Advanced Therapy Treatment Centres

Midlands-Wales Advanced Therapy Treatment Centre

Technoleg Iechyd Cymru
Health Technology Wales

Evaluating the natural disease progression and costs of peripheral limb disease (PAD) for patients with diabetes in the context of a revascularisation treatment.

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INDUSTRIAL STRATEGY

UK Research and Innovation

Coordinated by CATAPULT Cell and Gene Therapy

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Background and objectives

Peripheral arterial disease

Peripheral arterial disease (PAD) is a common condition caused by a narrowing of arteries carrying blood to parts of the body (Conte & Vale 2018). PAD is a form of peripheral vascular disease. The symptoms of PAD include muscular cramping and pain in the legs due to the decreased blood flow. Decreased blood flow to extremities can cause progressive harm, which extends beyond muscle pain. Diabetes is a significant risk factor for PAD (Vrsalovic et al 2017). The chronic nature of PAD means that studies assessing the natural progression require a long follow-up.

Advanced therapy medicinal product

Advanced therapy medicinal products (ATMPs) are medicines for human use that use genes, tissues, or cells. An autologous bone marrow-derived mononuclear cell revascularisation approach is being compared with standard care. The indication for this ATMP treatment is for critical limb ischemia in patients with diabetes unsuitable for endovascular or surgical revascularisation. Advanced therapy medicinal products represent challenges for health economic evaluation due to the possibility of transformative health outcomes. Lloyd-Williams & Hughes (2021) illustrate the general health economic considerations associated with ATMPs in their recent systematic review. The review highlights the uncertainty arising from long-term outcomes, the relative lack of certainty in health state utilities and the extensive use of assumption-based modelling approaches.

Comparative analysis

This assessment looks to analysis the impact of an ATMP revascularisation approach, the health economic comparison includes many of the limitations discussed above. The analytical approach taken is designed to minimise the issues associated with analysis of ATMPs. The analysis builds on the outcomes of a recent ATMP revascularisation clinical trial, which reported PAD status but lacked a long-term follow-up. To assess the long-term implications of ATMP revascularisation the natural disease progression is mapped onto the short-term trial outcomes along with resource use levels. The natural disease progression is estimated from routine data housed by the Secure anonymised information linkage (SAIL) database. Understanding the likely sustained impact, the short-term trial outcomes would have in the long term helps to minimise the common ATMP uncertainty of long-term effect. Estimating the costs associated with routine treatment using a large cohort helps to reduce the uncertainty in the model-based assessment.

Data

The evaluation approach taken within this report utilises routine data to maximise the duration of assessment. The Wales based Secure Anonymised Information Linkage (SAIL) databank offers anonymised person-based data for research purposes. The SAIL databank includes a wide range of linked data, which can offer an unparalleled insight into NHS patient data.

Markov model comparison

The focus of this analysis is that of the cost-utility analysis of an ATMP revascularisation treatment. A Markov model has been created to estimate the long-term impact of improvements to the PAD status of patients. The inclusion of real-world data from the SAIL databank can improve the accuracy of the long-term comparative assessment.

Objectives

The objective of this analysis is to assess the cost effectiveness of the ATMP revascularisation treatment versus standard care in patients with peripheral arterial disease and diabetes unsuitable for endovascular or surgical revascularisation. The analysis consists of two distinct components, firstly the natural disease progression of PAD/CLI and secondly the Markov model estimation. The outcomes from the natural disease progression are used to inform the transition probabilities within the Markov model.

Methods

SAIL

The Secure Anonymised Information Linkage (SAIL) database offers datasets of linked and anonymised data. The use of linked datasets allows for a detailed estimation of the natural disease progression. This analysis utilises four separate healthcare datasets and links patients using their unique patient identifier. The datasets have been selected as the combination of sets offer as much detail as can be achieved using the SAIL repository. The four datasets are the Annual District Death Extract, the Patient Episode Database for Wales, the Welsh Demographic Service Dataset, and the Welsh Longitudinal General Practice dataset.

Annual District Death Extract (ADDE) this data resource offers the date of death and the primary cause of death. This analysis utilises the date of death figure for the survival analysis and estimation of transition probabilities. Due to the nature of the condition, transition to death is not limited to reports where PAD or CLI are reported.

Patient Episode Database for Wales (PEDW) records all episodes of inpatient and day case activity within NHS Wales hospitals. In addition to the hospital episodes dates PEDW offers patient demographics and ethnicity. The episodes data includes diagnosis coding, admission details, consultant episode, spell, provider, super spell, and healthcare resource (HRG) group coding.

Welsh Demographic Service Dataset (WDSD) reports on demographics, dates or residence and registration within Wales and includes practise history and location. The final dataset used is the Welsh Longitudinal General Practice dataset (WLGP) which includes diagnosis, demographics, and prescriptions.

Inclusion criteria

The target study population is patients accessing Welsh NHS services who have PAD and diabetes. The inclusion criteria aim to capture this range of individuals from the routine datasets. The inclusion criteria are as follow:

1. Appearance of at least one of the specification ICD-10 codes in the Patient Episode Dataset for Wales (PEDW) or Welsh Longitudinal General Practice dataset (WLGP).
2. All residence in Wales and all admissions / attendances of non-Welsh residents to Welsh facilities.
3. Time period will be January 2000 (or relevant start date for data commencing after 2000) to December 31st 2018.
4. All genders
5. All ages (Patients under the age of 18 are not included).
6. Reported as having diabetes at entry to the dataset.

A list of the complete inclusion codes is included in the appendix. Diabetes type, whether type 1 or two 2 is not routinely collected, the cohort is a pooled sample.

The collected data includes information about the individual, such a week of birth, gender, initial drug treatments, diabetes status, and death. Week of birth is used to calculate age. These characteristics are used in the following statistics analysis to account for strong covariates in terms of their impact on PAD/CLI progression. Patients enter the dataset at the first identification of inclusion criteria and are followed for as long as the data coverage allows, this is a maximum of 19 years.

The duration an individual is considered within the dataset is dependent on the final observation across the linked data. An individual that enters the dataset is observed transitions through states but does not die or reach the end of the dataset is considered censored. Right censoring occurs when there is a loss to follow-up, this may be due to relocation or no subsequent healthcare contact. Due to the data coverage limits, individuals reaching 2019 are considered censored. Routine data points which are not indicative of an alternative Rutherford category to the current category are used to populate the timeline so that stable disease conditions can be observed. The exit point, or final data point for any individual will be either mortality or censoring, all reasons for censoring are treated equally.

Rutherford scale

To understand the natural disease progression of PAD and CLI using routine data there needs to be a staging system. The Rutherford scale offers a staging categorisation, which ranges from stage 0 asymptomatic to stage 6 severe ischemic ulcers or frank gangrene. An alternative scale, which could have been adopted, is that of the Fontain classification, the Rutherford scale (Rutherford & Becker 1991) was chosen due to the additional granularity offered by the extra stages it characterises. Rutherford categories, descriptions and PAD stages are illustrated in table 1.

Table 1: Clinical stages

PAD Stage	Rutherford category	Clinical description
0	0	Asymptomatic
I	1	Mild claudication
I	2	Moderate claudication
I	3	Severe claudication
I I	4	Ischemic rest pain
I I I	5	Minor tissue loss
I I I	6	Major tissue loss

Rutherford scale is not routinely recorded in clinical data, to categorise individuals as experiencing a specific Rutherford level meant that a characterisation approach was adopted. A maximal severity approach is taken for appointing patients to Rutherford categories. An individual may report a range of conditions, the highest state is dominant. Delineating between Rutherford 1-3 is particularly problematic with routine data, Rutherford 1, 2, and 3 are commonly grouped together, this is the approach taken here. The categories populated by the data are reported in table 2. Individuals experiencing Rutherford 1-3 can improve to the asymptomatic stage. Rutherford categories are assumed purely progressive once an individual has progressed to Rutherford 4 (Ischemic rest pain).

