University of Southern Denmark

CAST - Centre for Applied Health Services Research and Technology Assessment

University of Southern Denmark
J. B. Winsløws Vej 9B, 1st. floor
DK-5000 Odense C

Phone: 6550 1000
Fax: 6550 3880

Technical report

Modelling Cost-Effectiveness of Abdominal Aortic Aneurysm Screening

September 2011

Rikke Søgaard, associate professor, PhD
CAST, University of Southern Denmark

Jesper Laustsen, chief vascular surgeon, MD
Aarhus University Hospital, Skejby

Jes S. Lindholt, associate professor, PhD, DMSc
Vascular Research Unit, Viborg Hospital

Colophon

Title	Modelling Cost-Effectiveness of Abdominal Aortic Aneurysm Screening
Authors	Rikke Søgaard, Jesper Laustsen and Jes S. Lindholt
Institute	CAST – Centre for Applied Health Services Research and Technology Assessment
Publisher	University of Southern Denmark
Date of Release	September 2011
Printed at	University of Southern Denmark, Print and Sign
ISBN no.	978-87-92699-10-7

Foreword

This report is the first output of a two-year project of developing and validating a model for assessing the cost effectiveness of abdominal aortic aneurysm screening in Denmark. The report is intended to document and detail relevant methodological isues, primarily for the more technically interested reader. For the reader who is more interested in the results we refer to a forthcoming publication in a peer-reviewed journal (authored by the present author group).

The specified screening programme is adapted from a randomised controlled trial – the Viborg trial – which was conducted in Central Denmark from 1994 to 1998 and of which 14-years follow up has been reported. The screening programme includes one-off screening of men aged 65, rescreening of individuals with an aortic diameter of 25-29 mm after 5 years, follow up of individuals with an aneurysm between 30 and 55 mm, and referral for elective surgery of individuals with an aneurysm ≥55 mm.

In the forthcoming report about model results a comparison of four scenarios is reported: 1) no screening, 2) screening, 3) screening + rescreening as a one-off event after five years and 4) screening + rescreening every five years for lifetime. In the present report, for simplicity, we focus on the comparison of two scenarios only: 1) no screening and 3) screening + one-off rescreening. The documentation covers all of the structures and parameter estimates needed for the four scenarios, as scenario 2) differs from scenario 3) only by not referring 25-29mm to rescreening, and as scenario 4) differs from scenario 3) only by not repeating the rescreening regimen.

The project was sponsored by the Health Research Fund of Central Denmark Region and the Research Fund of Viborg Hospital. Further acknowledgements are referred to a separate section of the report.

Contents

Introduction

Abdominal aortic aneurysms

Abdominal aortic aneurysm (AAA) is assumed to be prevalent in about 4% of males over the age of 65 although variation exists across countries.[1] The natural disease history is progressive and may result in rupture with an associated mortality risk of up to 80%.[2] If an AAA on the other hand is detected at an earlier, asymptomatic state there will be treatment modalities reducing the mortality risk dramatically.

Incidental versus systematic detection

AAAs are normally asymptomatic until they have grown large and the risk of rupture is impending. The likelihood for incidental detection in asymptomatic patients is relatively small whereas it increases for the severity of symptoms and approaches one in case of rupture.

Population screening is a systematic approach for detecting AAAs in an early stage, where the likelihood of detection depends upon the accuracy of the diagnostic test modality. The most common test for AAA population screening is ultrasonography due to its feasibility as a non-invasive and relatively inexpensive test with high accuracy. The test has been found to have a sensitivity of 98.9% and a specificity of 99.9%.[3]

According to a Cochrane review from 2007 there are four key studies examining the effects of screening: the Chichester trial from the UK, the Viborg study from Denmark, the Western Australian study, and the Multicentre Aneurysm Screening Study (MASS) from the UK.[1,4-6] They all conclude that there is a significant effect of screening on mortality. In a Cochrane review of the literature a meta-analysis estimated the relative risk reduction of screening on AAA-related mortality at 0.40 (95 per cent CI 0.22; 0.53) and on all-cause mortality at 0.05 (95 per cent CI -0.07; 0.15).[7]

Treatment modalities

Whether detected incidentally or by systematic screening patients with an AAA ≥55 mm will be referred for surgical evaluation. Patients detected with aneurysms below this threshold value will be followed up regularly and referred for surgery if their aneurysm reaches the threshold size or if they develop symptoms. Patients with symptomatic AAA will be referred for acute surgical evaluation due to an increased risk of rupture. In case of rupture up to one of every two patients will die before reaching the hospital.

When evaluated by vascular surgeons a proportion of patients will be unfit for surgery for anatomical or physiological reasons and another proportion will decline to have surgery.

Until recent years, surgery was primarily performed as open aortic repair (OPEN) but the technique of endovascular aortic repair (EVAR) has now become part of standard practice in many countries. The availability of EVAR is an important alternative for two reasons: it is less invasive and it provides a treatment opportunity for a proportion of the patients who are ineligible for open surgery.

Review of existing models

Campbell et al. reported a systematic literature review of health economic models published up to 2005.[8] They identified 12 models with significant discrepancy between the results for which the reason was unclear due to poor reporting standards. It was noted that all models agreed on the following: a health care provider perspective, a cycle length of 1 year and perfect test accuracy of ultrasonography. Disagreement was observed on questions of whether to rescreen, at what age to perform screening (from 60 to 79 years), the time horizon for the model (from 15 years to life-time), whether opportunistic detection occurs, the attendance rate for screening (some assumed 100%), the impact of screening on the rupture rate (some assumed a 100% prevention), the threshold size for referral to elective surgery (from 40 to 60 mm) and the allowance for some patients being unfit for surgery. The authors concluded with a discussion about the fact that some (necessary) assumptions implicitly favour screening and that any assumption, which is not neutral, would bias results.

Since the review of Campbell et al. at least seven additional models have been published.[2,9-14] Discrepancies between the results of individual studies seem to persist although, apart from one, all studies estimate the average cost per quality-adjusted life-year (QALY) below the general threshold at around £30,000. The study proposing that population screening is cost-ineffective was a model for the Danish setting, which arrived at an average cost per QALY of £43,485.[9]

In a forthcoming systematic literature review Søgaard and Lindholt conclude that the literature published since the review by Campbell et al. still suffers low between-study convergent validity in terms of methodological choices.[15] Furthermore, the authors comment on some inappropriate assumptions, which could be relaxed in a future model.

Objective of the present work

Despite the availability of several reports of health economic modelling studies on the attractiveness of introducing population screening for AAA there are good reasons for conducting yet another study – even apart from the fact that results do not seem to be consistent. First, modelling is not an exact science and the methodological choices made during the process will impact results at least to some extent. Second, decision-models rarely hold external validity across countries due to various cultural and structural differences in health care systems. Third, the expected value of perfect information – defined by the net benefit of investing in further research from a societal viewpoint – has been estimated at £1 million per population of 250.000 males who turn 65, given a willingness-to-pay per QALY of £30,000.[9] This value represents uncertainty throughout many parameters and, as additional information disseminates, the rationale for an updated model becomes more and more outspoken. Fourth, the clinical management of AAA evolves as time goes by. For example, since some of the most recently published models, the EVAR modality has become part of routine practice and thus should be considered in a decision-scenario. Not least, it has been intensively discussed whether a modern screening programme include rescreening of attendees with “normal” aortic size after some years.

The objective of this work was to establish, document and validate a decision-analytic model that can be used to analyse the cost effectiveness different strategies for population screening for AAA in the Danish setting.

Model structure

Development of a proposed structure

A multidisciplinary team was established to discuss alternative model structures. At an early stage it was decided that a more detailed representation of the natural disease history than previously seen in health economic models (small, medium and large aneurysm) was required. The argument for this was primarily the exponentially increasing risk of rupture for increasing AAA-size with the risk being minimal in small aneurysms and approaching one in the largest aneurysms. It was furthermore clear, that a valid reflection of current practice should include the treatment modality of EVAR and distinguish between emergency surgery for intact versus ruptured aneurysms, as the expected costs and outcomes of the two have been found to differ significantly. Finally, it was decided that the model should include rescreening of individuals with an aortic diameter close to the threshold value at 30 mm.

Given the expected exponential form of the relationship between aneurysm size and rupture, it would be ideal to model relatively small size-intervals for larger aneurysms. However, the data availability on growth and rupture rates for the larger aneurysms in particular remains limited.

Balancing between the ideal scenario and what would be practically possible, it was decided to model the disease process using eight starting states: definitely no AAA (0-24 mm), probably no AAA (25-29 mm), small or medium-sized AAA with essentially no risk of rupture but with a significant risk of growth (30-49 mm), medium-sized AAA close to the iatrogenic threshold (50-54 mm) and four states of large AAAs above the iatrogenic threshold (55-59 mm, 60-69 mm, 70-79 mm and 80+ mm).

Figure 1 shows the proposed model structure. The associated structural assumptions are outlined in the following for individual, consecutive pathways in the model.

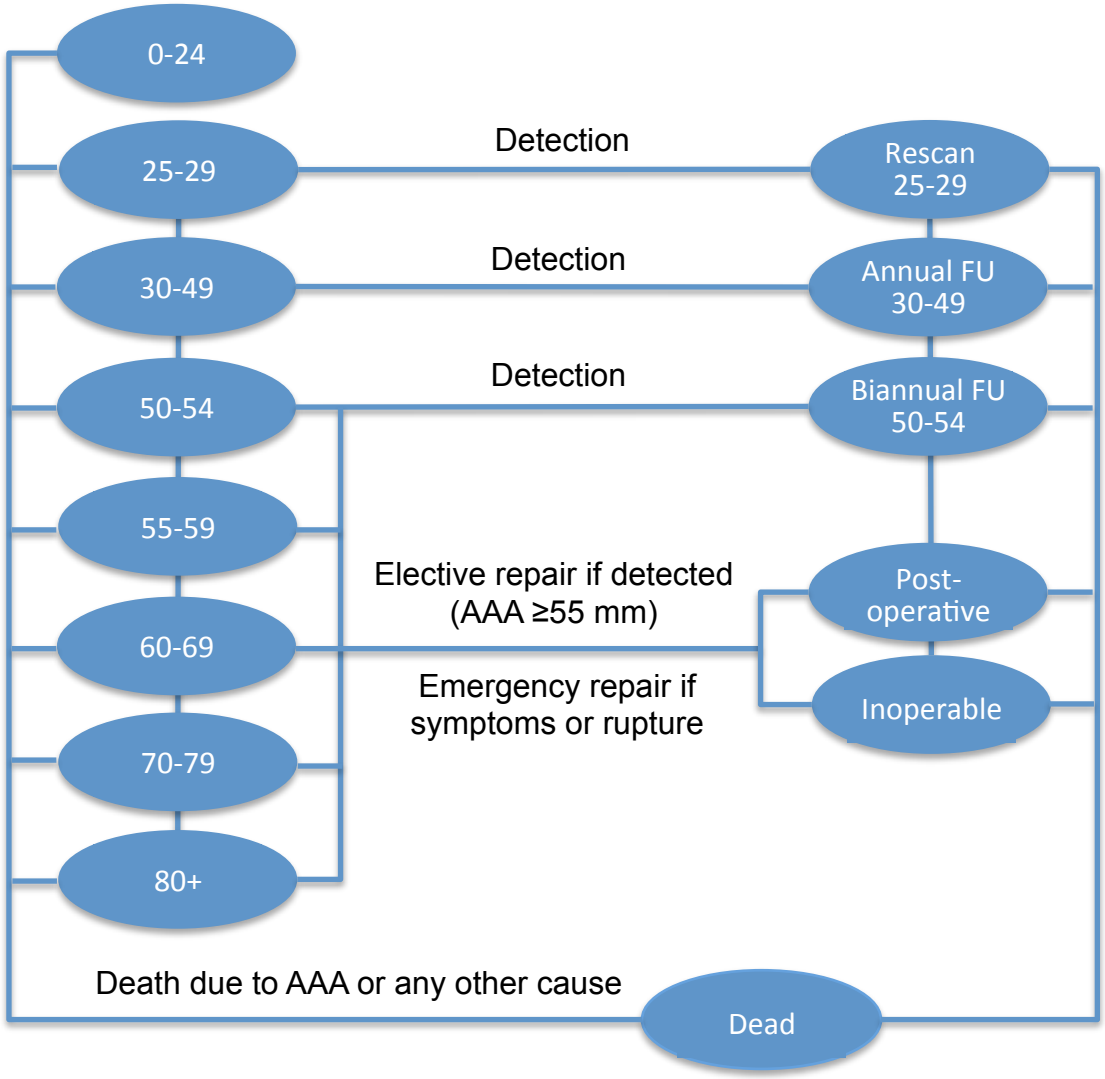

Figure 1 Markov model for the course of abdominal aortic aneurysms

Note: The diagram is a simplified presentation of the disease history and relevant modalities for intervention. The eight ovals to the left represent the starting states (numbers refer to the abdominal aortic diameter in millimetres). Individuals can then reside in their current states or move to a neighbouring state following the lines drawn. Detection of aneurysms can be incidental or follow from systematic screening.

