

**The economic evaluation of health care:  
theoretical considerations and application to the  
management of patients with abdominal aortic  
aneurysm**

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## Resumen

Esta tesis aborda la evaluación económica de programas sanitarios, examinando de forma particular la aplicación práctica del análisis coste-efectividad (ACE) en la gestión de pacientes con diagnóstico de aneurisma aórtico abdominal (AAA) asintomático. Un tema actual de investigación perteneciente al campo de la economía de la salud es la mejora en la generalibilidad o transferibilidad de los resultados de un ACE desde un contexto o país a otro, de manera que dichos resultados sean útiles a distintos decisores independientemente del lugar de donde se tome la decisión. En este sentido, esta tesis tiene en cuenta la perspectiva del decisor británico, pero debido a que su defensa se realiza en la Universidad de Granada, ha resultado interesante explorar en qué medida los resultados pueden ser relevantes para los responsables políticos en España. El primer capítulo analiza, a partir de la teoría de empresa, los factores que influyen en las diferencias existentes en el uso de recursos sanitarios entre países, y cómo estas diferencias pueden afectar a la validez interna y externa del ACE. Este trabajo ha sido enviado a la revista “*Health Economics*” y actualmente está siendo considerado para su publicación. En líneas generales, el estudio muestra que para que el ACE mejore en eficiencia, deben darse una serie de condiciones: (i) las organizaciones sanitarias deben ser técnicamente eficientes (ii) Debe haber acceso común a la tecnología (iii) que haya rendimientos constantes a escala respecto al número de pacientes tratados (iv) las organizaciones sanitarias actúen minimizando costes para cada nivel de actividad (v) las organizaciones sanitarias sean precio-aceptantes en el mercado de recursos sanitarios (vi) las organizaciones sanitarias midan sus resultados a través de un indicador de salud. Según el modelo, la variación en el uso de recursos sanitarios puede ser debida, entre otras causas, a la diferencia en los precios relativos de los recursos sanitarios entre países. Los estudios clínicos para comparar la diferencia en efectos clínicos y costes entre tratamientos en diferentes países deben tener en cuenta las causas de la heterogeneidad en el diseño y el análisis del estudio.

Actualmente, existen dos alternativas para el tratamiento quirúrgico del AAA: la cirugía abierta y el tratamiento endovascular (EVAR). Las actuales directrices clínicas recomiendan diferentes tratamientos en función del tamaño del aneurisma. Así, cuando el tamaño alcanza el límite de 5,5cm de diámetro, se recomienda la intervención quirúrgica, mientras que cuando el tamaño se encuentra entre 4,5 y 5,5cm se



recomienda el seguimiento de los pacientes con ecografía cada tres o seis meses. Un objetivo de esta tesis es evaluar estas opciones de tratamiento desde la perspectiva económica.

En el segundo capítulo se compara el EVAR frente a la cirugía abierta convencional para aquellos pacientes que han tomado la decisión de operarse. El estudio se publicó en la revista *“British Journal of Surgery”* (Epstein et al 2008). El modelo incluye los riesgos de mortalidad como consecuencia del aneurisma, por otros motivos cardiovasculares y no cardiovasculares, la incidencia de reintervenciones secundarias, y la incidencia de eventos adversos cardiovasculares no fatales. Los datos del modelo se tomaron principalmente del ensayo clínico aleatorio EVAR 1, y se completaron con los de otras fuentes. Para el caso base, el EVAR resultó más caro (la diferencia en costes totales por paciente fue 3.800£ (4.353€), con un intervalo de confianza del 95% (IC del 95%): 2.400£ a 5.200£), y con menos años de vida ajustados por la calidad (AVAC) (la diferencia media por paciente fue -0,02, IC del 95%: -0,19 a 0,17). Estos resultados sugieren que el EVAR no sería coste-efectivo dada la actual evidencia existente sobre la prótesis. Sin embargo, sigue existiendo una gran incertidumbre, y podría ser coste-efectivo en algunos de los escenarios evaluados.

En los siguientes capítulos (cap. 3, 4 y 5), con el fin de ampliar las estrategias para este tipo de paciente, se evalúan otras dos alternativas que pueden llevarse a cabo en función de diferentes tamaños del aneurisma: la estrategia de no operarse, y la opción de “espera vigilada”. Esta última opción puede ser modelada a través de un análisis de “opción real”, un tipo de programa dinámico.

El tercer capítulo revisa los métodos para valorar una opción real, y examina cómo afectaría al análisis el supuesto de aversión al riesgo. En la valoración de opciones normalmente se supone que quien toma la decisión es averso al riesgo, sin embargo en el ACE habitualmente se asume que quien toma las decisiones se mantiene neutral al riesgo. Así, se muestra que bajo ciertas hipótesis, la neutralidad del decisor frente al riesgo puede ser consistente con ambas perspectivas.