Table 2: Rutherford characteristics

Rutherford category	Clinical characterisation coding	Transition rules
0	Asymptomatic	Only reached via 1-3
1-3	Inclusion criteria only	Movement to any state
4	Mention of rest pain	Progressive
5	Mention of ulcer	Progressive
6	Mention of Gangrene	Progressive

A full list of the coding uses to populate each Rutherford category is included in the appendix.

Continuous prescriptions

One limitation of using routinely collected data is that improvements in a condition are hard to identify as they are often associated with the absence of a healthcare resource use. To incorporate improvement from Rutherford state 1-3 to the asymptomatic state a continuous prescription approach is adopted. Prescription data is used to identify periods of continuous prescription, following the initial diagnosis, which indicate the patient is experiencing sustained needs. A move to the asymptomatic state is assumed when the patient had no prescription events for a duration of 60 days. The continuous prescription duration may include multiple different drugs. A transition from state 1-3 to state 0 occurs at day 61 following the last prescription in that specific chain. This approach may suffer from underestimation of treatment, and therefore an overestimation of movement to the asymptomatic state where patients move to the use of over-the-counter drugs.

Resource use

The analysis takes on a limited NHS costing perspective and reports costs in 2020 (GBP). The NHs perspective is limited to the routine data sources included and captures events deemed to be associated with PAD, broader healthcare resource costs are not included.

The continuous prescription approach uses the prescription data to characterise individuals as experiencing either Rutherford 1-3 or the asymptomatic Rutherford 0. The prescription reporting does not differentiate GP contacts from repeat prescriptions. To estimate the resource use associated with prescription events a 'per prescription' costs is calculated.

Each prescription record incurs a cost, which is a combination of the GP consultation, the net ingredient cost, and the dispensing cost. The 2020 PSSRU estimates that the average number of prescriptions (calculated by the number of prescriptions per GP by the number of consultations per GP) is 4.25 (Curtis & Burns, 2020). This approach allows us to apply one GP consultation cost for every 4.25 prescription records. A GP consultation costs £39, therefore the contribution cost per prescription equates to £39/4.25 or £9.18. The 2019 net ingredient cost per prescription reported by the NHS prescribing statistics published by the to be £7.14 (this is a CPI adjustment from 2019 to 2020 levels). The dispensing cost associated with a single pharmaceutical activity is £1.27 (Pharmaceutical services negotiating committee, 2021). The total cost per reported prescription is £17.59.

HRG codes

To apply a cost to the hospital-based interventions the healthcare resource group (HRG) is matched with the appropriate cost. HRG codes consist of five characters, two letters followed by two numbers and a final letter. The first two letters refer to the chapter and sub-chapter, respectively. The specific intervention within the sub-chapter is shown by the two numbers. The final letter is known as a 'split', this signifies a level of severity within the HRG which could be complications, duration, ages, or a combination of factors.

The combination of treatment codes whilst in hospital help to build the final HRG c ode. Duration bands or 'trim points' are employed for treatments which require a prolonged hospital stay. Each inpatient HRG will have an expected duration, additional resources are estimated to be consumed where a patient's spell in hospital exceeds this trim point. Longer stays, higher levels of complication and more severe co-morbidities all contribute to the cost or 'tariff' applied to the HRG.

The tariff which is applied to each HRG is based on the average cost reported by hospitals in England for that procedure each year. The application of the HRG tariff to Wales based hospital activity can cause issues where the HRG clinical coding does not perfectly match, however, in this analysis there were no instances of unmatched HRGs. The HRG code applies the tariff to the hospital spell, this is year specific and therefore the costs have been CPI adjusted to reflect 2020 (GBP) using the bank of England CPI inflator. The approach of contemporary tariff application followed by inflation adjustment is preferred over an approach of applying the 2020 HRG tariff to all procedures due to the shift in process and practise of interventions.

Markov model

A Markov model is a stochastic modelling approach, which describes the sequence of possible event and the probability of each event depending only on the state attained in the previous event. Here a Markov model is used to estimate the natural disease progression of PAD. The comparative aspect of the analysis is derived from a short-term randomised control trial, which observes the restorative effect offered by a revascularisation intervention in terms of the resulting Rutherford category. A Markov model, which demonstrates the progression of PAD and CLI according to the entry Rutherford category, is used to estimate the outcomes experienced by the patient groups identified by the limited follow-up trial. The a priori assumption being that an intervention that reduces the entry Rutherford category level of the patients will result in improved long-term outcomes.

The Markov model takes a monthly cycle length with transition probabilities and monthly cycle costs specific to each state. The cycle length was chosen to reflect the possible speed of transition observed between Rutherford categories, amputation, and death. The range of states reflect the Rutherford categories and the two additional observed outcomes, namely, amputation and death. The starting age of the Markov cohort was 65 years. The Markov time horizon is a 35-year duration which is used to effectively cover a lifetime model. To accurately represent the clinically observed transitions within PAD and CLI the condition is treated as progressive once the ind ividual reaches Rutherford stage 4, death is an absorbing state. The Markov states and possible transitions are reported in table 3. The left column shows the initial cycle state, the row header shows the subsequent state. the Rutherford category is notated 'R x' within the table. Remaining in a state is a possible cycle outcome. Individual residing in the Asymptomatic, or 'Rutherford 0' state are not restricted from transitioning to having an Amputation or to death, however, these transitions were not observed within the data.

Table 3: Transition matrix

State End / Starting	Asymptomatic	R 1-3	R 4	R 5	R 6	Amputation	Death
Asymptomatic		A	B	C	D		
R 1-3	E		F	G	H	I	J
R 4				K	L	M	N
R 5					O	P	Q
R 6						R	S
Amputation							T

States and transitions are defined according to the routine data, event data matched to the Rutherford characteristics identifies the state a patient resides in at a given time. Transitions occur when routine data triggers a shift to an alternative state. figure X shows the possible states and transitions, each observed transition represents an individual survival function. The competing risk aspect of the disease, for example Rutherford 4 to Rutherford 5 vs. Rutherford 4 to Rutherford 6 is inherent in each survival equation given the limitation that each individual in a state can only transition from that state to one other state.

Quality of life (QoL) is included into the Markov model using a literature-based assessment of QoL for each state. estimates for QoL for each state are used to assess the overall quality adjusted life years (QALYs) achieved for each intervention approach. QALYs are discounted at a rate of 3.5% annually.

Health economics

The health economic analysis within this study focuses on defining the monthly Markov state specific resource use cost. The HRG code tariff cost and the prescription costs are combined to offer a total cost each individual incurs whilst in a particular state. As events are associated with state categorisation, the cost of an event, which moves the individual to a new state, such as amputation, is applied to the new state. The total resource costs observed for patients in a particular state is divided by the cumulative months those individuals resided within that state. An average monthly cost can be calculated by dividing the total cost by the exposure duration. The asymptomatic state incurs no resource use costs. In addition to the monthly state specific costs, there is an initial treatment cost of £11,680 associated with the cost of the product as well as extraction and infusion costs. Costs are discounted at a rate of 3.5% per year.