Structural assumptions

The choice of a Markov model implies two overall assumptions. First, the so-called Markov property states that individuals starting in a given state can be modelled in the same way. This means that the route to arriving in a state or the time spend in a state has no influence on subsequent parameters. For example, when individuals arrive at acute open surgery their probability for a successful outcome is independent on whether symptoms arose from a 30 mm or a 70 mm aneurysm. Second, the so-called stationarity assumption states that parameters are time-homogeneous, that is, do not vary from one cycle to another. There are limited possibilities for relaxing this assumption, which in the present context were taken advantage of to allow for increasing mortality rates as the population age.

Two general assumptions were made about the natural disease history: that individuals cannot progress more than one consecutive AAA-size-state per cycle and that decreasing AAA-size is not possible. The justification of the first part depends on whether the cycle length is defined to accomplish the pace of disease progress. This is dealt with in the section Length of Markov cycles. The justification for not allowing decreasing aneurysm-size also refers to biological evidence, as AAA is known to be a progressive and irreversible disease.

Figures 2 to 5 illustrate the starting states and decision pathways of the model. The diagrams should be read from left (state of departure) to right (terminal node; state of arrival after a cycle). When a branch is bolded it indicates that the subtree to the left is cloned. A unique subscript number defines the cloned, which is then reused in other parts of the model. When a terminal node is defined by a formula (e.g. "=Remain in state") rather than a description (e.g. "Dead other causes") it indicates that a Markov binding is defined. This means that different terminal states are defined within a clone. It should be possible to read from the formula name what the binding refers to.

The pathway from each of the starting states and the associated structural assumptions are described in the following.

1. **Aorta 0-24 mm:** Conditional upon not dying from non-AAA-related causes, individuals remain in this state until death. This implies an assumption about individuals not developing AAA later in life. The condition of not dying from competing causes applies for all of the following states hereafter. The node relating to screening is modelled to be able to assign a cost of screening for those who attend an eventual programme. It has no effect in a scenario without screening.

2. **Aorta 25-29 mm:** This state is similar to the previous, except that growth (and detection of growth) is now allowed. In a scenario with screening, individuals will be referred to a rescan after 5 years (if no growth) or annual follow up (if growth to ≥30 m), given that they attend.

3. **Aorta 30-49 mm:** This state is similar to the previous, only are detected cases referred to annual follow up (if no growth) or to biannual follow up (if growth to ≥50mm).

4. **Aorta 50-54 mm:** This state is an extended version of the above, as rupture and symptoms are now allowed. It is assumed that a symptomatic aneurysm will always be detected. This is a conservative assumption in that the difference between a regimen with and without screening thereby is restricted to the handling of non-symptomatic patients. This is further discussed in the section Anticipated effects of screening.

   The pathway first assesses whether rupture will occur. Accordingly, the patient either proceeds to acute surgery (conditional on reaching the hospital alive) or, if no rupture, to assessment of whether symptoms are present. If yes, the patient will be referred for acute surgery and if no, he will be either detected and proceed to biannual follow up (if no growth) or to elective surgery (if growth to ≥55 mm), or remain undetected in this (if no growth) or the next disease state (if growth t ≥55 mm).

Patients with symptoms but no rupture were allowed to refuse or to be unfit for surgery in which case they proceed to a state of inoperable where they remain until death from other causes unless they rupture. In case of rupture it is assumed that patients either receive acute surgery or die; they cannot proceed to inoperable.

It is assumed that elective surgery is offered without waiting time (there is no option for rupture while waiting for surgery). In practice, elective surgery might not be offered on the same day as indicated but given a 30-day treatment guarantee in the Danish health care system and the discretion of surgeons to prioritize the most severe candidates first this seems a justified assumption in order to moderate the complexity of the model structure.

After surgery patients will either proceed to a postoperative state (if the patient survives the first 30 days after surgery; here denoted successful surgery) or to an absorbing state of death (if the patient does not survive the first 30 days after surgery; here denoted unsuccessful surgery).

5. **Aorta 55-59 mm, Aorta 60-69 mm, Aorta 70-79 mm and Aorta >80 mm:** All starting states referring to aneurysms ≥55 mm (the threshold size for elective surgery) share identical decision pathways, except that 80+ mm cannot grow to the next state. The pathway first assesses whether rupture or symptoms will occur in which case the patient is referred for acute surgery as outlined in the previous state. If non-symptomatic the patient can either be detected and referred for elective surgical evaluation, or remain undetected in the state (if no growth) or proceed to the next disease state (if growth).

6. **Follow up 30-49 mm**: This pathway model a follow up regimen of annual monitoring. The node Follow up is defined as a tunnel state to account for follow up not occurring in every cycle.

   If individuals are grown while awaiting the annual follow up they become at risk of rupture and symptoms in which case they will leave the follow up regimen and proceed to surgical repair. If they are grown but non-symptomatic incidental detection may occur and lead to referral for biannual follow up.

   After the follow up assessment attendees either remain in the state (if no growth) or proceed to biannual follow up (if grown to 50-54 mm) or to elective surgery (if grown to ≥55 mm). Non-attendees will exit the follow up regimen as undetected cases.

7. **Follow up 50-54 mm**: This state is similar to the previous except that follow up occurs biannually.

8. **Postoperative**: After AAA repair the individuals will reside in a postoperative state until death from competing causes. It is assumed that relapse or a new AAA in a different region is not possible.

9. **Inoperable**: Patients who after surgical evaluation are considered inoperable or who refuse to have surgery proceed to this state and can exit only in case of symptoms, rupture or death.

10. **Dead**: Patients who die because of rupture or within 30 days from surgical repair upon rupture are assigned a tracker for AAA-related death and absorbed in this state. Individuals who die from competing causes are assigned a tracker for non-AAA-related death and also absorbed in this state.

11. **Rescan**: This state is effective only for a scenario with screening. It defines a one-off repetition of the initial screening after five years unless the resident has developed rupture or symptoms in the meantime. The node Rescan is defined as a tunnel, which is open only after having stayed a number of cycles equivalent to 5 years in the state. After this time residents will leave the state; if detected with an aneurysm they proceed to the relevant states for detected aneurysms (follow up or elective surgery, depending on the size of their AAA) and if undetected or not grown at all they proceed to the relevant states for undetected aneurysms or to Aorta 25-29 mm.

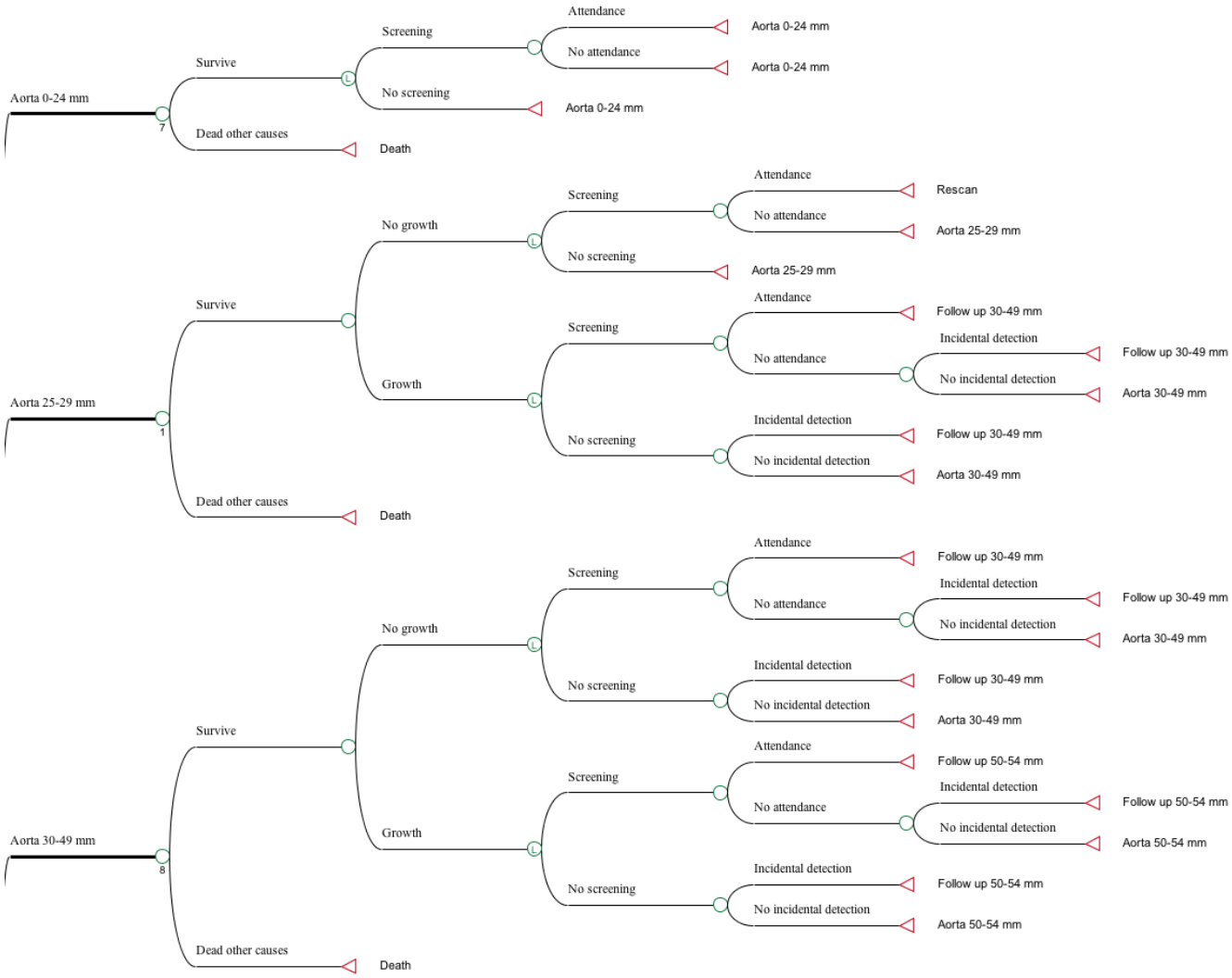

Figure 2 Decision pathways of the proposed model: starting states for aortic diameters <50 mm