En el cuarto capítulo se utiliza programación dinámica para estimar el valor de la opción de “espera vigilada”, mostrando el método a través de una versión simplificada del modelo con dos periodos. En el quinto capítulo se presenta la estimación de todos los parámetros y los resultados del modelo completo. Este análisis está basado en un trabajo

preliminar publicado en la revista “*Health Technology Assessment*” (Chambers et al 2009). Las tasas del crecimiento y ruptura de los diferentes tamaños de AAA se estimaron a partir de una revisión de la literatura clínica. En el caso base del modelo, para pacientes de 74 años de edad que puede someterse a ambas opciones de tratamiento y asumiendo una disposición a pagar de 20.000£ por AVAC, la cirugía abierta es coste-efectiva para un AAA  $\geq 4.5$ cm, En cambio, el seguimiento es coste-efectivo siempre que el tamaño del AAA se encuentre entre 4,0 y 4,5 cm. Si la disposición a pagar fuese de 30.000£ por AVAC, el tratamiento endovascular (EVAR) sería coste-efectivo para un AAA  $\geq 4.5$ cm, y el seguimiento sería coste-efectivo para un AAA  $< 4.5$ cm. En los análisis de sensibilidades realizados para este grupo de pacientes, estos umbrales oscilaron entre  $\pm 1$ cm. El análisis basal del modelo predice un umbral más bajo (el tamaño de AAA) para someterse a cirugía que lo que indican las directrices clínicas actuales. Sin embargo, como los resultados del análisis son sensibles a los supuestos del modelo, pueden existir otros escenarios más acordes con las recomendaciones de las actuales guías de práctica clínica. Para pacientes que no pueden someterse a cirugía abierta, teniendo en cuenta una disposición a pagar de 20.000£ por AVAC, el seguimiento es coste-efectivo para una aneurisma de 5,0 a 5,5cm y EVAR es coste-efectivo para un AAA 5,5-6.5cm.

El modelo del segundo capítulo compara el EVAR con la cirugía abierta a partir de evidencia recogida de ensayos clínicos aleatorios (ECA). Se espera que estos datos tengan una alta validez interna, por lo que normalmente son muy aceptables para informar acerca de las decisiones clínicas. El modelo en el quinto capítulo está actualizado en base a datos de estudios observacionales que informan sobre la historia natural de la enfermedad, con una validez interna más baja.

En los análisis de decisión en los que se dispone de datos procedentes de ensayos clínicos aleatorios, los estudios observacionales se toman normalmente en cuenta como exploratorios o simplemente como una ayuda para el diseño del estudio clínico. Sin embargo, el modelo que examina la opción de “espera vigilada” que está basado en un modelo de programación dinámica puede ser de gran utilidad, por ejemplo, cuando una alta proporción de pacientes no se adhiere al protocolo del estudio y cambia de la estrategia conservadora (sin cirugía) a la intervención (cirugía), como pasó en el ensayo EVAR 2. En estos casos, la interpretación de los resultados no está clara y su transferibilidad puede ser limitada. El “National Health Service Research and

Development Health Technology Assessment Programme” ha financiado un nuevo análisis de coste-efectividad con los datos de 8 años de seguimiento de los ensayos clínicos EVAR 1 y EVAR 2, y los métodos descritos en esta tesis tendrán un papel importante en este trabajo.

## Abstract

This thesis is concerned with the economic evaluation of health-care programmes, and in particular the practical application of cost-effectiveness analysis (CEA) to the management of patients with a diagnosed asymptomatic abdominal aortic aneurysm (AAA).

A current theme of research in the field of health economics is to try and improve the generalisability or transferability of a CEA from one setting so that it is useful to other decision makers. This thesis takes the perspective of the UK decision-maker, but as it is presented at the University of Granada, it is reasonable to ask to what extent the results are relevant to policy-makers in Spain, or could be made more relevant to them. Chapter 1 uses the theory of the firm to analyse how health care resource use might vary between countries, and reflects on how these differences might affect the internal and external validity of CEA. This paper has been submitted to Health Economics for consideration for publication. It is shown that the following conditions for health-care provider behaviour are required for CEA to improve efficiency: (i) Providers are technically efficient. (ii) There is common technology (iii) There are constant returns to scale with respect to patient numbers. (iv) Providers minimise costs for a given output (v) Providers are price-takers in markets for health-care inputs (vi) Providers use an indicator of health as their measure of output. Variations in clinical resource use patterns might arise in part because of variation in the relative prices of health-care inputs. Clinical studies that compare the clinical outcomes and costs of health-care treatments should consider the causes of heterogeneity in the design and analysis of the study.