Survival Analysis

The Markov model is estimated using the twenty observed transitions (A-T) illustrated in figure X. Each transition needs to be populated by a monthly baseline hazard. The baseline monthly hazard is the percentage of individuals within a state which transition to the next state in a monthly cycle. The statistical analysis is undertaken using STATA 17[1]. The stset and streg commands are used to set and fit the data to survival functions. To adjust the risk models, from data based on days, to the monthly cycle, the scale was set to 30.42 which is the average days in a month. A maximum likelihood estimation approach is used for this parametric survival time model. The poisson distribution is selected as it offers a time invariant average transition and allows for accounting for covariates. Given the progressive nature of PAD/CLI most models as estimated as single failure. Where transitions are observed multiple times for single individual, for example: between asymptomatic and Rutherford 1-3, the analysis will be clustered by patient, this approach helps to account for individual heterogeneity. To account for variation in population of interest in the Markov model the survival modelling includes estimates for age and gender. Initial testing ide ntified age as having a non-linear influence on risk of transition and is therefore estimated using age bands. The age bands deployed reflect commonly used 10-year segments with the extreme end of the age distribution pooled to offer an under 30 and over 80 group.

The Markov model assumes homogeneity within states; therefore, the transition probabilities are an average of the survival duration observed. Due to this limitation, the modelling cannot account for a dynamic risk estimate such as that offered by the Gompetz distribution. Survival modelling estimates the baseline risk for the omitted group, in this case Males aged between 60 and 69. The hazard ratios reported for alternative age bands and for the binary gender covariate can be used to calculate an age-sex adjusted transition probability. In this analysis the age bands and gender identifier are matched to the Markov model cohort.

Descriptive statistics

The cohort consists of 7,417 individuals with an average of 5.1 transitions each. The average ago of the cohort is 68.9 years. There are 2,460 (33%) females and 4,957 males (66%). The baseline reports on medication usage and the 'have you ever smoked status' is reported in table 4. The age bands of the cohort are reported in table 5.

Table 4: Baseline medication

Regimen	Number of individuals (percentage of cohort)
Aspirin	5,135 (69%)
Ace inhibitors	5,094 (69%)
Clopidogrel	1,284 (17%)
Ever smoked	6,257 (84%)

[1] https://www.stata.com/

Table 5: Age band coverage at entry to cohort

Age band	Number of individuals (percentage of cohort)
Less than 40	76 (1%)
40 to 49	293 (4%)
50 to 59	1,177 (16%)
60 to 69	2,188 (29%)
70 to 79	2,491 (34%)
80 to 89	1,093 (15%)
90 plus	99 (1%)

Transition coverage

There are twenty separate transitions to modelled in this analysis. Each survival model is estimated using the Poisson distribution, a baseline hazard is reported alongside hazard ratios for each age band in comparison to the omitted group (aged 60 -69), male is the omitted gender. The cohort of 7,417 individuals transitions through Rutherford states to populate each observed transition. Due to general data protection regulations, transitions with fewer than 5 observed instances are reported as redacted numbers. Transitions with higher population offer a richer amount of data with which to estimate the survival function, conversely, where there are scant levels of observed transitions, there will be data to accurately fit the models. The impact of transitions where there is little evidence is somewhat minimised due to the low likelihood of failure to that state. Table 6 illustrates the population of each observed transition.

Table 6: Population by transition

State End Starting	Asymptomatic	R 1-3	R 4	R 5	R 6	Amputation	Death
Asymptomatic	0	14,186	7	Redacted	Redacted	0	0
R 1-3	14,195	1,975	1,592	597	74	360	2,332
R 4	0	0	702	141	19	69	640
R 5	0	0	0	174	8	110	436
R 6	0	0	0	0	46	88	148
Amputation	0	0	0	0	0	156	477

The majority of transitions occurred for the lower severity groups, namely Rutherford zero and Rutherford 1-3. The Rutherford zero state saw nearly all transitions back to Rutherford 1-3, this represents an individual stopping medication to move to the asymptomatic group after the 60 day continuous prescription rule and then subsequently experiencing symptoms and receiving treatment. The continuous prescription rule in combination with routine data has resulted in no patients remaining within the asymptomatic group, this is because the observed data will censor the individual if they have not had a subsequent resource use as opposed to the scenario where an individual is asymptomatic until the end of the observed data period. The transition population trend is that higher severity states are less populated. A greater percentage of higher severity states progress to amputation and death.

Results

Survival analysis

Baseline hazard

The Poisson distribution survival models each include age bands and a gender variable. The results tables are reported according to the covariate of interest in the same 20 transition table as previously shown. Table 7 reports the baseline hazard function, which is the constant in the s urvival model. The baseline hazard is the risk of transitioning from the initial state row to the column header ending state during a month cycle.

Table 7: Transition probabilities

State End Starting	Asymp-tomatic	R 1-3	R 4	R 5	R 6	Amputa-tion	Death
Asymptomatic		0.492862	0.000869	1.17E-26	1.03E-26		
R 1-3	0.037658		0.003146	0.001295	0.000422	0.001506	0.005199
R 4				0.001662	0.000424	0.001765	0.007724
R 5					0.000411	0.007242	0.013459
R 6						0.011645	0.010977
Amputation							0.018844

Table X shows that the most likely transition occurs between individuals starting in the asymptomatic Rutherford zero state and moving to Rutherford 1-3. There is a 49.3% chance of base transition between these states for a single month cycle. Given the broadly progressive status of PAD/CLI post Rutherford four it is not surprising to observe states where individuals can move backwards and forwards as being the most populated and fasted moving. The clinical narrative for this transition is that an individual entered the cohort and is deemed to have PAD, subsequently briefly stops receiving medication and then restarts medication which results in a move back to Rutherford 1-3.

The risk of transitioning from the Asymptomatic state to either Rutherford five or six is so low that the figures are reported as exponents. The risk of transitioning to the more severe states increases as the initial state is more severe, this approach reflects the distributions observed by the transition coverage in table X. Broadly, the risk of mortality increases as the initial Rutherford category rises, the exception to this is that the mortality observed for individuals experiencing Rutherford five is higher than those in the Rutherford six group. Amputation risk is increasing with initial Rutherford state.

Gender

Gender is coded with the omitted variable as male, the interpretation for the results in table X is that the multiplicative risk can be seen as baseline * risk ratio of gender when estimating the baseline risk for a female. The omitted characteristics of Males aged 60-69 means that they experience the baseline hazard risk * 1 * 1. All covariate risk ratios should be considered in the context of the associated baseline hazard. Figures further away from 1 represent a more extreme influence of the covariate. Table 8 shows the hazard ratios for females. Figures are reported to 2 significant figures for each covariate risk ratio.

Table 8: Female transition multipliers

State End Starting	Asymp-tomatic	R 1-3	R 4	R 5	R 6	Amputa-tion	Death
Asymptomatic		0.86	0.27	1.84E+07	2.80E+07		
R 1-3	1.05		1.21	1.05	0.55	0.68	0.85
R 4				1.11	0.73	0.68	0.9
R 5					1.18	0.73	1.06
R 6						0.64	1.03
Amputation							0.95

The risk ratios estimated for gender are relatively close to 1 for most of the highly populated transitions. Extreme risk ratios are observed for transitions which have very low population coverage and low baseline hazards. Females are more likely to improve their condition from Rutherford 1-3 to the asymptomatic state (1.05) and subsequently less likely to return to Rutherford 1-3 (0.86).

Age

Age bands can capture nonlinear relationships between age and transition. The same baseline multiplication approach can be used to estimate the risk of transition for an individual for a given age band as was explained for the gender variable. Lower (less than 1) risk ratios for younger patients would represent a slow disease progression compared to the omitted group. Table 9 illustrates the risk ratios for individuals under 40 years of age when beginning a state.