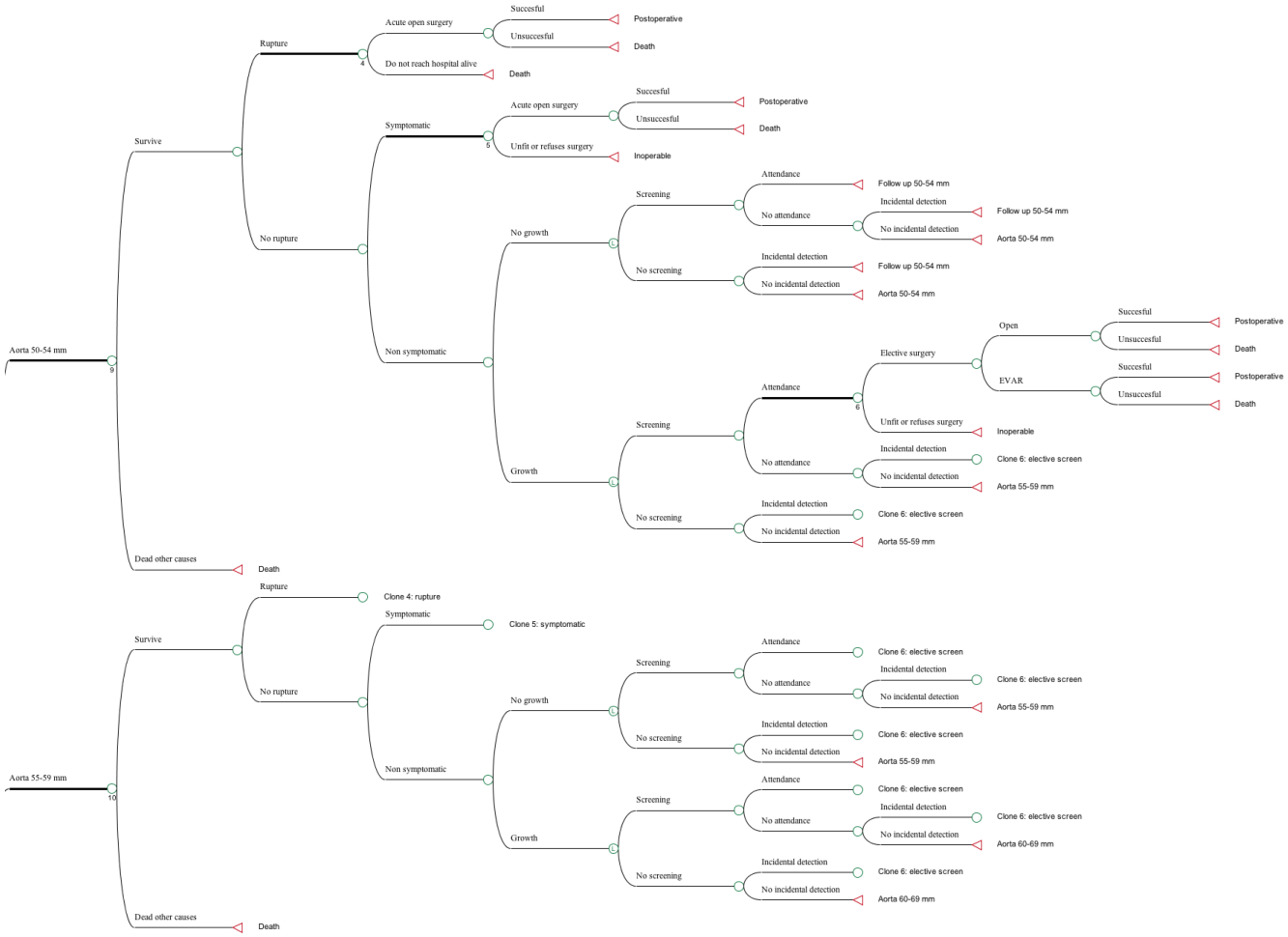

Figure 3 Decision pathways of the proposed model: starting states for aortic diameters ≥50 mm

Note: all of the states for AAA ≥55 mm have the same structure (except that 80+ mm aneurysms cannot grow). The illustrated regimen for aneurysms of 55-59 mm thus applies for the larger states as well and these are therefore not shown. The bolded bars indicate that a clone is defined by what follows to the right. In this figure the regimens for surgical evaluation are defined by clone numbers 4, 5 and 6. Clones are simply used to keep the structure simple instead of repeating identical structures that occur in different states.

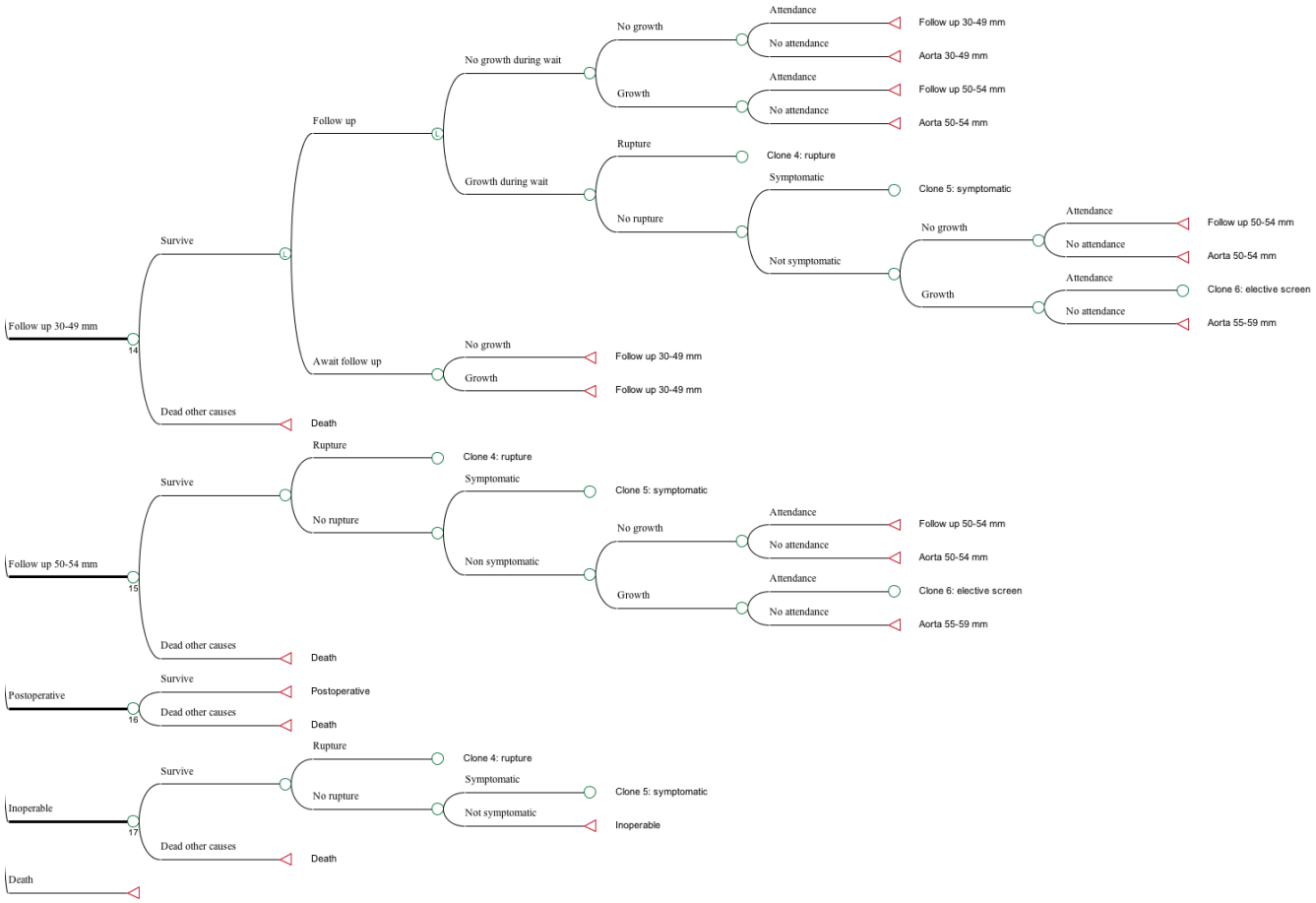

Figure 4 Decision pathways of the prposed model: death, inoperable and follow up states

Note: the clones are defined in Figure 3.

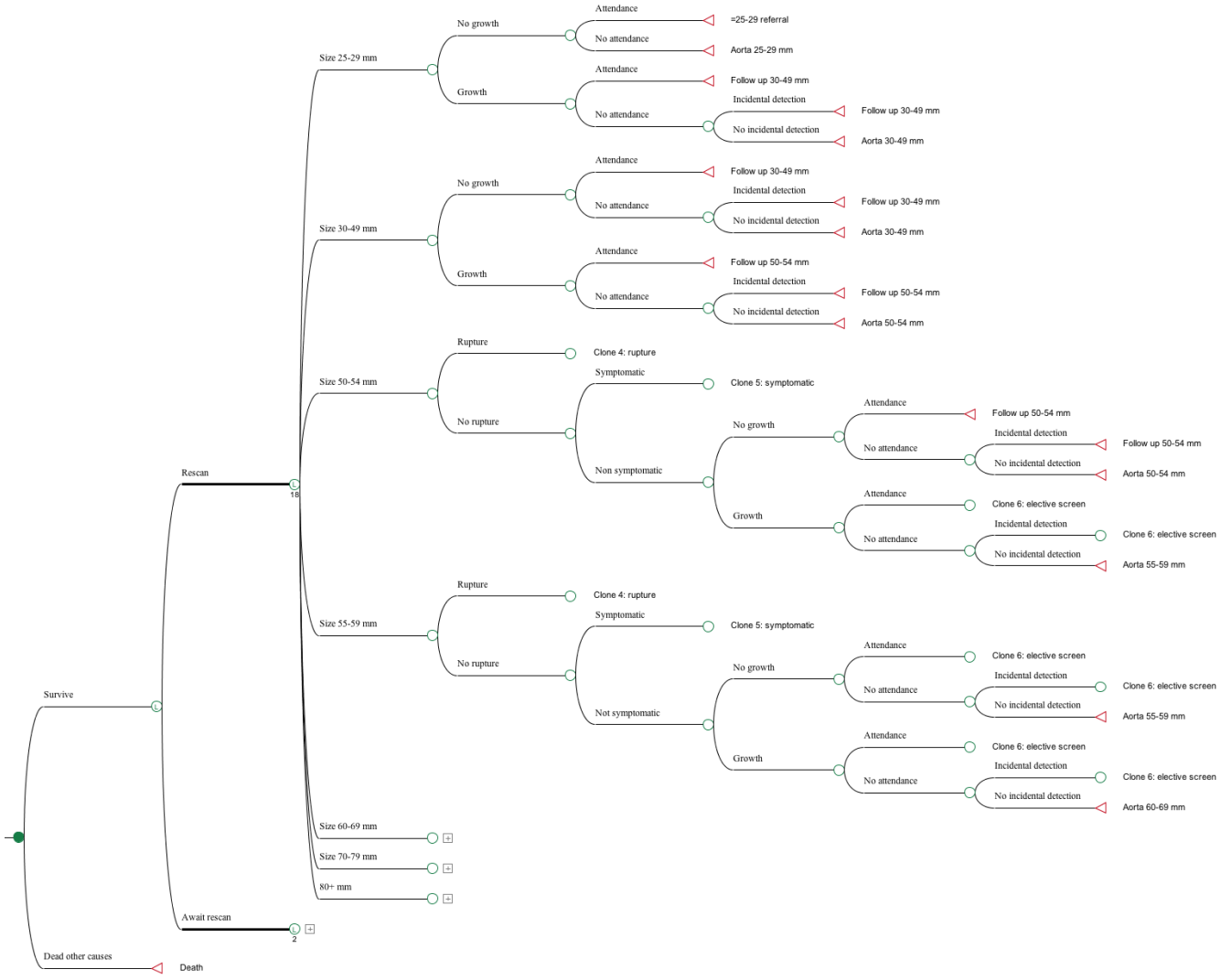

Figure 5 Decision pathways of the proposed model: the rescan state

Note: the clones are defined in Figure 3. The subtree “Await rescan” is collapsed for matters of overview. It is built similar to the “Rescan” subtree except that there is no discrimination between attendance/non-attendance. The subtrees “60-69 mm”, “70-79 mm” and “80+ mm” are similarly collapsed; they are similar in structure as “55-59 mm” (except that 80+ mm cannot grow). The terminal state “=25-29 referral” equals “Aorta 25-29” (it is defined as a so.called binding as a practical technicality).

Anticipated effects of screening

In a systematic literature review Silverstein et al. introduced the dichotomisation of symptomatic versus non-symptomatic AAA to underline that not only ruptured aneurysms require acute treatment. The authors defined symptomatic as follows: "*Patients with known aneurysms may develop increasing aneurysm tenderness, acute back pain, or abdominal pain, suggesting a change in the aneurysm's status but without clinical evidence of hypovolemia. Such aneurysms have been called "active," "expanding," or suspected of "leaking"*."[2] Patients with non-ruptured, symptomatic patients were found to constitute one out of ten patients referred to acute surgery.

Except for the referred study by Silverstein et al. non-ruptured, symptomatic aneurysms have not been considered in previous health economic models. This might have lead to an underestimation of the incidence of acute surgery.

