	278	120
Duration of hospital stay (days)	16.2	13.9	5.17	10	7	14
Blood products, ml			360	1463	370	3436
Radioscopy (min)					71	
Contrast (ml)					222	
Transfer to rehabilitation	15.4%	5%				

ICU=intensive care units. Vaislic et al. does not report an estimate of the resources consumed. n/a = not reported

One study estimated the lifetime costs of spinal cord injury as $463,116 for the first year and $61,550 for each year subsequently. However, this estimate was based on data from a single US centre. This may not be generalizable to European settings, and the paper did not estimate the HRQOL of patients.

To address these questions, a second systematic literature review was undertaken to quantify the impact of SCI on health related quality of life and costs. 67 studies were included(4). Although there was considerable heterogeneity in terms of setting, perspective, study design and severity of disability, some general conclusions could be draw. The estimated lifetime expenditure per individual with SCI ranged from $0.5 million to $2.0 million, with greater costs associated with earlier age at injury, neurological level, United States healthcare setting, and the inclusion of non-healthcare items in the study. HRQOL is negatively associated with neurological level of injury, particularly on mobility and physical dimensions. However, some studies indicate that mental health scores do not tend to be lower for people with more severe neurological injury. Furthermore, longitudinal studies show that most dimensions of QoL appear to improve over time, at least over the first year since the injury.

Unit costs

Unit costs were requested from a survey of the participating centres in April and May 2022. The centre in Germany was able to provide detail about costs of tests (MRI, CT) and consumable items (coils, stent grafts etc.) but information about staff unit costs was considered confidential. The centre in Poland was able to give estimates of the cost of consumables and staff (Table 4). The data obtained from the survey were compared, where available, with national unit costs collected by NHS England (2021-22) and the Personal and Social Services Research Unit (PSSRU) in 2021. The unit costs for most consumable items in Poland and Germany seem to be within same range. The exception is the cost of an endovascular stent used in the aneurysm repair, which the German centre estimates may reach 80000€, depending on the complexity of the device. D'Oria et al. found the median cost of the stent graft and other central supplies to be $17272 (interquartile range 8683-27931)(5). The cost of outpatient visit appears considerably greater in England than Germany or Poland. This may be because the unit costs for England can include office-based procedures. The cost per hour of medical professionals appears considerably greater in England. This may be because the data for England impute the cost of non-patient facing time (administration, training, management etc.) into the estimate. These differences in the estimates of unit costs will be considered in sensitivity analyses.

Table 4. Cost per item from the survey of centres, compared with published unit costs for England.

Items	Silesian Center for Heart Diseases in Zabrze, Poland, euros 2022	University Leipzig, euros 2022	NHS England 2021-22 reference costs, and PSSRU unit costs 2021, £
Outpatient visit	40	50	107-554 for a cardiothoracic OP visit, depending if first or follow up attendance and grade of physician.
Angio CT of arteries	160-161	120	40 – 293, depending on duration and use of contrast
Angio MRI of aorta	315		95-346 depending on number of areas and use of contrast
Cost per hour of staff			
Surgeon	28		31-123 depending on grade
Radiographer	33-44		37-147 depending on grade
Anaesthetist	33-44		31-123 depending on grade
MISACE items			
Coils	100	10 - 250	
Aneurysm repair items			
Wire	120		
Sheath	87		
Microcatheter	305		
Catheter	20		
Coil pusher	110		
Endovascular stent graft	7395	10000-80000	
Blood product pack	50		
Operating room per minute	5.84		
Cost per day in normal hospital bed	448		

Cost per day in intensive care	886		
Open repair graft	100-500		

Within study economic analysis

The base-case health economic analysis will be a within-study cost-utility analysis. The analysis will take a one year time horizon.

The clinical study is collecting EQ-5D at baseline and 1 year, time in surgery, intensive care and hospital, resource use for staff and consumables during the procedures and during the hospital stay, impact on kidney function, and use of rehabilitation and other healthcare after discharge from hospital.

Missing data

A common methodological problem in within-trial cost effectiveness analyses is missing data. Costs for each patient are "composite" variables, that is, they are the unit-cost weighted sum of several resource use items, collected at different time points. If even one of these items is missing in a patient's record, the total cost for that patient cannot be computed. A similar problem can occur for the calculation of QALYs, which are composite variables calculated as the "area under the curve" of HRQOL observations taken at different time points. Hence we conducted a methodological review of methods for handling missing data in within-trial economic evaluations, and developed code in STATA and R to implement those methods in the PAPAartis study. The study found that multiple imputation with predictive mean matching was likely to offer a flexible and robust approach (6), though results are sensitive to the method chosen and so sensitivity analyses should be conducted using alternative methods.