Table 9: Age related transition ratios for the individuals aged less than 40

State End Starting	Asymp-tomatic	R 1-3	R 4	R 5	R 6	Amputa-tion	Death
Asymptomatic		0.24	0.00	0.25	0.12		
R 1-3	1.44		1.54	1.89	1.96	1.66	0.62
R 4				3.71	15.58	0.00	0.58
R 5					0.00	1.59	1.44
R 6						115.98	0.00
Amputation							0.14

The reported risk ratios include instances of extreme values, close to zero and above 10. Taking the estimates for individuals starting in Rutherford category 6 we see that there is a risk ratio of 115 for transitioning to amputation and 0.00 for mortality. The interpretation of these two figures is that individuals under 40 who experience Rutherford 6 are very likely to receive an amputation but are unlikely to die beforehand. Similar to the conclusion drawn from the gender covariates, individuals are more likely to transition from Rutherford 1-3 to the asymptomatic state, and less likely to regress back.

A broad categorisation of the covariates is that there are multiple instances of extreme values, either this cohort transitions very quickly to the next state or has no instances of that transition within the dataset. These more extreme values are to be expected given the relatively small sample size for this age band.

Individuals aged between 40 and 49 represented around 4% of the entrants to the dataset. Table 10 illustrates the covariate risk ratios associated with this age band. The general overview of this group is that there is a range of extreme values, this is similar to the estimates observed for th e under 40 group. Risk ratios range from low figures up to 1.63 for Rutherford 1-3 to amputation. Broadly the rates are characterised as higher transitions from Rutherford 1-3 and lower from other states.

Table 10: Transition ratios for individuals aged 40 to 49

State Starting End	Asymptomatic	R 1-3	R 4	R 5	R 6	Amputation	Death
Asymptomatic		0.41	0.00	0.61	0.47		
R 1-3	1.19		1.36	1.18	0.96	1.63	0.57
R 4				1.19	0.00	0.40	0.53
R 5					0.00	0.38	1.06
R 6						0.54	0.32
Amputation							0.30

As the age bands increase the population coverage improves this trend continues until the 70-79 group, entrants older than 80 are less commonly observed. The 50-59 group represents 16% of the individuals at entrance to the cohort. Table 11 presents the covariate estimates for this group. The combination of increased recovery to the asymptomatic state followed by a reduction in symptom recurrence is observed for the 50- to 59-year-old group. Amputations are more likely for each starting state. The mortality rates observed in this group is lower, compared to the baseline hazard, for all initial Rutherford categories.

Table 11: Transition ratios for individuals aged 50 to 59

State Starting End	Asymptomatic	R 1-3	R 4	R 5	R 6	Amputation	Death
Asymptomatic		0.64	0.71	0.87	0.81		
R 1-3	1.05		1.19	1.09	1.22	1.18	0.64
R 4				0.84	0.99	1.72	0.55
R 5					0.70	1.35	0.62
R 6						1.71	0.86
Amputation							0.67

Collectively the age groups below the omitted 60- to 69-year-old band share some characteristics. The younger age bands experience a low level of mortality. Movement from the asymptomatic state is lower for every plausible transition option. Transitions from the Rutherford 1-3 state are broadly higher than observed in the baseline group.

The age bands which are older than the baseline hazard group are covered by three groups, the 70-79 group, the 80 – 89 and the 90+ age band. The 70-79 age band is populated by 34% of the data for individuals entering the dataset, this number can rise or fall as people age and have subsequent transitions. Table 12 reports the risk rates associated with each of the observed transitions.

Table 12: Transition ratios for individuals aged 70 to 79

State End Starting	Asymp-tomatic	R 1-3	R 4	R 5	R 6	Amputa-tion	Death
Asymptomatic		0.86	0.87	0.73	2.36E+07		
R 1-3	0.99		1.23	1.31	1.01	1.19	1.80
R 4				0.90	0.60	0.75	1.47
R 5					0.54	1.36	1.36
R 6						1.92	2.25
Amputation							1.49

The mortality risk rates for each state are greatly higher than the omitted baseline group, each risk rate is above 1. The general rates of amputation are over 1, with the exception of individuals starting in the Rutherford category 4 state. excluding mortality, the general characterisation of the risk rates is that they are close to 1, this group is relatively close to the baseline group in the progression of PAD/CLI.

The 80-89 years age band represents approximately 15% of the overall dataset. The mortality ratios indicate a marked increase in transition to the death state for the age band. The transition to more sever Rutherford states is higher in this group than estimated for the baseline risk. The level of amputation risk from Rutherford 1-3 is higher followed by a decrease for states 4 and 5. Individuals beginning the cycle in Rutherford 6 are more than 2 times more likely to transition to the amputation state. Transition ratios for individuals aged between 80 and 89 are reported in table 13.

Table 13: Transition ratios for individuals aged 80 to 89

State Starting End	Asymp-tomatic	R 1-3	R 4	R 5	R 6	Amputa-tion	Death
Asymptomatic		0.84	1.98	8.18E+07	0.41		
R 1-3	0.98		1.08	1.71	1.24	1.13	3.46
R 4				1.61	1.57	0.62	2.91
R 5					1.01	0.67	2.56
R 6						2.09	2.55
Amputation							2.82

The oldest age band included in the analysis was individual aged 90+, this group had a population of just under 100 individuals at entrance to the dataset. The risk ratio estimate for this group are offered by table 14. The risk ratios include three instances of zero risk, this reflects there being no observed transition for this group. The mortality estimates are the highest observed for any age group, the starkest ratio occurs in individuals in the Rutherford 1-3 category where the mortality ratio is over 7 times higher for this group in comparison with the base case.

Table 14: Transition ratios for individuals aged 90+

State Starting End	Asymp-tomatic	R 1-3	R 4	R 5	R 6	Amputa-tion	Death
Asymptomatic		1.48	0.00	0.31	0.17		
R 1-3	1.13		0.96	3.14	1.59	0.65	7.19
R 4				3.24	4.60	0.00	4.68
R 5					0.00	0.86	4.23
R 6						1.29	5.87
Amputation							3.04

Economic analysis

The economic analysis looks to estimate the average monthly cost for each Rutherford category. The nature of the asymptomatic group being characterised by zero resource use means that there is no resource cost associated with this group. The costing analysis is that of a disease specific limited NHS primary and secondary cost scope. The routine data disease state characterisation is driven by recorded events, for example, the continuous prescription approach means the Rutherford 1-3 will incur a high level of prescription resource use. The resource use cost for each state is reported in table 15.

Table 15: Monthly resource use cost by Rutherford scale

Rutherford Category	Monthly average costs
Asymptomatic	£0.00
Rutherford 1-3	£48.59
Rutherford 4	£50.99
Rutherford 5	£196.25
Rutherford 6	£232.83
Amputation	£391.35

The average monthly resource use costs increase as the severity of Rutherford category increases. The highest cost state is that of amputation, this state incurs the initial amputation procedure into the monthly estimates. Rutherford 4 is estimated to be associated with £50.99 per month in costs, this is only slightly higher than the PAD Rutherford 1-3 state. The small difference between these two states may be due to the characterisation approach for Rutherford 4 which includes minor procedures but doesn't require for there to be a continuous prescription as is the case for Rutherford 1-3.

Quality of life status

To assess the differences between health outcomes for PAD/CLI there needs to be an estimation of quality of life. Literature estimates reflect a worsening quality of life as Rutherford states progress, with in increase following amputation. The estimates for QoL across the Rutherford states are reported in table 16. Death is estimated as zero. There is a significant reduction in quality of life for transitioning between Rutherford 1-3 to Rutherford 4+.