The present work acknowledges the existence of a subgroup of non-ruptured, symptomatic patients that require acute surgical evaluation. Given the above definition of symptomatic aneurysms it is assumed that they will be detected due to the symptoms per se, and thus irrespective of whether a screening programme is available. This is a conservative assumption as it limits the potential for systematic detection to asymptomatic individuals. Table 1 illustrates the rationale for systematic screening, which is restricted to the lower right cell: undetected, non-symptomatic cases.

Table 1 The rationale for systematic screening: undetected, non-symptomatic cases.

	Symptomatic aneurysm	Non-symptomatic aneurysm
Detected incidentially	Automatic referral for acute surgery	Automatic referral for follow up or elective surgery
Undetected	Automatic referral for acute surgery	Remain undetected

The benefit of screening can be attributed to the fact that success rates after elective surgery are much more favourable than success rates after acute surgery (and in case of rupture some patients will not even reach the hospital for acute surgery). In a regimen with systematic screening, individuals detected with a 30-54 mm asymptomatic aneurysm can be followed and offered surgical evaluation immediately after the aneurysm has exceeded the threshold for surgical intervention. Individuals detected with an asymptomatic aneurysm ≥55 mm can referred for elective surgery rather than awaiting symptoms or rupture.

In terms of costs, a detected population – whether detected incidentially or by systematic screening –will use more resources than an undetected population due to more follow up procedures and more elective repairs. On the other hand, this will, to some extent, be counterbalanced by fewer acute repairs.

Effect modification

When individuals are detected with an aneurysm, or even when they attend a screening programme and present with a poor cardiovascular health, the health professionals will often recommend patients to consult their general practitioner for a cardiovascular health check. This may result in the initiation of medical prevention (e.g. prescription of statins) and/or life-style changes (e.g. quitting smoking), which in turn may reduce the likelihood of developing an aneurysm and/or the growth of existing aneurysms.

During the process of developing the model structure it was discussed whether to encompass such effect modifiers as structural elements. The associated complexity and lack of clear-cut evidence however lead to a decision of not doing so.

Length of Markov cycles

Based on biological evidence of the growth rate of aneurysms, but also the time intervals used for monitoring detected aneurysms, a cycle length of six months was adapted. Shorter cycle lengths might have been more appropriate in terms of reflecting the real world but they would also have lead to higher levels of complexity and therefore imprecision. The choice is believed to represent a compromise for which eventual differences between scenarios with and without screening will validly manifest.

Populating the model

General methodology

Conversion between rates and probabilities

Conventional formulas for converting rates into probabilities were used when the original parameter estimates were not available in the relevant form.[16] First, if an event occurs at a constant rate r per time unit t, then the probability p that an event will occur during t is

$$p = 1 - e^{-rt}$$

Second, it may be appropriate to firstly transform a probability into a rate and then back to a probability as rates have convenient mathematical properties that probabilities do not. Using the same notation as above, probabilities were converted into rates by

$$r = -(1/t)\ln(1-p)$$

Half-cycle correction

A discrete Markov-chain model assumes that transitions occur between cycles and thus remain constant through cycles. If survival, say, is calculated on the basis of membership of a state in the end of a Markov cycle it will be underestimated and vice versa if it is calculated on the basis of membership in the beginning of a Markov cycle. Half-cycle correction, to allow for transition events occurring on average mid-way through each cycle, has been part of best practice for

reasons of generating unbiased descriptive model outcomes.[17] It was accordingly implemented in the present model.

Discounting rate

Costs, life years and QALYs were discounted by an annual rate of 3%.

Distribution in starting states

There is significant variation in the prevalence between countries.[18] National data from the recent VIVA study was used to estimate a prevalence distribution (see Table 2).[19]

Table 2 Aortic diameter across 18,695 men included in VIVA screening trial

	Aortic diameter (mm)								
	<25	25-29	30-49	50-54	55-59	60-69	70-79	80+	All ≥30
Number (n)	17594	493	507	41	22	15	11	12	608
Prevalence (%)	94.11%	2.64%	2.71%	0.22%	0.12%	0.08%	0.06%	0.06%	3.25%

Transition to non-AAA-related death

The probability for non-AAA-related mortality (hereafter referred to as all-cause mortality although it strictly speaking does not include AAA-related mortality) was specified to increase as the model population age. National mortality statistics were used to inform mortality rates for individual age strata from age 65 through age 99+. Table 3 shows selected estimates.

Table 3 National mortality rates for selected age-strata

	Age (years)						
	65	70	75	80	85	90	95
Rate per 100,000 person years	1,742	2,794	4,408	7,379	12,877	23,745	33,596

Note: Rates refer to observations of 2008-2009 and were provided by Statistics Denmark.

National mortality statistics were adjusted according to the known excess mortality associated with AAA. Relative risks were generated for relevant strata using data from the Viborg trial and the Danish Registry for Vascular Surgery. For each individual in the registries an expected mortality rate was drawn from national mortality statstics by matching on age and calendar time. The expected mortality rate was then related to the observed rate from the point in time when the individual became at risk (in the Viborg data by time of randomisation and in the Danish Registry for Vascular Surgery by time of surgery + 30 days not to include AAA-related mortality) until death or censoring. Table 4 shows the relative risks (the probabilistic specification of these estimates assumed no variation in the underlying national mortality statstics).

It was not possible to inform all-cause mortality of inoperable patients from Danish data because the EVAR, which is anticipated to have affected who are inoperable, is a relatively new modality in routine practice. An estimate was therefore adapted from the British EVAR-II study,

which followed a population of inoperable patients.[20] After 4 years of follow up a mortalty rate of 0.2210 per year could be calculated. The corresponding expected rate from national mortality statistics is 0.0860.

Table 4 Relative risk for all-cause mortality as compared with the normal population

	Source	Events	Age group	Individuals (n)	Relative risk
30-49 mm	Viborg	86	64-74 years	160	1.4612
50-54 mm	Viborg	16	64-74 years	24	1.6699
≥55 mm	DRVS	116	64-69 years	412	2.1452
Inoperable	EVAR-II	160	> 65 years	207	2.5683

Note: Relative risks were estimated by comparing observed rates in patients with expected rates for the normal population, except for the estimate for inoperable patients, which was inferred from the British EVAR-II trial report. DRVS=Danish Registry for Vascular Surgery, NA = not applicable.

It shold be noted that the relative risks for aneurysms ≤55 mm are probably minimum estimates as those attending follow up regimens typically have a healthier life style than those not attending, who could not be included in the estimations. This is reflected in a comparison between attendees at screening with normal-sized aortic diameter and the general population, which results in a relative risk of only 0.8301 (the estimate was not used in the model).

Based on meta-analysis of long-term follow up data of the four screening trials it has been concluded that screening significantly reduces all-cause mortality.[21] However, to avoid double counting of an effect on AAA-related mortality in the model a new meta-analysis has been conducted to assesses the influence on non-AAA-related mortality only. Long-term data split on AAA-related versus non-related mortality was not available for the Australian trial and the meta-analysis is therefore based on the three remainder trials only (see Figure 6).

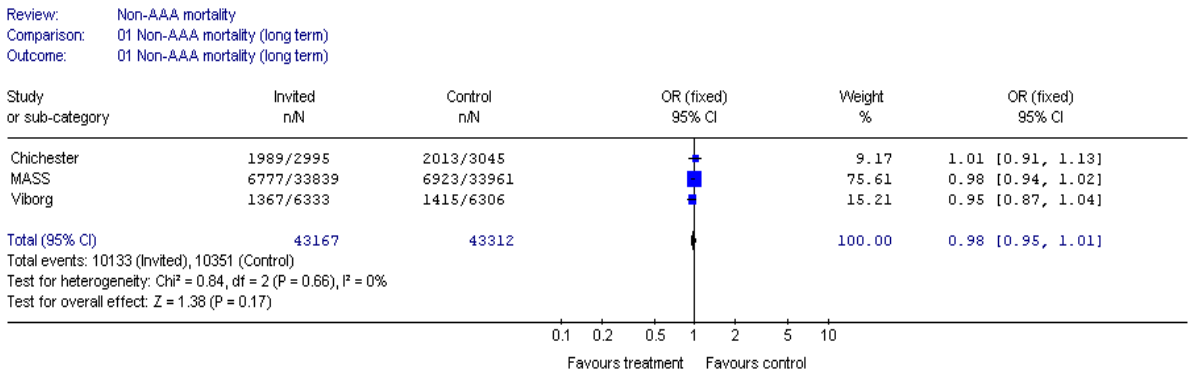

Figure 6 Meta-analysis of the effect of screening on non-abdominal aortic aneurysm-related mortality

Transition to the next disease state

Growth

The model defines six transitions due to growth of aneurysms. This is a more detailed process than seen in previous models – and rather ambitious due to limited data availability. There is some evidence for growth rates in smaller aneurysms, which has been recently summarized in a meta-analysis.[22] But for the larger aneurysms, there is almost no evidence, as patients will normally be referred for surgical evaluation immediately after detection of an aneurysm ≥55 mm (unless they refuse).

For the smaller aneurysms, the recent meta-analysis provided an estimate of an overall growth rate at 4.96 mm/year (95% CI 4.25; 5.66) for aneurysms sized 30-49 mm.[22] However, the relationship was noted to be exponential in that a 30 mm aneurysm would on average take 9.6 years to reach 55 mm whereas 40 mm aneurysm would take only 4.0 years. The studies included in the review covered original estimates from 1976 to 2005 and aneurysm sizes from 30 to 55 mm. In order to use these estimates in the model they need to be transformed into transition probabilities for the defined starting states, i.e. the probability for a 30-49 mm aneurysm growing larger than 49 mm within a cycle of 6 months. Such transformation requires knowledge about the distribution of individuals in size-intervals, which is not available.

For the larger aneurysms, a systematic literature search was specified to identify relevant evidence. The search was specified as follows: “abdominal aortic aneurysm” AND (growth rate OR expansion rate) AND (diameter OR size) and applied in PubMed, EMBASE and Web of Science in June 2010. After the exclusion of doublets, a net of 167 abstracts were evaluated for relevance. Only 2 references were found to report original observations of large aneurysms.[23,24] One of these, a large Canadian cohort study by Brown et al., was excluded due to the fact that many patients were excluded and referred to elective surgery during the observation time. The second study, an American study by Lederle et al., did not report the parameters in the desired form and it has not been possible to initiate a new statistical analysis upon correspondence with the authors.

Cross checking of reference lists and personal correspondence lead to the notice of two further studies. Brady et al. examined growth rates in a cohort of 1793 individuals with aneurysms between 28 mm and 85 mm, who were followed from 1991 through 1998 (UK Small Aneurysm Trial and Study).[25,26] The average growth rate was estimated at 2.6 mm per year (95% confidence interval (CI) 2.5; 2.6) and it was noted that various covariates were only weakly associated except for the aneurysm-size at baseline, which, for each interval of 10 mm, was found to increase the growth rate by an extra 1.3 mm/year (95% CI 1.1; 1.6). In a forthcoming work by Sweeting and Thompson a similar approach is taken.[27] Using data from the MASS trial (1046 subjects detected with a screening-detected aneurysm <55 mm and at least one follow up measurement) the authors propose alternative hierarchical mixed effects models to describe growth. The alternative models differ according to the specification of time-growth-relationships (linear or quadratic), the time-variables adapted (age or time since screening) and whether a classical or a Bayesian MCMC approach was used to fit them. The relevant model for the present application describes an average diameter at the first screen at 38.3 mm (SE 0.2) with an estimated growth rate of 1.49 mm/year (SE 0.09) + 0.108 mm/year^2 (SE 0.012).

All in all, the literature provides no estimates for growth rates in the 25-29 mm state and the states >49 mm, except for predictions based on observations from smaller aneurysms and/or patients classified as inoperable. In order to adapt these estimates assumptions about the size-distribution are required to transform growth rates into transition probabilities. Original data of the Viborg and VIVA trials was therefore used to estimate transition rates for smaller aneurysms and to predict transition rates for the larger aneurysms.

A simple linear model was chosen in order to provide a conservative set of estimates that would not favour screening. Table 5 shows the observed rates for aneurysms between 25 and 49 mm (both trials referred patients on to CT-evaluation upon reaching 50 mm after which no monitoring was performed) and Table 6 shows the predicted values for aneurysms ≥50 mm, based on observations of growth in 30-49 mm aneurysms.