There are currently two surgical treatments for AAA: endovascular repair (EVAR) and open repair. Current clinical guidelines recommend elective surgery for AAA  $\geq 5.5$ cm in diameter and patients with AAA 4.5-5.5cm should be followed up with ultrasonography every 3 or 6 months. One aim of this thesis is to evaluate these management options from an economic perspective. Chapter 2 compares endovascular and open repair in patients for whom the decision to operate has been made. The paper was published in the British Journal of Surgery (Epstein et al 2008). The model includes the risks of death from aneurysm, other cardiovascular and non-cardiovascular causes, the incidence of secondary re-interventions and the incidence of non-fatal cardiovascular events. Data were taken largely from the EVAR trial 1 and

supplemented from other sources. Under the base-case assumptions, EVAR cost £3,800 (95% CI £2,400 to £5,200) more per patient than open repair but produced fewer lifetime QALYs (mean -0.02, 95% CI -0.19 to 0.17). These results suggest EVAR is unlikely to be considered cost-effective based on existing devices, costs and evidence, but there remains considerable uncertainty. Under particular assumptions EVAR may be considered cost-effective.

The remaining chapters of the thesis aim to broaden the comparisons to include watchful waiting and no surgery for patients of different AAA sizes. Watchful waiting can be modelled using ‘real option’ analysis. Chapter 3 briefly reviews the theory of option pricing. Option pricing models normally assume that the decision maker is risk-averse. CEA on the other hand usually assumes the decision maker is risk-neutral. It is shown, that under certain assumptions, risk-neutrality can be consistent with both frameworks. Chapter 4 illustrates the method of dynamic programming to estimate the value of an option to delay surgery, using a simplified model with only two periods. Chapter 5 presents the detailed parameter estimates for the full model and the results for a lifetime analysis. This model is based on preliminary work that was published in Health Technology Assessment (Chambers et al 2009). The risk of rupture and growth of AAA of different sizes were estimated from a search of the clinical literature. In the base-case model for patients aged 74 years and fit for open surgery, and at a value of £20,000 per QALY, open repair is cost-effective for aneurysms  $\geq 4.5$ cm but surveillance is cost-effective for AAA of 4.0-4.5cm. At a value of £30,000 per QALY, endovascular repair is cost-effective for aneurysms  $\geq 4.5$ cm and surveillance for AAA  $< 4.5$ cm. These thresholds vary by up to  $\pm 1.0$ cm in other scenarios for this patient group. The base-case model predicts a lower threshold for operating on AAA in patients fit for open surgery than current clinical guidelines. However, results are sensitive to model assumptions and there are plausible scenarios where the model accords with current guidelines.

For patients unfit for open surgery, surveillance is cost-effective at a value of £20,000 per QALY for AAA 5.0-5.5cm and endovascular repair is predicted to be cost-effective for aneurysms 5.5-6.5cm. For AAA  $\geq 6.5$ cm the optimum policy is complex because some studies have shown that risks of late mortality after EVAR appear to increase in patients with large aneurysm. At a value of £30,000 per QALY, endovascular repair is cost-effective for aneurysms  $\geq 4.5$ cm and surveillance for AAA 4-4.5cm.

The model in Chapter 2 compares EVAR with open repair using evidence from randomised controlled trials (RCT). These data would be expected to have a high internal validity and such evidence is usually considered acceptable for clinical decision making. The model in Chapter 5 depends on data from observational studies to inform the natural history of the disease, with a lower internal validity. In decision problems where an RCT is available, such models will normally mainly be seen as exploratory or possibly as an aid to design further clinical studies. However, watchful waiting models using dynamic programming may have a useful explanatory role, for example, when there are high rates of crossover in an RCT from conservative care to an intervention such as surgery. This was the case in the EVAR 2 trial. In these cases, the crossovers dilute the treatment effect estimated by the RCT and the results may be of limited generalisability. Funding has been secured from the National Health Service Research and Development Health Technology Assessment Programme for a cost-effectiveness analysis of the 8 year results of the EVAR 1 and EVAR 2 trials and the methods described in this thesis are expected to play an important role in this work.

## Introducción

Esta tesis aborda de la evaluación económica de programas sanitarios, y de la aplicación del análisis de coste-efectividad (ACE) en la evaluación de estrategias para el manejo de pacientes asintomáticos con diagnóstico de aneurisma aórtico abdominal (AAA).