Table 16: Quality of life estimates across Rutherford states

Rutherford Category	Quality of life scores
Asymptomatic	0.785
Rutherford 1-3	0.700
Rutherford 4	0.350
Rutherford 5	0.350
Rutherford 6	0.350
Amputation	0.484

Markov model

The Markov model runs for 420-month long cycles. The comparative approach between the revascularisation technique and that of standard care is based on the Rutherford category entry distribution. Following treatment with the ATMP revascularisation intervention a proportion of individuals reported a reduction in their PAD/CLI symptoms, this improvement corresponds to an overall group average reduction in Rutherford category compared with those receiving standard care. The Markov model entry distributions for both groups are reported in table 17.

Table 17: Rutherford state model entry distributions

Rutherford Category	Revascularisation ATMP	Standard care
Asymptomatic	5%	0%
Rutherford 1-3	59%	15%
Rutherford 4	16%	38%
Rutherford 5	14%	31%
Rutherford 6	0%	0%
Disability	5%	8%
Death	2%	8%

Individuals follow the Markov transition probabilities estimated in the survival analysis. The Markov model is run for an effective lifetime horizon. Quality adjusted life years are estimated for both groups with a yearly discount rate of 3.5%. Costs are discounted at 3.5%. The intervention group experienced an estimated 4.25 QALYS over the model duration with the control group accruing 2.61 QALYS. The increase in QALYS for the intervention group is therefore 1.64.

The costs for each group were estimated over the same lifetime horizon with the intervention group using £22,675 in healthcare resource costs compared to £11,215 in the comparator group. The control group, on average, experienced more progressed Rutherford states and therefore used a greater level of resources, this is partially offset by the higher mortality associated with the more advanced Rutherford states. Table 18 reports the QALYs, resource use levels and the base case incremental cost effectiveness ratio.

Table 18: Markov model outputs

	Rutherford Category	Intervention group (A)	Standard care
QALYs	4.25	2.61	1.64
Total costs	£22,675	£11,215	£11,460
ICER			£6,982 per QALY

The ICER value of £6,982 is below the commonly accepted threshold of £20,000 per QALY suggesting that the intervention is cost effective.

Conclusion

The reduction in Rutherford scale achieved by the revascularisation intervention results in an increase to the QALYs of 1.64. The total costs associated with the intervention pathway exceed that of normal care to the amount of £11,460 over the model horizon. The resulting incremental cost effectiveness ratio is estimated at £6,982 per QALY.

The ATMP intervention would be considered cost effective when assessed against the £20,000 threshold. This finding should be considered in the context of the analysis and the limitations of the adopted approach.

Discussion and limitations

Whist the ICER suggests that revascularisation is a highly cost-effective intervention there are a range of uncertainties that need to be considered when drawing conclusions. The nature of ATMPs and the long-term impact they may have favoured the approach undertaken within this analysis, however, given the brevity of the clinical trial evidence, there is a question as to the sustained impact of the intervention. Within this analysis we have assumed that individuals are homogenous within each Rutherford state, an assumption which treats the impact of the intervention as being sustained for the entire modelling horizon.

The modelling approach adopted in this assessment is in the absence of long-term clinical trial data. The routine data natural disease progression modelling is a pragmatic alternative in the absence of clinical trial data, the approach has inherent limitations. The patient population was matched according to the disease condition and Rutherford state, however, matching according to the nature of the patient being unable to undertake routine revascularisation was not possible. The Markov model adopted in this analysis restricts the transitions to a single estimate, these static transitions omit information surrounding changes to progression according to duration in state.

The use of routine data offered the ability to assess the intervention over a longer horizon than was captured by the clinical trial, routine data has general limitations that should be considered. The historic data may not reflect the current treatment received by the patient cohort. The Rutherford scale was not routinely reported. There is uncertainty as to the accuracy of the characteristic based method. There is a time accuracy issue associated with the characteristic based Rutherford scale estimation where patients only progress to the more advanced CLI states when they receive treatments associated with that state. This approach is likely to underestimate the clinical impact of PAD/CLI due to later progression.

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Appendix

Appendix 1 Clinical coding for inclusion and Rutherford identification.

Appendix 1a Codes for inclusion

Code	Code Description	Code - level
14F7.	H/O: arterial lower limb ulcer	include
24FG.	O/E left leg pulses all absent	include
C107.	Diabetes mellitus with peripheral circulatory disorder	include
C1071	Diabetes mellitus, adult, + peripheral circulatory disorder	include
C1072	Diabetes mellitus, adult with gangrene	include
C1073	IDDM with peripheral circulatory disorder	include
C1074	NIDDM with peripheral circulatory disorder	include
C107z	Diabetes mellitus NOS with peripheral circulatory disorder	include
C1088	Insulin dependent diabetes mellitus - poor control	include
C1095	Non-insulin dependent diabetes mellitus with gangrene	include
C109F	Non-insulin-dependent d m with peripheral angiopath	include
C10E6	Type 1 diabetes mellitus with gangrene	include
C10F5	Type 2 diabetes mellitus with gangrene	include
C10FF	Type 2 diabetes mellitus with peripheral angiopathy	include
G73..	Other peripheral vascular dis.	include
G731.	Thromboangiitis obliterans	include
G7310	Buerger's disease	include
G732.	Peripheral gangrene	include

Code	Code Description	Code - level
G7320	Gangrene of toe	include
G7321	Gangrene of foot	include
G733.	Ischaemic foot	include
G73y0	Diabetic peripheral angiopathy	include
G73z.	Peripheral vascular dis. NOS	include
G73z0	Intermittent claudication	include

Appendix 1a Consideration codes for inclusion (only when code from Appendix 1a 1 is also found).

Code	Code Description	Code - level
14N41	H/O: lower limb amputation	include with consideration
1M1..	Pain in lower limb	include with consideration
2G42.	O/E - Amputated right leg	include with consideration
2G43.	O/E - Amputated left leg	include with consideration
55A2.	Lower limb arteriogram abnorm.	include with consideration
7A6G8	Thrombin inject pseudoaneurysm	include with consideration
C108.	Insulin dependent diabetes mellitus	include with consideration
C1080	Insulin-dependent diabetes mellitus with renal complications	include with consideration
C1081	Insulin-dependent diabetes mellitus with ophthalmic comps	include with consideration
C1082	Insulin-dependent diabetes mellitus with neurological comps	include with consideration
C1084	Unstable insulin dependent diabetes mellitus	include with consideration
C1085	Insulin dependent diabetes mellitus with ulcer	include with consideration
C1089	Insulin dependent diabetes maturity onset	include with consideration

Code	Code Description	Code - level
C109.	Non-insulin dependent diabetes mellitus	include with consideration
C1093	Non-insulin-dependent diabetes mellitus with multiple comps	include with consideration
C1094	Non-insulin dependent diabetes mellitus with ulcer	include with consideration
C10E3	Type 1 diabetes mellitus with multiple complications	include with consideration
C10E5	Type 1 diabetes mellitus with ulcer	include with consideration
C10F3	Type 2 diabetes mellitus with multiple complications	include with consideration
C10F4	Type 2 diabetes mellitus with ulcer	include with consideration
G70..	Atherosclerosis	include with consideration
I708	Atherosclerosis of other arteries	include with consideration
I709	Generalized and unspecified atherosclerosis	include with consideration
I743	Embolism and thrombosis of arteries of lower extremities	include with consideration
I744	Embolism and thrombosis of arteries of extremities, unspecified	include with consideration
I745	Embolism and thrombosis of iliac artery	include with consideration
I748	Embolism and thrombosis of other arteries	include with consideration
I749	Embolism and thrombosis of unspecified artery	include with consideration
L890	Stage I decubitus ulcer and pressure area	include with consideration
L891	Stage II decubitus ulcer	include with consideration
L892	Stage III decubitus ulcer	include with consideration
L893	Stage IV decubitus ulcer	include with consideration
L899	Decubitus ulcer and pressure area, unspecified	include with consideration
L97X	Ulcer of lower limb, not elsewhere classified	include with consideration
M270z	Decubitus ulcer press area NOS	include with consideration
M271.	Non-pressure ulcer lower limb	include with consideration