Transition rates were assumed to be equal in a screened and a non-screened population. This seems to be justified for aneurysms <55 mm unless participation in a screening program leads to a healthier life-style. There is no consensus in the literature about this issue and hence the conservative approach of using equal probabilities was taken.

Table 5 Observed annual transition rates due to growth in the Viborg and VIVA trials

Size of aorta (mm)	25-29	30-34
Person time	648	363
Events of progression	48	33
Transition rate per year used in the model	0.07	0.09

Note: The observations for the first stratum refer to 248 individuals with an aortic diameter of 25-29 mm at the initial scanning in the Viborg trial, who were invited for rescan after 3-5 years. The observations for the second stratum refer to a pooling of follow up observations during the fist year after screening in the VIVA and the Viborg trials.

Table 6 Prediction of annual transition rates due to growth for larger aneurysms

Size of aorta (mm)	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
Person time	178	93	61	31	NA	NA	NA	NA	NA	NA
Events of progression	66	45	35	16	NA	NA	NA	NA	NA	NA
Observed rate	0.37	0.48	0.57	0.52	NA	NA	NA	NA	NA	NA
Predicted rate	0.41	0.46	0.51	0.57	0.62	0.67	0.72	0.78	0.83	0.88
Used in model		0.09			0.62	0.67	0.39			0.44

Note: predictions were based on OLS regression of trial observations of the Viborg and VIVA trials. The regression equation was: growth probability = = 30.212 + 5.258 * sizegroup.

Transition to AAA-related death

Rupture

A systematic literature search was specified as follows: "abdominal aortic aneurysms" AND "rupture" AND (diameter OR size) and applied in PubMed, EMBASE and Web of Science. The

search had a time restriction of year 2000 to date, as older estimates were considered outdated due to general advances in cardiovascular prevention. The literature search identified only four relevant studies.[23,24,28,29] After close examination of study methodologies the EVAR-II report was excluded since only patients fit for EVAR were included. These candidates often have a less complex aneurismal morphology and accordingly a lower risk of rupture. Furthermore, the protocol excluded patients with symptoms or a rapidly expanding aneurysm (they were referred to surgery). The study by Brown was similarly considered inappropriate on grounds of the sample being too selected, however in relation to patients with large aneurysms only. Table 7 shows the remainder studies.

Table 7 Rupture rates of aneurysms based on available original studies

	Lederle		Brown		Brown		
Aneurysm (mm)	Events	Person years	Events	Person years	Events	Person years	(Combined) Annual rate
30-49	NR	NR	NR	NR	0	2912[3]	0.00
50-54	NR	NR	6[2]	607[2]	NR	NR	0.01
55-59	6	62	NA	NA	NR	NR	0.10
60-69	8	130	NA	NA	NR	NR	0.06
70-79	9[1]	73[1]	NA	NA	NR	NR	0.12
80+	22[1]	57[1]	NA	NA	NR	NR	0.39

[1]Estimates were partly read form a figure and are approximate. Of the study sample of n=198 one patient was a female. [2]Estimates refer to aneurysms of 50-59 mm. [3]The numbers of person years observed for the estimation of the rate of surgery was adapted. NR = not reported. NA = Not adapted due to the sample not being appropriate for the present purpose.

The probability for rupture among patients who are inoperable is likely to be higher than in operable patents. However no estimates were dentified for inoperable patients it was therefore assumed that the rate could be approximated by the risk in aneurysms size 80+. An inconsistency was noted in Lederle et al. who observed no ruptures in the stratum of 60-64 mm aneurysms (but several ruptures in smaller and larger strata). Linear interpolation was therefore used to inform the model by consistent rupture rates, which resulted in a rupture rate of 14/130 for the stratum of 60-69 mm.

Proportion with rupture who reaches the hospital alive

The probability of reaching the hospital alive was judged to be highly context-specific due to infrastructure, iatrogenic thresholds, etc. For that reason, a parameter estimate was modelled using data from the Danish Registry for Vascular Surgery and the National Cause of Death Register. Due to the limited number of observations all ages and both females and males were used for the estimation. The derivation is detailed in Table 8.

Table 8 Derivation of the probability for reaching the hospital alive after rupture.

	1994-2002	2003	2004	2005	2006	2007	2008	Total
Number of procedures with rupture	1852	212	238	244	209	195	198	3148
Number of ruptures	4067	475	527	530	481	472	402	6954
Postoperative alive	919	108	133	150	119	126	139	1694
Deaths due to rupture	3148	367	394	380	362	346	263	5260
Reaching surgery (%)	45.54	44.63	45.16	46.04	43.45	41.31	49.25	45.27

Note: The numbers of primary procedures due to rupture and the number alive 30 days postoperative were extracted from the Danish Registry for Vascular Surgery. The number of deaths due to rupture was informed from the National Cause of Death Register using a definition of: I71.3, I71.8 and I71.9 plus I71.4 given that an admission due to rupture (I71.3) was at the same time registered. The probability for reaching surgery was calculated as 1–(procedures with rupture/number of ruptures).

Postoperative mortality

The 30-day postoperative mortality rates were estimated from Danish Registry for Vascular Surgery for the years 2005-2009, as shown in Table 9.

The mortality rate after elective surgery has been found to be significantly reduced in a screened population due to early detection and surgical candidates accordingly being detected with smaller aneurysms. A recent meta-analysis estimated this benefit at an odds ratio for postoperative mortality after elective surgery in screened populations of 0.37 (95% CI 0.20; 0.68).[30] That estimate was adapted for the present model.

Table 9 Derivation of the probability of death within 30 days after surgery

	2005	2006	2007	2008	2009	Total
Elective repair						
Number of primary procedures	279	325	334	352	399	1689
Number of deaths within 30 days	8	10	9	8	15	50
Probability of death within 30 days (%)	2.87	3.08	2.69	2.27	3.76	2.96
Acute repair without rupture						
Number of primary procedures	67	72	64	48	53	304
Number of deaths within 30 days	5	8	1	7	5	26
Probability of death within 30 days (%)	7.46	11.11	1.56	14.58	9.43	8.55
Acute repair with rupture						
Number of primary procedures	196	171	164	165	136	832
Number of deaths within 30 days	76	72	64	60	50	322
Probability of death within 30 days (%)	38.78	42.11	39.02	36.36	36.76	38.70

Note: The number of repairs and the number of deaths were extracted from the Danish Registry for Vascular Surgery. For estimation of death after repair for rupture only cases surviving the day of surgery were included.

Transition to inoperable and postoperative states

In recent years a general tendency of patients undergoing surgery being older and in more severe disease states (previously considered unfit for surgery) has been noticed in the Danish Registry for Vascular Surgery. This is interpreted as the result of advances in surgical techniques and skills. The information of parameters in the present section was therefore based on context-specific and recent observations.

Incidental detection

In a health care system without systematic screening the probability for incidental detection of aneurysms ≥55 mm will equal the number referred to elective surgery / prevalent cases. These parameters were informed from Danish Registry for Vascular Surgery and from age strata 65-74 years of the Viborg and the VIVA research registries. Prevalence was assumed to follow a linear extrapolation for older ages (assumption is examined in Figure 6) in order to estimate the prevalence for all men > age 65. Table 10 details the derivation of the probability for incidental detection.

Incidental detection might also occur for smaller aneurysms although many health professionals will not act on aortic diameters below 40 mm. Furthermore, even if an aortic diameter is considered to be a clinically relevant aneurysm, systematic follow up is not always provided. The model assumed that no incidental detection occurrs for aneurysms ≤55 mm. This could present a bias against screening as the costs of eventual follow up are disregarded, and a bias for screening as the opportunity for early detection of surgical indication is missed. The model was structurally build to facilitate sensitivity analysis of including incidental detection of smaller aneurysms, which was set to a zero probability in the base-case analysis.

Table 10 Derivation of the annual probability of incidental detection of aneurysms ≥55mm

Age group	65-69	70-74	75-79	80-84	85-89	90-94	95-99	100+	Total
Men (n)	132791	97689	69038	46330	23588	7351	1423	104	378314
Prevalence (%)	0.32	0.47	0.63	0.76	0.90	1.03	1.19	0.96	NA
Prevalent	425	459	435	352	212	76	17	1	1977
Elective operations	61	77	48	24	4	0	0	0	214
Detected but not operated	5	6	4	2	0	0	0	0	18
All detected	66	84	52	26	4	0	0	0	232
Detected (%)	15.51	18.20	12.00	7.42	1.85	0.00	0.00	0.00	11.72

Note: The number of elective surgeries was adapted from Danish Registry for Vascular Surgery for the year 2008 where no systematic screening was offered in Denmark. The number of elective surgeries was reduced according to the fact that 35% of patients undergoing elective surgery have a diameter <55 mm and another 7.7% are operated on an indication which is not due to aneurysm-related symptoms (according to trial observations in the VIVA study as per July 2011 for N=72). The size of the general population was informed from Statistics Denmark (as per July 2008). NA=not applicable.

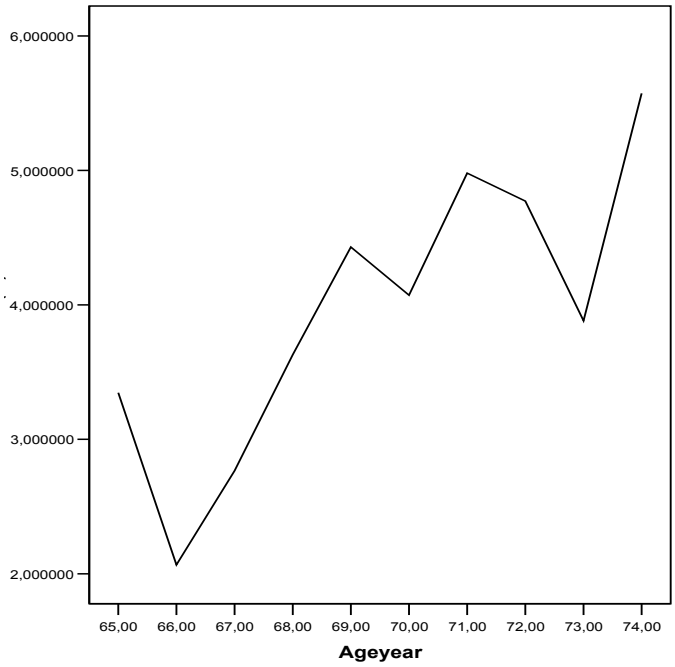

Figure 7 Association between prevalence of aneurysms ≥55 mm (1/1,000) and age in the Viborg and the VIVA trials (n=13.526)

Detection by screening

Attendance was estimated from the recent VIVA trial where 18,729 of 25,097 invited (74.63%) attended screening. The diagnostic accuracy of ultrasonography was assumed to be 100% according to Lindholt et al.[3]

Attendance at follow up is ongoing in the VIVA trial and estimates from the older Viborg trial were therefore adapted. In the Viborg trial it was observed that of the 169 individuals, who were referred for follow up (aneurysm ≥30 mm; not dead before the scheduled follow up), 150 complied with the invitation.[1] A compliance of 89% was accordingly used for base-case modelling. Attendance at rescan was estimated from the Viborg trial where 248 of 286 eligible individuals (86.71%) attended rescan after 3-5 years.[29] Fourty-eight of 248 individuals (19.35%) attending rescan were found to have an aortic diameter ≥30 mm and all detected aneurysms were observed to be ≤49 mm.

Proportion with symptoms

Patients who develop symptoms before rupture are referred to acute surgery. The probability for this can be derived from the ratio between referral to acute surgery with and without rupture. For this calculation, the numbers of procedures with and without ruptures were informed from the Danich Registry for Vascular Surgery for the years 2002-2010; 478 acute procedures without rupture / 1472 acute procedures with rupture resulted in a ratio of 0.3248. This estimate was adjusted to account for the fact that only a proportion of patients will reach the hospital alive in case of rupture and finally, the probability of being operated on symptoms rather than rupture was allowed to increase for increasing aneurysm-sizes (see Table 11).