Unit costs

Unit costs will be informed by the survey of centres, published studies(4,5,7,8), national unit cost tariffs and unit cost databases(9). For patients requiring haemodialysis, Lorenzo et al (2010)(7) estimated a detailed bottom-up microcosting study, and found that the mean cost per patient per year in Spain was 43234€ (SD 13932), of which 51% were the sessions, 27% medicines, 17% hospitalizations, 3% transport, and 2% ambulatory visits. Shukri et al (2022) found similar results in Germany: the mean cost of HD was 47501€ and the mean cost of PD was 46235€ (excluding transportation costs).

Study population

The population will concur with the full analysis set as stipulated in the Statistical Analysis Plan(1)

Setting & location

The PAPAartis study includes centres from several European countries with a focus on Germany (n=10), but also including one from each of Austria, France, Italy, the Netherlands, Poland, Sweden, Switzerland and the United Kingdom. The base case analysis will apply HRQOL tariffs for Germany(10).

Use of real world data alongside randomised data

The task envisaged the use of non-randomised registry data (European Registry of Endovascular Aortic Repair Complications, EuREC) to compare MIS2ACE versus standard care using non-randomised data. This task was originally planned because relatively few patients were anticipated as available to be recruited within the Randomised Controlled Trial, and the aim of the task was to take advantage of the registry data to complement the results emerging from the RCT.

However, shortly after beginning the PAPAartis project, and after commencing detailed discussions with the principal investigator of the registry (Professor Martin Czerny) it became clear that the EuREC was unsuitable for the task originally planned. There were not sufficient variables collected in the Registry study to enable identification of Type II or III Crawford aneurysms, and hence identification of suitable controls in the registry data would be impossible.

At the same time, the PAPAartis investigators were successful in a bid to the German Research Foundation (DFG) to incorporate several more German and Austrian sites into the project, increasing the sample size and including patients with Type I, II and III aneurysm.

Hence it was decided by the PAPAartis investigators that the Registry data would not be necessary, as a reasonably large sample size would be available from the combined H2020 and DFG sites and the combined data would include Type I, II and III aneurysms. As the analysis of these additional DFG sites was not originally envisaged or funded in the health economics, it was decided to request that the EU resources originally envisaged in WP3 for the analysis of Registry data be used instead for the analysis of the additional patient data emerging from the DFG sites. By making this amendment, we achieve the same aims as in the GA (health economic analysis of a greater number of patients with a wider range of clinical indications) with the same person-month resources.

Interventions and Comparators

The intervention is MIS²ACE, followed by open repair or endovascular repair according to the clinician´s choice. The standard procedures are open repair or endovascular repair according to the clinician´s choice, without MIS²ACE.

Perspective

The primary perspective is that of national health care services. A sensitivity analysis will include indirect costs, including productivity losses from paid work, time lost from usual activities, paid and unpaid assistance with usual activities. Time lost from paid work will be costed using the human capital approach, based on the occupation of the patient. Time lost from other usual activities (including for retired and economically inactive individuals) will be costed at the average hourly salary for all employees. Paid and unpaid assistance with usual activities will be costed at the average hourly rate for a professional carer at home.

Outcomes

Health outcome will be measured by quality adjusted life years, QALY.

Dates of estimation, currency, conversion

The price year will be 2022. Currency will be converted from local currency to euros at purchasing power parity(11).

Uncertainty

Scenario analyses will be used to estimate the costs and QALY in the one-year time horizon using estimates of EQ-5D tariffs from other countries and a range of unit costs. Different methods for handling missing data will be used. Bootstrapping will be used to estimate confidence intervals for incremental cost and QALY and cost-effectiveness acceptability curves (CEAC).

Lifetime cost-utility analysis

As a secondary analysis, a state transition model will be constructed. This model will consist of a preliminary decision tree to allocate patients into four health states at one year: no complications, permanent hemodialysis, permanent SCI, or dead. Extrapolation beyond one year will then be conducted using the Markov model, assuming that the only transitions will be from the 3 alive states to dead. Discounting will be applied at 3% per year for costs and QALYs.

Using the model, expected survival (given age and gender), cumulative mean costs over that lifetime, and mean QALY (that is, quality adjusted mean survival) will be estimated for each arm in the study.

Likewise, mean lifetime costs, expected survival and HRQOL will be estimated for patients requiring hemodialysis. The rates of mortality, annual costs and HRQOL weights will be based on the literature (7,8).

Individuals with no SCI or permanent hemodialysis will be assumed to have normal rates of mortality and HRQOL for a man or woman of that age (based on population health surveys and official life tables) and no further TAAA-related healthcare costs, other than routine monitoring.

For the lifetime cost-utility analysis, univariate deterministic sensitivity analysis will be conducted by varying key parameters across plausible upper and lower limits. Monte-Carlo simulation will be used to estimate the cost-effectiveness acceptability curve.

Engagement by patients and clinicians

The PAPAartis study included a qualitative study of patient perceptions of the procedures and the quality of care(12). This work underlined the importance to patients of avoiding spinal cord injury and becoming a burden on families. The study also found that family support and the socioeconomic condition of the patient influenced the recovery process after surgery. These findings may justify a secondary analysis that considers societal impacts.

Reporting

Reporting will be conducted according to methodological guidelines(3).

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