Appendix 1c clinical categorisation codes

Code	Code Description	Code - type	Rutherford category
1DC..	pain character	READ_CD	RUTH4-PAIN
1DC1.	Burning pain	READ_CD	RUTH4-PAIN
1DC2.	Aching pain	READ_CD	RUTH4-PAIN
1DC6.	Tightening pain	READ_CD	RUTH4-PAIN
1DC8.	Generalised pain	READ_CD	RUTH4-PAIN
1DCA.	Rest pain	READ_CD	RUTH4-PAIN
1DCE.	Heavy pain	READ_CD	RUTH4-PAIN
1DCH.	Throbbing pain	READ_CD	RUTH4-PAIN
1M1..	Pain in lower limb	READ_CD	RUTH4-PAIN
1M11.	Foot pain	READ_CD	RUTH4-PAIN
1M110	Ischaemic foot pain at rest	READ_CD	RUTH4-PAIN
1M51.	Intermittent pain	READ_CD	RUTH4-PAIN
1M52.	Chronic pain	READ_CD	RUTH4-PAIN
1M	Pain	READ_CD	RUTH4-PAIN
8BAA.	pain relief	READ_CD	RUTH4-PAIN
8BAB.	pain control	READ_CD	RUTH4-PAIN
8BAO.	pain and symptom management	READ_CD	RUTH4-PAIN
8H69.	Refer to pain clinic	READ_CD	RUTH4-PAIN
8HVk.	Private referal to pain management service	READ_CD	RUTH4-PAIN
9NNh.	Under care pain manage specialist	READ_CD	RUTH4-PAIN
9b8F.	Pain management (specialty)	READ_CD	RUTH4-PAIN

Code	Code Description	Code - type	Rutherford category
N2451	Foot pain	READ_CD	RUTH4-PAIN
N2452	Pain in leg	READ_CD	RUTH4-PAIN
N2454	Calf pain	READ_CD	RUTH4-PAIN
L890	Stage I decubitus ulcer and pressure area	ICD10	RUTH5-ULCER
L891	Stage II decubitus ulcer	ICD10	RUTH5-ULCER
L892	Stage III decubitus ulcer	ICD10	RUTH5-ULCER
L893	Stage IV decubitus ulcer	ICD10	RUTH5-ULCER
L899	Decubitus ulcer and pressure area, unspecified	ICD10	RUTH5-ULCER
L97X	Ulcer of lower limb, not elsewhere classified	ICD10	RUTH5-ULCER
14F7.	H/O: arterial lower limb ulcer	READ_CD	RUTH5-ULCER
C1085	Insulin dependent diabetes mellitus with ulcer	READ_CD	RUTH5-ULCER
C1094	Non-insulin dependent diabetes mellitus with ulcer	READ_CD	RUTH5-ULCER
C10E5	Type 1 diabetes mellitus with ulcer	READ_CD	RUTH5-ULCER
C10F4	Type 2 diabetes mellitus with ulcer	READ_CD	RUTH5-ULCER
M270z	Decubitus ulcer press area NOS	READ_CD	RUTH5-ULCER
M271.	Non-pressure ulcer lower limb	READ_CD	RUTH5-ULCER
C1072	Diabetes mellitus, adult with gangrene	READ_CD	RUTH6-GANGRENE
C1095	Non-insulin dependent diabetes mellitus with gangrene	READ_CD	RUTH6-GANGRENE
C10E6	Type 1 diabetes mellitus with gangrene	READ_CD	RUTH6-GANGRENE
C10F5	Type 2 diabetes mellitus with gangrene	READ_CD	RUTH6-GANGRENE

Code	Code Description	Code - type	Rutherford category
G732.	Peripheral gangrene	READ_CD	RUTH6-GANGRENE
G7320	Gangrene of toe	READ_CD	RUTH6-GANGRENE
G7321	Gangrene of foot	READ_CD	RUTH6-GANGRENE
L890	Stage I decubitus ulcer and pressure area	ICD10	RUTH5-ULCER
L891	Stage II decubitus ulcer	ICD10	RUTH5-ULCER
L161	L16.1 Emergency bypass of aorta by anastomosis of axillary artery to femoral artery	OPCS4	Operation
L162	L16.2 Bypass of aorta by anastomosis of axillary artery to femoral artery NEC	OPCS4	Operation
L163	L16.3 Bypass of aorta by anastomosis of axillary artery to bilateral femoral arteries	OPCS4	Operation
L504	L50.4 Emergency bypass of artery of leg by anastomosis of aorta to deep femoral artery NEC	OPCS4	Operation
L506	L50.6 Emergency bypass of artery of leg by anastomosis of iliac artery to femoral artery NEC	OPCS4	Operation
L513	L51.3 Bypass of artery of leg by anastomosis of aorta to common femoral artery NEC	OPCS4	Operation
L514	L51.4 Bypass of artery of leg by anastomosis of aorta to deep femoral artery NEC	OPCS4	Operation
L516	L51.6 Bypass of artery of leg by anastomosis of iliac artery to femoral artery NEC	OPCS4	Operation
L581	L58.1 Emergency bypass of femoral artery by anastomosis of femoral artery to femoral artery NEC	OPCS4	Operation
L582	L58.2 Emergency bypass of femoral artery by anastomosis of femoral artery to popliteal artery using prosthesis NEC	OPCS4	Operation

Code	Code Description	Code - type	Rutherford category
L583	L58.3 Emergency bypass of femoral artery by anastomosis of femoral artery to popliteal artery using vein graft NEC	OPCS4	Operation
L584	L58.4 Emergency bypass of femoral artery by anastomosis of femoral artery to tibial artery using prosthesis NEC	OPCS4	Operation
L585	L58.5 Emergency bypass of femoral artery by anastomosis of femoral artery to tibial artery using vein graft NEC	OPCS4	Operation
L586	L58.6 Emergency bypass of femoral artery by anastomosis of femoral artery to peroneal artery using prosthesis NEC	OPCS4	Operation
L587	L58.7 Emergency bypass of femoral artery by anastomosis of femoral artery to peroneal artery using vein graft NEC	OPCS4	Operation
L591	L59.1 Bypass of femoral artery by anastomosis of femoral artery to femoral artery NEC	OPCS4	Operation
L592	L59.2 Bypass of femoral artery by anastomosis of femoral artery to popliteal artery using prosthesis NEC	OPCS4	Operation
L593	L59.3 Bypass of femoral artery by anastomosis of femoral artery to popliteal artery using vein graft NEC	OPCS4	Operation
L594	L59.4 Bypass of femoral artery by anastomosis of femoral artery to tibial artery using prosthesis NEC	OPCS4	Operation
L595	L59.5 Bypass of femoral artery by anastomosis of femoral artery to tibial artery using vein graft NEC	OPCS4	Operation
L596	L59.6 Bypass of femoral artery by anastomosis of femoral artery to peroneal artery using prosthesis NEC	OPCS4	Operation
L597	L59.7 Bypass of femoral artery by anastomosis of femoral artery to peroneal artery using vein graft NEC	OPCS4	Operation
L601	L60.1 Endarterectomy of femoral artery and patch repair of femoral artery	OPCS4	Operation
L602	L60.2 Endarterectomy of femoral artery NEC	OPCS4	Operation
L603	L60.3 Profundoplasty of femoral artery and patch repair of deep femoral artery	OPCS4	Operation