Table 11 Derivation of the annual probability for undergoing acute surgery due to symptoms

Aneurysm (mm)	Probability rupture	Reach hospital alive	Probability acute surgery with rupture	Ratio between acute procedures with versus without rupture	Probability acute surgery without rupture
30-49	0.0000	0.4527	0.0000	0.3248	0.0000
50-54	0.0098	0.4527	0.0045	0.3248	0.0014
55-59	0.0922	0.4527	0.0418	0.3248	0.0136
60-69	0.1025	0.4527	0.0464	0.3248	0.0151
70-79	0.1160	0.4527	0.0525	0.3248	0.0171
80+	0.3225	0.4527	0.1460	0.3248	0.0474

Proportion who refuse or are unfit for surgery

A proportion of patients will be inoperable due to being unfit or refusing to have surgery (both applying only to surgery without rupture). Table 12 presents the probability for such reported in the four RCTs examining the efficacy of screening.[1,5,31,32]

Table 12 Proportion of patients who refuse or are unfit for aneurysmal repair

Study	Referrals	Unfit or refused	Probability	Reference
Chichester	64	27	0.4219	Vardulaki et al. (2002)
Viborg	93	9	0.0968	Lindhold et al. (2005)
Western Australia	NR	NR	NA	Norman et al. (2004)
MASS trial	330	32	0.0970	Scott et al. (2005)
Combined	487	68	0.1396	NA
Combined, adjusted[1]	487	39.96	0.0821	NA

[1]Adjusted according to the proportion of patients formerly inoperable but today treated by endoscopic surgery. NR=not reported. NA=not applicable.

The combined estimate was derived in populations being offered fewer treatment modalities than patients are offered today. In particular, since EVAR has become part of routine practice the proportion of unfit is anticipated to have decreased significantly. This is however not yet reflected in the literature for which reason the estimate was adjusted according to the proportion of patients today undergoing EVAR (detailed in the following section).

Proportion treated by EVAR

The proportion getting having endovascular surgery was estimated from recent annual reports of national databases. Two registries were considered to be similar to the (future) Danish setting: the Swedish and the English. Numbers of registries were pooled with the Danish to provide a combined estimate (see Table 13). The distribution of patients between endovascular and open repairs does not differ between regimens with versus without screening.[33]

Table 13 The proportion treated by endovascular repair

	EVAR	All surgeries	Probability
The Danish Registry for Vascular Surgery (2009)	194	743	0.2611
The Swedish Vascular Registry (2009)	348	789	0.4411
The English National Vascular Registry (2008)	1580	3614	0.4372
Combined	2122	5146	0.4123

EVAR=endoscopic vascular aorta repair.

Cost parameters

The economic evaluation was undertaken from a restricted health care perspective meaning that apart from the costs of the screening programme, only costs directly related to vascular repair were included. As a general rule, item costs were informed from recent, Danish sources (see Table 14).

Table 14 Item costs (2009-£)

Parameter	Mean	SD[1]	Sample size	Source
Invitation and screening	20	1	6,333	Lindholt et al. 2010
Follow up scan	205	103	6,333	DRG tariff
Elective open repair	11,108	918	25	Lindholt & Sørensen 2010
Acute open repair without rupture	19,788	6414	23	Lindholt & Sørensen 2010
Acute open repair with rupture	25,733	12934	24	Lindholt & Sørensen 2010
Endovascular repair	17,377	8689	194	DRG tariff, adjusted[2]

[1]Standard deviations are not available for Danish DRG tariffs and an assumption about these amounting to 50% of mean estimates was made. [2]Tariff loaded to account for the cost of postoperative complications not included in the standard tariff.

Costs were converted to Pounds Stirling and, where relevant, inflated to price year 2009. Two items were valued using Diagnosis-Related Grouping (DRG) tariffs. As no measure of variance is available for these tariffs, a standard deviation of 50% of the mean and an underlying sample size corresponding to the total number of procedures performed per year were assumed in order to specify a Gamma distributions.

Screening

The cost of the screening programme was adapted from the Viborg trial, conducted in the Central Denmark Region from 1994 through 1998.[34] Although these estimates refer to resource use more than 10 years back in time, they were not valued before the year 2009 (using 2007 unit costs). A programme cost per 6,000 participants was calculated, based on actual costs, and included the fixed cost of scanning equipment, invitation costs and the variable costs of scans. The resulting costs were £20.21 per invitee and £15.51 per participant when adjusting for an attendance rate of about 77%.[34] Costs were estimated from absolute programme costs and thus no standard deviations were available; a variance corresponding to 5% of mean costs was assumed.

Follow up scan

The DRG tariff for an uncomplicated ultrasonography conducted at a hospital of £205 was adapted (procedure code PG14N, diagnosis DI719).

Elective open repair

A cost estimate of £11,108 was adapted from a recent micro costing study.[35] The study was conducted as a retrospective cohort study where 25 patient files were retrieved and resource use systematically collected, including postoperative complications occurring up to a year after the procedure. Valuation was undertaken using various sources for the reflection of true opportunity costs.

Acute repair with and without rupture

The above-mentioned costing study was also adapted to inform the cost of acute repairs: £25,733 for procedures with rupture and £19,788 for procedures without rupture.[35]

Endovascular abdominal repair

No Danish cost estimates are available for the EVAR procedure, except for a DRG tariff (procedure code KPDQ10, diagnosis DI714), which amounts to £14,785. The tariff does not include postoperative complications, which have been found to be significantly more frequent in endovascular than in open surgery. For that reason a load factor of 1.18 was applied to account for readmissions and reinterventions that would be paid separately under the DRG system. The load factor was informed from an external study as described below.

In a recent study from the UK, the costs of complications incurring after the primary admission for aneurysmal repair amounted to £442 for open procedures and £2,283 for endovascular procedures – a significant extra cost of 18% for the endovascular procedure and an insignificant extra cost of 4% for the open procedure.[36] The study was based on 1,252 patients with aneurysms ≥5.5 cm, who were randomly allocated to receive either open or endovascular elective repair at 37 hospitals in the UK. Patients were followed for complications, reinterventions, mortality and resource use until the end of 2009, representing a follow up time of up to 8 years. Costing of primary repairs was based on resource use of endovascular devices, theatre occupation times, blood products used, radiation exposure times, postoperative interventions, length of stay on wards, intensive therapy units and high dependency units. The results were overall comparable with those of the Danish micro costing study.[35] Costing of aneurysm-related readmissions was based on readmissions for the primary aneurysm procedure and in-patient graft-related reinterventions. Unit costs were adapted from national average tariffs[37,38], market prices of blood products[39] and from ad hoc data from participating centres. Costs were discounted by an annual rate of 3.5%. Endovascular repair was found to be more costly than open repair with a cost difference at £1,177 (SD 791) for the primary procedure and £1841 (SD 474) for readmissions. It should be noted that the British study is about 10 years old and that the stent technology has improved over time (reduced risk of leakage). This could lead to an overestimation of the complication costs of EVAR but the direction of such will be against screening.

Omitted costs included in sensitivity analysis

The restricted health care perspective used leave out some cost categories that might be important to a societal decision about introducing population screening. First, when citizens are invited to attend a screening programme they will either take time off from work, which leads to production loss, or they will take time off from private activities, which also have a cost. Second, there will be transportation costs for the citizens to attend the screening and/or for professionals to get to decentral screening locations. Omitted cost categories in the base-case were included for sensitivity analyses (see Table 15).

Table 15 Additional cost parameters used for sensitivity analysis (2009-£)

Cost parameter	Cost	Source
Transportation	7.96	Vammen et al. 2001
Private time	7.85	Vammen et al. 2001
Production loss	2.69	Vammen et al. 2001

Parameter estimates for private costs were adapted from a micro costing study conducted in relation to the Viborg trial, where a subsample (n=379) responded to a questionnaire about the time spend attending screening as well as the distance to the screening location and the time forgone getting there.[40] On average, attendees spend 1.5 hours on transportation for an average distance of 25 kilometres. Twenty per cent of attendees were in paid employment and ten per cent were accompanied to the location typically by their spouse. Production loss was valued using the national average gross wage for men aged 65-69 at £13.44/hour and private time was values using the net equivalent at £9.78/hour. Accompanying females' time was valued at £6.28/hour and £8.71/hour if in paid work. Taximeter costs were valued using the government's official tariff per kilometre of £0.32.

Quality-adjusted life years

The benefits of screening are realised late in life where the health-related quality of life is generally less than perfect. Danish population norms were used to adjust for this (see Table 16).[41]

Table 16 Population norms for health-related quality of life

Age group	Mean	SD	n
65-69	0.8877	0.1437	459
70-74	0.8478	0.1876	403
75-79	0.8432	0.1825	292
80-84	0.8023	0.2164	152
85-90	0.7993	0.2019	57
90-94	0.7524	0.2236	8

Note: estimates for 10-year age strata were reported in Sørensen et al. (2009) up to age 79 but in order to inform older age groups the authors kindly provided ad hoc estimates as shown. The estimate for the age strata 90-94 was used for ages ≥90 years.

A relevant discussion concerns to which extent individuals experience a decrement in quality of life when being invited for screening and thereby reminded about their risk of cardiovascular disease. While there might be temporary effects associated with being invited for and attending screening, more significant effects are expected for individuals detected with aneurysms. For patients detected with an aneurysm below the threshold for curative treatment there will be a (long-term) follow up period in which the course of their disease is uncertain. For patients detected with an aneurysm eligible for elective or acute surgery there may be temporary anxiety until successful treatment is completed. Finally, it seems a relevant issue whether surgically treated patients return to the population norm after treatment.

A systematic literature review from 2008 identified 25 studies examining quality of life in AAA of which only 9 reported utility estimates.[42] The authors concluded that results in general were inconsistent and that no conclusion (nor meta-analysis) was justified.

The referred literature search was updated in June 2010 using the search terms "abdominal aortic aneurysm*" AND ("quality of life" OR utility OR "patient reported outcome*" OR "quality-adjusted life year*" OR QALY* OR euroqol OR EQ-5D) in a Medline search. The time limit was defined from Jan 1, 2007 to July 1, 2010. Of the resulting 62 references only 8 were found to be relevant upon examination of abstracts and these were obtained in full.

Five studies concerned the outcome after endovascular (versus open) surgery.[43-47] None of these reports a statistically significant decrement in quality of life over the course of time from pre- to postoperatively and none reports a statistically significant difference between surgical techniques. One study reported the outcome of elective open repair versus repair after rupture and reported that study participants compared well with the normal population and, that no difference was observed between groups, except for elective patients performing slightly better than acute patients in a dimension concerning social life after a follow up time of up to 8 years.[48] One study with the difference between younger and older patients (below/above 80 years, n=25/20) and identified only minor difference related to the functional ability.[49] The study dealt with the way information are given prior to surgery and found that patients' quality of life was stable over time and seemed independent of whether they received individualized or standard information.[50]
The effect on quality of life of being invited to screening or of being diagnosed with AAA thus seems to remain hypothetical due to a limited literature. Accordingly, no adjustments were made in the base-case analysis.

In a study conducted alongside the Viborg trial a random sample of trial participants were selected and invited to report quality of life (using the ScreenQL questionnaire) at different points in time, allowing for various subgroups from the screening arm to be compared with controls from the non-screening arm.[51] A score difference of 2.33% was observed between invited (n=439) and non-invited (n=231) at a point in time before attending screening. On the other hand, attendees more than normalised after screening and actually scored 2.21% higher than controls. A score difference of 5.85% was observed between attendees (n=286) and attendees detected with an aneurysm requiring follow up (n=106) in a point in time after screening had taken place. These estimates were used to adjust baseline utility, as detailed in Table 17, for incorporation in sensitivity analysis.

Table 17 Quality of life effects associated with screening

	Adjustment factor	Period
From invitation to screening	-2.33%	3 months
After screening if no aneurysm	2.21%	3 months
After screening if aneurysm <55 mm	-5.85%	Follow up period

Note: the adjustment factor was informed from an observational study conducted alongside the Viborg screening trial as reported by Lindholt et al. 2000.

The overall estimation of quality-adjusted life years (QALYs) was based on the Danish scoring algorithm.[52]

Specification of probability distributions

A consistent approach was applied for the specification of probability distributions according to the type of parameters. Table 18 provides a complete list of specifications and the following describes the chosen distributions. Where relevant for specifications the conventional equation for conversion between standard errors and standard deviation was used:[53]

$$SE=SD / \sqrt{n}$$

Prevalence (distribution in starting states)

The distribution of individuals in starting states follows 8 independent probabilities that should always sum to one (all individuals have an aortic diameter whether measurable or not). The Dirichlet distribution, which includes k independent distributions for which probabilities α are normalized by their sum was accordingly use.[54] It is parameterized with a list of k probabilities:

$$Dirichlet(\alpha_1, \alpha_2,...\alpha_k)$$

Transition probabilities

Probabilities follow a continuous distribution bounded by 0 and 1. The Beta distribution with a mean of r/n, where r is occurrences and n is sample size, was accordingly chosen. Approximation is possible from conventional means and standard errors if r and n are unknown.[55]

Beta(n,r) [integer form] or
Beta(α,β) [real number form] where
α=mean^2*(1-mean)/(se^2) and
β=mean*(1-mean)/(se^2)- α

Costs

In the present context costs are always positive and expected to follow a skewed distribution with a long tale to the right. Most individuals have zero costs or only the screening cost while a very few have high costs due to surgical intervention. The Gamma distribution was chosen because it can be approximated from conventional means and standard deviations:

Gamma(α,λ) where
α is the shape of the distribution and
λ is the scale of the distribution, which can be approximated by
α=(mean^2)/(se^2)
λ=mean/(se^2)

Utilities
Utility values are continuous and, in principle, range from 0 to 1. The Beta distribution was therefore used.

Relative risks and odds ratios
These parameters represent ratios that are additive on the log scale and hence the lognormal distribution was adapted:

Lognormal(μ,σ) where
μ=mean of logs
σ=standard deviation of logs

However for some estimates the necessary information for specifying the lognormal distribution was not available and the normal distribution was therefore used.

Table 18 Overview of model parameters

Description	Mean	Distribution	Source
Prevalence/disease distribution	3.25	Dirichlet(94.11; 2.64;2.71;0.22;0.12;0. 08;0.06;0.06)	VIVA/Viborg trials
Attendance initial screening	0.75	Beta(24615,18378)	
Attendance rescan	0.87	Beta(286,248)	
Attendance follow up	0.89	Beta(169,150)	
Proportion endovascular repair	0.41	Beta(5146,2122)	DRVS
Post elective repair mortality	0.03	Beta(1689,50)	
Post acute repair mortality	0.09	Beta(304,26)	
Post rupture repair mortality	0.39	Beta(832,322)	
Proportion symptoms 50-54 mm	0.00	Beta(1472,2)	
Proportion symptoms 55-59 mm	0.01	Beta(1472,20)	
Proportion symptoms 60-69 mm	0.01	Beta(1472,22)	
Proportion symptoms 70-79 mm	0.02	Beta(1472,25)	
Proportion symptoms 80+ mm	0.05	Beta(1472,70)	
Contraindication surgical repair	0.08	Beta(487,40)	Vardulaki et al. 2002, Lindholt et al. 2005, Scott et al. 2005
Growth rate 25-29 mm (annual)	0.07	Beta(648,48)	VIVA/Viborg trials
Growth rate 30-49 mm (annual)	0.09	Beta(363,33)	
Growth rate 50-54 mm (annual)	0.62	Fixed	Assumption based on extrapolation of data from VIVA/Viborg trials
Growth rate 55-59 mm (annual)	0.67	Fixed	
Growth rate 60-69 mm (annual)	0.39	Fixed	
Growth rate 70-79 mm (annual)	0.44	Fixed	
Rupture rate 50-54 mm (annual)	0.01	Beta(607,6)	Lederle et al. 2002 Brown et al. 2003
Rupture rate 55-59 mm (annual)	0.10	Beta(62,6)	
Rupture rate 60-69 mm (annual)	0.11	Beta(130,14)	
Rupture rate 70-79 mm (annual)	0.12	Beta(73,9)	
Rupture rate 80+ mm (annual)	0.39	Beta(57,22)	
Incidental detection of ≥ 55 mm	0.12	Beta(1977,232)	DRVS, VIVA/Viborg trials National patient registry
Reaching hospital alive with rupture	0.45	Beta(6954,3148)	DRVS, National Death-Cause Registry
Costs of endovascular repair	17377	Gamma(4,0)	Lindholt et al. 2010, Lindholt & Sørensen 2009
Costs of follow up scan	205	Gamma(248,1)	
Costs of open acute	19778	Gamma(10,0)	
Costs of open acute with rupture	25733	Gamma(4,0)	
Costs of open elective	11108	Gamma(146,0)	
Costs of screening per invitee	20	Gamma(400,20)	
Excess mortality 30-49 mm (OR)	1.46	Fixed	DRVS, VIVA/Viborg trials, national mortality statistics
Excess mortality 50-54 mm (OR)	1.70	Fixed	
Excess mortality >55 mm (OR)	2.15	Fixed	
Excess mortality inoperable (OR)	2.57	Fixed	
Reduced non-AAA-related mortality in screened individuals (OR)	0.98	Normal(0.98,0.02)	Original analysis reported in the present report
Reduced post elective mortality in the screened (OR)	0.37	Normal(0.37,0.14)	Lindholt & Norman 2011

Note: DRVS = Danish Registry for Vascular Surgery, OR = odds ratio.

Model validation

Kim and Thompson has recently shown how model validation can be undertaken.[56] Using the model built on the MASS trial they demonstrated three forms of validation: internal validation by comparing model predictions with observations from the trial it is built on (given that the model is built on a single trial), prospective validation by letting the model predict the course of future trial follow ups (given that additional long term follow up is available) and external validation by comparing model predictions with results of a trial that has not been used to informed the model.

The present model represents a synthesis of evidence and hence it is not build on a single trial that can be used for internal validation. Simple checks for logical consistency was therefore used to assess the internal model validity. Also, it should be noted that internal validity is a prerequisite for external validity, hence if external validity can be established, the model should also be overall internally valid.

The Viborg trial was recently reported with long term follow up in terms of key events, costs and life years.[34] It has been drawn on to inform some parameters of the present model (attendance, detection rate at rescan, transition rates for small aneurysms and costs of screening) but the parameters known to be the most potent has been informed from elsewhere (rupture rates, transition rates of medium- and large-sized aneurysms, costs of surgery, incidental detection rate, postoperative mortality etc.) and the trial results are therefore, to some extent, relevant for assessing model validity. Nevertheless, it should be underlined that the model was build and informed to represent a modern scenario and that about 15 have passed since the Viborg trial was initiated in 1994. Accordingly, predicted event rates are expected to be in the lower than those observed in the Viborg trial, due to the improvements in general cardiovascular health and treatment regimens.

Trackers were defined in the model to count key events over time. It should be mentioned that simulation is a stochastic process that will result in different results from trial to trial. If there is large variation in the input distributions of the model, the individual trials simulated will lead to different predictions. In case of relatively rare events, as for example rupture or acute surgery for symptoms, a very large number of simulations is needed to provide stable predictions. For the present purpose 100,000 random walks (microsimulations) were specified to generate probabilities, which were then multiplied by the cohort sizes of the Viborg trial to enable comparison of model predictions versus trial observations (n=6,306 control arm, n=6,333 screening arm).

Two alternations had to be made to the model in order for it to match the Viborg trial: follow up limited to 10 years (as the trial defined staggered inclusion and followed the participants for an average of 10 years) and start-age redefined to 68 years (as the trial included men aged 65-74, who had a baseline mean age of 68 years). The validation exercise thus assumes that the average follow up time of 10 years could be compared with a fixed follow up time of the model. This assumption seems reasonable for events that fall in the early years after screening whereas for events that fall primarily later in life (e.g. rupture due to undetected aneurysms) a fixed 10-year follow up may lead to fewer events than staggered inclusion with up to 14 years of follow up. In such case the difference-in-difference comparison of trial observations and model

predictions should be used to judge the model validity. We also assume that the average 68-year-old individual is comparable to a cohort with a mean age of 68 years. The tables 19-21 show comparisons between the numbers of key events observed in the Viborg trial versus the numbers predicted by the model.

Although no statistical differences were noted between model predictions and trial observations, we noted that the model reflected a more peaceful epidemiology with fewer ruptures and fewer patients developing symptoms, leading to fewer surgeries and fewer AAA-related deaths. Similarly, the number of detected aneurysms was lower for the model. Overall, the differences between model predictions and trial observations were as expected and reflected a conservative, modern model. The differences in all-cause mortality could be fully explained by informing the model with 10 year old mortality rates.

Tables 22 and 23 compares the timing of events with relevant sources. These do also seem to compare well between model predictions and reality.

Table 19 Predicted versus observed number of key events in a scenario without screening

	Model predictions	Viborg trial	Difference
Detection			
Incidental	34	NA	NA
By screening	0	0	0
Total detection	34	NA	NA
Elective surgery			
EVAR	14	NA	NA
OPEN	17	NA	NA
Total elective surgery	31	44	-13
Acute surgery			
For rupture	17	36	-19
For symptoms	4	8	-4
Total acute surgery	21	44	-23
Rupture	37	70	-33
Mortality			
AAA-related	29	55	-26
Non-AAA-related	1973	2121	-148
Total mortality	2002	2176	-174

Note: estimates refer to a time horizon of 10 years for a cohort of 6,306 individuals. All-cause mortality from the Viborg trial was limited to that occuring before 10 years of follow up. NA = not applicable.

Table 20 Predicted versus observed number of key events in a scenario with screening

	Model predictions	Viborg trial	Difference
Detection			
Incidental	18	0	NA
By screening	182	238	-56
Total detection	200	238	-38
Elective surgery			
EVAR	29	NA	NA
OPEN	38	NA	NA
Total elective surgery	68	89	-21
Acute surgery			
For rupture	9	16	-7
For symptoms	2	4	-2
Total acute surgery	11	20	-9
Rupture	21	23	-2
Mortality			
AAA-related	17	19	-2
Non-AAA-related	1936	2163	-227
Total mortality	1954	2182	-228

Note: estimates refer to a time horizon of 10 years for a cohort of 6,333 individuals. All-cause mortality from the Viborg trial was limited to that occuring before 10 years of follow up. NA = not applicable.

Table 21 Difference-in-difference summary: predicted versus observed effects of screening for a number of key events

	Model predictions	Trial observations	Difference
Detection			
Incidental	-16	NA	NA
By screening	182	238	-56
Total detection	166	NA	NA
Elective surgery			
EVAR	15	NA	NA
OPEN	21	NA	NA
Total elective surgery	36	45	-9
Acute surgery			
For rupture	-8	-20	12
For symptoms	-2	-4	2
Total acute surgery	-10	-24	14
Rupture	-16	-47	31
Mortality			
AAA-related	-11	-36	25
Non-AAA-related	-37	42	-79
Total mortality	-48	6	-54

Note: estimates refer to a time horizon of 10 years, unless otherwise stated, and a cohort of 12,639 individuals (n=6,306 control arm, n=6,333 in screening arm). All-cause mortality from the Viborg trial was limited to that occuring before 10 years of follow up. NK = not known.

Table 22 Predicted life expectancy versus national statistics for a man aged 65 years

		Model predictions	
	National statistics	Screening	Control
Life expectancy	81.57	80.86	81.05

Note: National statistics can be found at www.statistikbanken.dk.

Table 23 Predicted age by time of AAA-related aneurysm mortality

		Model predictions	
	DRVS	Screening	Control
Age by time of death due to rupture	73	73.50	74.37

Note: DRVS = Danish Registry for Vascular Surgery.

Acknowledgements and funding

A group of key stakeholders and field experts were invited to observe the development of the model: Professor in epidemiology at Research Unit of Clinical Epidemiology, Center for National Clinical Databases, Odense University Hospital, Anders Green, MD, DMSc; Consultant at the National Board of Health, Ole Andersen, MD, MHM, DMSc; Chairman at the Department of Vascular Surgery at Rigshospitalet, Henrik Sillesen, MD, DMSc; and Professor in health services research at Centre for Health Services Research and Technology Assessment, University of Southern Denmark, Jan Sørensen, MSc. This work has benefitted significantly from the inputs of these experts, which were received at different stages of the project: after development of a proposed model structure and after the model structure had been validated but no cost-effectiveness results had been revealed. The final report does however not necessarily represent the view of these stakeholders and, in particular, any errors remain the responsibility of the authors alone.