Code	Code Description	Code - type	Rutherford category
L604	L60.4 Profundoplasty of femoral artery NEC	OPCS4	Operation
L631	L63.1 Percutaneous transluminal angioplasty of femoral artery	OPCS4	Operation
L635	L63.5 Percutaneous transluminal insertion of stent into femoral artery	OPCS4	Operation
L652	L65.2 Revision of reconstruction involving iliac artery	OPCS4	Operation
L653	L65.3 Revision of reconstruction involving femoral artery	OPCS4	Operation
L662	L66.2 Percutaneous transluminal stent reconstruction of artery	OPCS4	Operation
L665	L66.5 Percutaneous transluminal balloon angioplasty of artery	OPCS4	Operation
L667	L66.7 Percutaneous transluminal placement of peripheral stent in artery	OPCS4	Operation
L711	L71.1 Percutaneous transluminal angioplasty of artery	OPCS4	Operation
X09	X09 Amputation of leg	OPCS4	AMPUTATION
X091	X09.1 Hindquarter amputation	OPCS4	AMPUTATION
X093	X09.3 Amputation of leg above knee	OPCS4	AMPUTATION
X094	X09.4 Amputation of leg through knee	OPCS4	AMPUTATION
X095	X09.5 Amputation of leg below knee	OPCS4	AMPUTATION
X098	X09.8 Other specified amputation of leg	OPCS4	AMPUTATION
X099	X09.9 Unspecified amputation of leg	OPCS4	AMPUTATION
X10	X10 Amputation of foot	OPCS4	AMPUTATION
X101	X10.1 Amputation of foot through ankle	OPCS4	AMPUTATION
X102	X10.2 Disarticulation of tarsal bones	OPCS4	AMPUTATION

Code	Code Description	Code - type	Rutherford category
X103	X10.3 Disarticulation of metatarsal bones	OPCS4	AMPUTATION
X104	X10.4 Amputation through metatarsal bones	OPCS4	AMPUTATION
X108	X10.8 Other specified amputation of foot	OPCS4	AMPUTATION
X109	X10.9 Unspecified amputation of foot	OPCS4	AMPUTATION
X11	X11 Amputation of toe	OPCS4	AMPUTATION
X111	X11.1 Amputation of great toe	OPCS4	AMPUTATION
X112	X11.2 Amputation of phalanx of toe	OPCS4	AMPUTATION
X118	X11.8 Other specified amputation of toe	OPCS4	AMPUTATION
X119	X11.9 Unspecified amputation of toe	OPCS4	AMPUTATION

Appendix 2 Poisson survival analysis output

Appendix 2a.1 Survival analysis transitions

State Starting / End	Asymptomatic	R 1-3	R 4	R 5	R 6	Amputation	Death
Asymptomatic		A	B	C	D		
R 1-3	E		F	G	H	I	J
R 4				K	L	M	N
R 5					O	P	Q
R 6						R	S
Amputation							T

Note: constant is the baseline hazard. Omitted variable is male aged 60-69.

Appendix 2a.1 Asymptomatic to Rutherford 1-3

Variable	Hazard ratio	Standard error	P value
Gender	0.861	0.057	0.02
Age less than 40	0.242	0.063	>0.01
Age 40-49	0.411	0.064	>0.01
Age 50-59	0.636	0.061	>0.01
Age 70-79	0.855	0.064	0.04
Age 80-89	0.840	0.077	0.06
Age 90plus	1.482	0.306	0.06
Constant	0.493	0.049	>0.01

Note: constant is the baseline hazard. Omitted variable is male aged 60-69. Transition matrix transition (A)

Appendix 2a.2 Asymptomatic to Rutherford 4

Variable	Hazard ratio	Standard error	P value
Gender	0.270	0.297	0.23
Age less than 40	0.000	0.000	>0.01
Age 40-49	0.000	0.000	>0.01
Age 50-59	0.707	0.867	0.78
Age 70-79	0.867	0.850	0.89
Age 80-89	1.976	2.011	0.50
Age 90plus	0.000	0.000	>0.01
Constant	0.001	0.001	>0.01

Note: constant is the baseline hazard. Omitted variable is male aged 60-69. Transition matrix transition (B)

Appendix 2a.3 Asymptomatic to Rutherford 5

Variable	Hazard ratio	Standard error	P value
Gender	1.840E+07	1.850E+07	>0.01
Age less than 40	2.515E-01	6.120E-01	0.571
Age 40-49	6.057E-01	1.472E+00	0.837
Age 50-59	8.648E-01	2.097E+00	0.952
Age 70-79	7.259E-01	1.573E+00	0.882
Age 80-89	8.180E+07	2.140E+08	>0.01
Age 90plus	3.103E-01	7.563E-01	0.631
Constant	1.170E-26	3.880E-26	>0.01

Note: constant is the baseline hazard. Omitted variable is male aged 60-69. Transition matrix transition (C)

Appendix 2a.4 Asymptomatic to Rutherford 6

Variable	Hazard ratio	Standard error	P value
Gender	2.80E+07	2.81E+07	>0.01
Age less than 40	0.124419	0.0997672	0.01
Age 40-49	0.468775	0.3705657	0.34
Age 50-59	0.805122	0.6270112	0.78
Age 70-79	2.36E+07	2.97E+07	>0.01
Age 80-89	0.414305	0.3184509	0.25
Age 90plus	0.169788	0.1383716	0.03
Constant	1.03E-26	2.34E-26	>0.01

Note: constant is the baseline hazard. Omitted variable is male aged 60-69. Transition matrix transition (D)

Appendix 2b Transitions from Rutherford state 1-3

Appendix 2b.1 Rutherford state 1-3 to Asymptomatic

Variable	Hazard ratio	Standard error	P value
Gender	1.05	0.05	0.29
Age less than 40	1.44	0.31	0.09
Age 40-49	1.19	0.12	0.09
Age 50-59	1.05	0.07	0.41
Age 70-79	0.99	0.05	0.86
Age 80-89	0.98	0.06	0.75
Age 90plus	1.13	0.20	0.50
Constant	0.038	0.00	>0.01

Note: constant is the baseline hazard. Omitted variable is male aged 60-69. Transition matrix transition (E)

Appendix 2b.2 Rutherford state 1-3 to Rutherford 4

Variable	Hazard ratio	Standard error	P value
Gender	1.21	0.06	>0.01
Age less than 40	1.54	0.38	0.08
Age 40-49	1.36	0.18	0.03
Age 50-59	1.19	0.09	0.03
Age 70-79	1.23	0.08	>0.01
Age 80-89	1.08	0.09	0.37
Age 90plus	0.96	0.25	0.88
Constant	0.003	0.00	>0.01

Note: constant is the baseline hazard. Omitted variable is male aged 60-69. Transition matrix transition (F)

Appendix 2b.3 Rutherford state 1-3 to Rutherford 5

Variable	Hazard ratio	Standard error	P value
Gender	1.05	0.09	0.61
Age less than 40	1.89	0.73	0.10
Age 40-49	1.18	0.29	0.51
Age 50-59	1.09	0.15	0.53
Age 70-79	1.31	0.14	0.01
Age 80-89	1.71	0.21	0.00
Age 90plus	3.14	0.83	0.00
Constant	0.001	0.00	0.00

Note: constant is the baseline hazard. Omitted variable is male aged 60-69. Transition matrix transition (G)