Professor Anders Green undertook the original analysis of the relative all-cause mortality (Table 4) and Professor Jan Sørensen provided detailed utility estimates for the normal population (Table 16).

The leading librarian of the Research Library of Viborg Hospital, Hanne Margit Gronemann Christensen, conducted the systematic literature searches relating to transition probabilities. The Danish Registry for Vascular Surgery (www.karbasen.dk) provided ad hoc estimates from the database. A previous version of the paper was presented at the 31st Nordic Health Economists Study Group (NHESG) meeting by discussant Lars Ehlers.

The Health Research Fund of Central Denmark Region and the Research Fund of Viborg Hospital funded the present work. The sponsors had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

References

1. Lindholt JS, Juul S, Fasting H, Henneberg EW. Screening for abdominal aortic aneurysms: single centre randomised controlled trial. *BMJ.* Apr 2 2005;330(7494):750.

2. Silverstein MD, Pitts SR, Chaikof EL, Ballard DJ. Abdominal aortic aneurysm (AAA): cost-effectiveness of screening, surveillance of intermediate-sized AAA, and management of symptomatic AAA. *Proc (Bayl Univ Med Cent).* Oct 2005;18(4):345-367.

3. Lindholt JS, Vammen S, Juul S, Henneberg EW, Fasting H. The validity of ultrasonographic scanning as screening method for abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg.* Jun 1999;17(6):472-475.

4. Ashton HA, Buxton MJ, Day NE, et al. The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. *Lancet.* Nov 16 2002;360(9345):1531-1539.

5. Norman PE, Jamrozik K, Lawrence-Brown MM, et al. Population based randomised controlled trial on impact of screening on mortality from abdominal aortic aneurysm. *BMJ.* Nov 27 2004;329(7477):1259.

6. Scott RA, Wilson NM, Ashton HA, Kay DN. Influence of screening on the incidence of ruptured abdominal aortic aneurysm: 5-year results of a randomized controlled study. *Br J Surg.* Aug 1995;82(8):1066-1070.

7. Cosford PA, Leng GC. Screening for abdominal aortic aneurysm. *Cochrane Database Syst Rev.* 2007(2):CD002945.

8. Campbell H, Briggs A, Buxton M, Kim L, Thompson S. The credibility of health economic models for health policy decision-making: the case of population screening for abdominal aortic aneurysm. *J Health Serv Res Policy.* Jan 2007;12(1):11-17.

9. Ehlers L, Overvad K, Sorensen J, Christensen S, Bech M, Kjolby M. Analysis of cost effectiveness of screening Danish men aged 65 for abdominal aortic aneurysm. *BMJ.* 2009;338:b2243.

10. Henriksson M, Lundgren F. Decision-analytical model with lifetime estimation of costs and health outcomes for one-time screening for abdominal aortic aneurysm in 65-year-old men. *Br J Surg.* Aug 2005;92(8):976-983.

11. Kim LG, Thompson SG, Briggs AH, Buxton MJ, Campbell HE. How cost-effective is screening for abdominal aortic aneurysms? *J Med Screen.* 2007;14(1):46-52.

12. Mani K, Alund M, Bjorck M, Lundkvist J, Wanhainen A. Screening for abdominal aortic aneurysm among patients referred to the vascular laboratory is cost-effective. *Eur J Vasc Endovasc Surg.* Feb 2010;39(2):208-216.

13. Montreuil B, Brophy J. Screening for abdominal aortic aneurysms in men: a Canadian perspective using Monte Carlo-based estimates. *Can J Surg.* Feb 2008;51(1):23-34.

14. Wanhainen A, Lundkvist J, Bergqvist D, Bjorck M. Cost-effectiveness of different screening strategies for abdominal aortic aneurysm. *J Vasc Surg.* May 2005;41(5):741-751; discussion 751.

15. Søgaard R, Lindholt JS. Evidence for the credibility of health economic models for health policy decision-making: A systematic literature review regarding the case of screening for abdominal aortic aneurysms. *Journal of Health Services Research and Policy.* 2011;Accepted for publication.

16. Fleurence RL, Hollenbeak CS. Rates and probabilities in economic modelling: transformation, translation and appropriate application. *Pharmacoeconomics.* 2007;25(1):3-6.

17. Briggs A, Sculpher M. An introduction to Markov modelling for economic evaluation. *Pharmacoeconomics.* Apr 1998;13(4):397-409.

18. A comparative study of the prevalence of abdominal aortic aneurysms in the United Kingdom, Denmark, and Australia. *J Med Screen.* 2001;8(1):46-50.

19. Grøndal N, Søgaard, R., Henneberg, E.W., Lindholt, J.S. The Viborg vascular (VIVA) screening trial of 65-74 year old men in the central region of Denmark: study protocol. *Trials.* 2010 2010:11-67.

20. Endovascular Repair of Aortic Aneurysm in Patients Physically Ineligible for Open Repair. *N Engl J Med.* Apr 30 2010.

21. Lindholt JS, Norman P. Screening for abdominal aortic aneurysm reduces overall mortality in men. A meta-analysis of the mid- and long-term effects of screening for abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg.* Aug 2008;36(2):167-171.

22. Powell JT, Sweeting MJ, Brown LC, Gotensparre SM, Fowkes FG, Thompson SG. Systematic review and meta-analysis of growth rates of small abdominal aortic aneurysms. *Br J Surg.* May 2011;98(5):609-618.

23. Brown PM, Zelt DT, Sobolev B. The risk of rupture in untreated aneurysms: the impact of size, gender, and expansion rate. *J Vasc Surg.* Feb 2003;37(2):280-284.

24. Lederle FA, Johnson GR, Wilson SE, et al. Rupture rate of large abdominal aortic aneurysms in patients refusing or unfit for elective repair. *JAMA.* Jun 12 2002;287(22):2968-2972.

25. Brady AR, Thompson SG, Fowkes FG, Greenhalgh RM, Powell JT. Abdominal aortic aneurysm expansion: risk factors and time intervals for surveillance. *Circulation.* Jul 6 2004;110(1):16-21.

26. Brady AR, Thompson S. *Making predictions from hierarchical models for complex longitudinal data, with application to aneurysm growth.* Cambridge: MRC Biostatistics Unit;2002.

27. Sweeting MJ, Thompson SG. *Making predictions from complex longitudinal data, with application to planning monitoring intervals in a national screening programme.* Cambridge: MRC Biostatistics Unit;2010.

28. Brown PM, Sobolev B, Zelt DT. Selective management of abdominal aortic aneurysms smaller than 5.0 cm in a prospective sizing program with gender-specific analysis. *J Vasc Surg.* Oct 2003;38(4):762-765.

29. Lindholt JS, Vammen S, Juul S, Fasting H, Henneberg EW. Optimal interval screening and surveillance of abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg.* Oct 2000;20(4):369-373.

30. Lindholt JS, Norman PE. Meta-analysis of postoperative mortality after elective repair of abdominal aortic aneurysms detected by screening. *Br J Surg.* May 2011;98(5):619-622.

31. Scott RA, Thompson SG. Screening, surgical repair, and the management of abdominal aortic aneurisms. *J Med Screen.* 2005;12(2):57-58.

32. Vardulaki KA, Walker NM, Couto E, et al. Late results concerning feasibility and compliance from a randomized trial of ultrasonographic screening for abdominal aortic aneurysm. *Br J Surg.* Jul 2002;89(7):861-864.

33. Thompson AR, Rodway A, Mitchell A, Hafez H. Screening and ultrasound surveillance of large abdominal aortic aneurysms do not improve suitability for endovascular repair. *J Vasc Surg.* Feb 2006;43(2):265-269; discussion 269.

34. Lindholt JS, Sorensen J, Sogaard R, Henneberg EW. Long-term benefit and cost-effectiveness analysis of screening for abdominal aortic aneurysms from a randomized controlled trial. *Br J Surg.* Jun 2010;97(6):826-834.

35. Lindholt JS, Sørensen J. Hospital costs of abdominal aortic aneurysm repair [in Danish]. *Dan Med Bull.* [Epub] Nov 2 2009.

36. Greenhalgh RM, Brown LC, Powell JT, Thompson SG, Epstein D, Sculpher MJ. Endovascular versus open repair of abdominal aortic aneurysm. *N Engl J Med.* May 20 2010;362(20):1863-1871.

37. NHS Scotland. *Cost book 2008/2009 (release 24/11/09)*. Edinburgh: ISD Scotland; 2009.

38. *NHS Trust reference cost schedules 2007-08*. London: Department of Health; 2009.

39. National Blood Service. *National Blood and Blood Components Price List 2009-2010*. London: NBS; 2009.

40. Vammen S, Lindholt JS, Juul S, Henneberg EW, Fasting H. Screening for Abdominal Aortic Aneurysms: An Analysis of the Private and Indirect Costs in a Hospital-based Screening Program. *International Journal of Angiology.* 2001;10:246-249.

41. Sorensen J, Davidsen M, Gudex C, Pedersen KM, Bronnum-Hansen H. Danish EQ-5D population norms. *Scand J Public Health.* Jul 2009;37(5):467-474.

42. Muszbek N, Thompson MM, Soong CV, Hutton J, Brasseur P, van Sambeek MR. Systematic review of utilities in abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg.* Sep 2008;36(3):283-289.

43. Lederle FA, Freischlag JA, Kyriakides TC, et al. Outcomes following endovascular vs open repair of abdominal aortic aneurysm: a randomized trial. *JAMA.* Oct 14 2009;302(14):1535-1542.

44. Tarride JE, Blackhouse G, De Rose G, et al. Cost-effectiveness analysis of elective endovascular repair compared with open surgical repair of abdominal aortic aneurysms for patients at a high surgical risk: A 1-year patient-level analysis conducted in Ontario, Canada. *J Vasc Surg.* Oct 2008;48(4):779-787.

45. Dick F, Grobety V, Immer FF, et al. Outcome and quality of life in patients treated for abdominal aortic aneurysms: a single center experience. *World J Surg.* Jun 2008;32(6):987-994.

46. Hynes N, Sultan S. A prospective clinical, economic, and quality-of-life analysis comparing endovascular aneurysm repair (EVAR), open repair, and best medical treatment in high-risk patients with abdominal aortic aneurysms suitable for EVAR: the Irish patient trial. *J Endovasc Ther.* Dec 2007;14(6):763-776.

47. Prinssen M, Buskens E, de Jong SE, et al. Cost-effectiveness of conventional and endovascular repair of abdominal aortic aneurysms: results of a randomized trial. *J Vasc Surg.* Nov 2007;46(5):883-890.

48. Hill AB, Palerme LP, Brandys T, Lewis R, Steinmetz OK. Health-related quality of life in survivors of open ruptured abdominal aortic aneurysm repair: a matched, controlled cohort study. *J Vasc Surg.* Aug 2007;46(2):223-229.

49. Kurz M, Meier T, Pfammatter T, Amann-Vesti BR. Quality of life survey after endovascular abdominal aortic aneurysm repair in octogenarians. *Int Angiol.* Jun 2010;29(3):249-254.

50. Stiggelbout AM, Molewijk AC, Otten W, et al. The impact of individualized evidence-based decision support on aneurysm patients' decision making, ideals of autonomy, and quality of life. *Med Decis Making.* Sep-Oct 2008;28(5):751-762.

51. Lindholt JS, Vammen S, Fasting H, Henneberg EW. Psychological consequences of screening for abdominal aortic aneurysm and conservative treatment of small abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg.* Jul 2000;20(1):79-83.

52. Wittrup-Jensen KU, Lauridsen J, Gudex C, Pedersen KM. Generation of a Danish TTO value set for EQ-5D health states. *Scand J Public Health.* Jul 2009;37(5):459-466.

53. Altman DG, Bland JM. Standard deviations and standard errors. *BMJ.* Oct 15 2005;331(7521):903.

54. Briggs AH, Ades AE, Price MJ. Probabilistic sensitivity analysis for decision trees with multiple branches: use of the Dirichlet distribution in a Bayesian framework. *Med Decis Making.* Jul-Aug 2003;23(4):341-350.

55. *TreeAge Pro*. Williamstown: TreeAge Software, Inc; 2009.

56. Kim LG, Thompson SG. Uncertainty and validation of health economic decision models. *Health Econ.* Jan 2010;19(1):43-55.