Appendix 2b.4 Rutherford state 1-3 to Rutherford 6

Variable	Hazard ratio	Standard error	P value
Gender	0.55	0.16	0.04
Age less than 40	1.96	2.00	0.51
Age 40-49	0.96	0.71	0.96
Age 50-59	1.22	0.42	0.57
Age 70-79	1.01	0.30	0.98
Age 80-89	1.24	0.46	0.57
Age 90plus	1.59	1.63	0.65
Constant	0.0004	0.00	0.00

Note: constant is the baseline hazard. Omitted variable is male aged 60-69. Transition matrix transition (H)

Appendix 2b.5 Rutherford state 1-3 to Amputation

Variable	Hazard ratio	Standard error	P value
Gender	0.68	0.08	0.00
Age less than 40	1.66	0.85	0.32
Age 40-49	1.63	0.44	0.07
Age 50-59	1.18	0.19	0.31
Age 70-79	1.19	0.16	0.19
Age 80-89	1.13	0.20	0.48
Age 90plus	0.65	0.46	0.55
Constant	0.002	0.00	0.00

Note: constant is the baseline hazard. Omitted variable is male aged 60-69. Transition matrix transition (I)

Appendix 2b.6 Rutherford state 1-3 to Death

Variable	Hazard ratio	Standard error	P value
Gender	0.85	0.04	0.00
Age less than 40	0.62	0.24	0.22
Age 40-49	0.57	0.11	0.01
Age 50-59	0.64	0.06	0.00
Age 70-79	1.80	0.10	0.00
Age 80-89	3.46	0.21	0.00
Age 90plus	7.19	0.77	0.00
Constant	0.005	0.00	0.00

Note: constant is the baseline hazard. Omitted variable is male aged 60-69. Transition matrix transition (J)

Appendix 2c Transitions from Rutherford state 4

Appendix 2c.1 Rutherford state 4 to Rutherford 5

Variable	Hazard ratio	Standard error	P value
Gender	1.11	0.19	0.56
Age less than 40	3.71	2.71	0.07
Age 40-49	1.19	0.53	0.69
Age 50-59	0.84	0.24	0.56
Age 70-79	0.90	0.20	0.64
Age 80-89	1.61	0.40	0.05
Age 90plus	3.24	1.54	0.01
Constant	0.002	0.00	>0.01

Note: constant is the baseline hazard. Omitted variable is male aged 60-69. Transition matrix transition (K)

Appendix 2c.2 Rutherford state 4 to Rutherford 6

Variable	Hazard ratio	Standard error	P value
Gender	0.73	0.37	0.54
Age less than 40	15.58	17.41	0.01
Age 40-49	0.00	0.00	0.99
Age 50-59	0.99	0.70	0.99
Age 70-79	0.60	0.39	0.43
Age 80-89	1.57	1.02	0.49
Age 90plus	4.60	4.97	0.16
Constant	0.0004	0.00	>0.01

Note: constant is the baseline hazard. Omitted variable is male aged 60-69. Transition matrix transition (L)

Appendix 2c.3 Rutherford state 4 to Amputation

Variable	Hazard ratio	Standard error	P value
Gender	0.68	0.19	0.17
Age less than 40	0.00	0.00	0.99
Age 40-49	0.40	0.41	0.37
Age 50-59	1.72	0.53	0.08
Age 70-79	0.75	0.23	0.35
Age 80-89	0.62	0.28	0.30
Age 90plus	0.00	0.00	0.98
Constant	0.002	0.00	>0.01

Note: constant is the baseline hazard. Omitted variable is male aged 60-69. Transition matrix transition (M)

Appendix 2c.4 Rutherford state 4 to Death

Variable	Hazard ratio	Standard error	P value
Gender	0.90	0.08	0.23
Age less than 40	0.58	0.58	0.59
Age 40-49	0.53	0.18	0.07
Age 50-59	0.55	0.10	>0.01
Age 70-79	1.47	0.16	>0.01
Age 80-89	2.91	0.33	>0.01
Age 90plus	4.68	1.02	>0.01
Constant	0.008	0.00	>0.01

Note: constant is the baseline hazard. Omitted variable is male aged 60-69. Transition matrix transition (N)

Appendix 2d Transitions from Rutherford state 5

Appendix 2d.1 Rutherford state 5 to Rutherford 6

Variable	Hazard ratio	Standard error	P value
Gender	1.18	0.88	0.82
Age less than 40	0.00	0.00	1.00
Age 40-49	0.00	0.00	0.99
Age 50-59	0.70	0.81	0.76
Age 70-79	0.54	0.49	0.50
Age 80-89	1.01	0.93	0.99
Age 90plus	0.00	0.00	1.00
Constant	0.0004	0.00	>0.01

Note: constant is the baseline hazard. Omitted variable is male aged 60-69. Transition matrix transition (O)

Appendix 2d.2 Rutherford state 5 to Amputation

Variable	Hazard ratio	Standard error	P value
Gender	0.73	0.16	0.15
Age less than 40	1.59	1.62	0.65
Age 40-49	0.38	0.39	0.34
Age 50-59	1.35	0.40	0.31
Age 70-79	1.36	0.32	0.20
Age 80-89	0.67	0.23	0.25
Age 90plus	0.86	0.63	0.84
Constant	0.007	0.00	>0.01

Note: constant is the baseline hazard. Omitted variable is male aged 60-69. Transition matrix transition (P)

Appendix 2d.3 Rutherford state 5 to Death

Variable	Hazard ratio	Standard error	P value
Gender	1.06	0.10	0.58
Age less than 40	1.44	0.84	0.54
Age 40-49	1.06	0.37	0.86
Age 50-59	0.62	0.14	0.03
Age 70-79	1.36	0.19	0.03
Age 80-89	2.56	0.35	>0.01
Age 90plus	4.23	0.89	>0.01
Constant	0.013	0.00	>0.01

Note: constant is the baseline hazard. Omitted variable is male aged 60-69. Transition matrix transition (Q)

Appendix 2e Transitions from Rutherford state 6

Appendix 2e.1 Rutherford state 6 to Amputation

Variable	Hazard ratio	Standard error	P value
Gender	0.64	0.16	0.08
Age less than 40	115.98	85.61	>0.01
Age 40-49	0.54	0.27	0.22
Age 50-59	1.71	0.54	0.09
Age 70-79	1.92	0.56	0.02
Age 80-89	2.09	0.71	0.03
Age 90plus	1.29	1.31	0.81
Constant	0.012	0.00	>0.01

Note: constant is the baseline hazard. Omitted variable is male aged 60-69. Transition matrix transition (R)

Appendix 2e.2 Rutherford state 6 to Death

Variable	Hazard ratio	Standard error	P value
Gender	1.03	0.19	0.89
Age less than 40	0.00	0.08	0.99
Age 40-49	0.32	0.15	0.02
Age 50-59	0.86	0.26	0.62
Age 70-79	2.25	0.48	>0.01
Age 80-89	2.55	0.63	>0.01
Age 90plus	5.87	2.42	>0.01
Constant	0.011	0.00	>0.01

Note: constant is the baseline hazard. Omitted variable is male aged 60-69. Transition matrix transition (S)

Appendix 2f Transitions from Amputation

Appendix 2f.1 Amputation to Death

Variable	Hazard ratio	Standard error	P value
Gender	0.95	0.10	0.67
Age less than 40	0.14	0.14	0.05
Age 40-49	0.30	0.12	>0.01
Age 50-59	0.67	0.11	0.01
Age 70-79	1.49	0.17	>0.01
Age 80-89	2.82	0.40	>0.01
Age 90plus	3.04	1.06	>0.01
Constant	0.019	0.00	>0.01

Note: constant is the baseline hazard. Omitted variable is male aged 60-69. Transition matrix transition (T)