El objeto del análisis coste-efectividad es determinar la distribución óptima o eficiente de los recursos sanitarios. En la literatura sobre economía de la salud se puede encontrar dos definiciones de eficiencia. Desde la perspectiva de la economía del bienestar ('welfare economics'), el gobierno debe actuar para mejorar el bienestar social o la suma de utilidades de todos los individuos. La perspectiva alternativa ('extra-welfarist') tiene un punto de partida más parcial y limitado. Su objetivo es maximizar la salud esperada de la población, a través de una medida como por ejemplo, los años de vida ajustados por calidad (AVAC), dado un presupuesto asignado a la atención sanitaria. La mayoría de los analistas de ACE recogen esta segunda perspectiva. Por otro lado, aunque algunos autores distinguen entre el análisis coste-utilidad, en el que el objetivo es maximizar los AVAC, y el ACE, en el que el objetivo es maximizar otra medida de salud, en esta tesis se sigue la taxonomía de Garber y Phelps (1997) en la que el término ACE se usa indistintamente para cualquier tipo de análisis.

### *La transferibilidad de los resultados del ACE*

Un tema actual de investigación en el campo de la economía de la salud es tratar de mejorar la generalibilidad o transferibilidad de los resultados del ACE desde un contexto o país a otro, para que el estudio sea útil a otros decisores (Drummond y Pang 2001, Thompson et al 2006, Manca et al 2007). Esta tesis tiene en cuenta la perspectiva del decisor británico, pero como su defensa se realiza en la Universidad de Granada, ha resultado interesante explorar la relevancia de los resultados para la toma de decisiones en el sistema sanitario español. El primer capítulo analiza, a partir de la teoría de empresas los factores que influyen en las diferencias en el uso de recursos sanitarios entre países, y cómo estas diferencias podrían afectar la validez interna y externa del ACE.

### *El manejo del AAA*

El AAA es una patología que consiste en una dilatación de la aorta. En la mayoría de los casos el AAA puede romperse sin presentar síntomas previos, con la consecuencia de hemorragia interna masiva. La mayoría de las aneurismas son asintomáticos y son diagnosticados por casualidad durante revisiones clínicas por otros motivos de salud. No obstante, algunos países (por ejemplo, Suecia y Reino Unido) han implementado programas de cribado en hombres con edad comprendida entre 60 y 65 años.

La tasa de mortalidad en pacientes con ruptura de AAA es del 80% (Chambers et al 2009). El riesgo de ruptura es mayor cuanto mayor es el tamaño del AAA (Michaels 1992). En cuanto a la prevalencia, aunque resulta difícil estimarla debido a que la mayoría de las AAA son asintomáticas, algunos programas de cribado afirman que se encuentra entre el 1,3 y 12,7% en función de la edad y la definición del AAA (Wilmink y Quick 1998).

La práctica clínica actual recomienda la intervención quirúrgica cuando el tamaño del AAA alcanza el límite de 5,5cm de diámetro, y para un AAA  $\geq 4,5$  cm con un aumento en el tamaño de  $\geq 0,5$  cm durante los últimos seis meses. Del mismo modo, para pacientes asintomáticos con una aneurisma menor de 4,5cm, se aconseja un seguimiento con realización de ecografías cada 6 meses, reduciéndose a 3 o 6 meses para pacientes con AAA de 4,5 a 5,5 cm de diámetro (Chambers et al 2009). Actualmente existen dos alternativas para el tratamiento quirúrgico del AAA: la cirugía abierta y el tratamiento endovascular (EVAR). La cirugía abierta tiene un riesgo importante de mortalidad y morbilidad, mientras que el EVAR al ser menos invasivo, tiene menor riesgo de mortalidad intraoperatoria, menos días de estancia hospitalaria y menor pérdida de sangre (EVAR 2005a). Sin embargo, se asocia con mayor riesgo de complicaciones y reintervenciones a largo plazo por lo que normalmente se recomienda un seguimiento más intensivo (EVAR 2005a). Además, esta técnica no invasiva es el único tratamiento quirúrgico para pacientes que no son aptos para someterse a operación con cirugía abierta (EVAR 2005b).

Uno de los objetivos de esta tesis es evaluar estas estrategias desde una perspectiva económica. Para ello, el método convencional para evaluar los tratamientos se basa en comparar los costes y beneficios esperados en salud a través de un análisis coste-eficacia (ACE).



El modelo en el segundo capítulo estima los costes esperados a lo largo de la vida del paciente y los AVAC del EVAR frente a la cirugía abierta, para pacientes que se consideran aptos para cirugía abierta y adecuados anatómicamente para EVAR. Este trabajo ha sido publicado en la revista “British Journal of Surgery” (Epstein et al 2008).

El AVAC mide el efecto del tratamiento, tanto en términos de mortalidad como de morbilidad, asignando en cada periodo de tiempo un valor que corresponde a la calidad de vida relacionada con la salud (CVRS) en ese período. El valor de la CVRS se encuentra en una escala en la que 1 representa la salud plena y 0 la muerte, siendo posibles los valores negativos para puntuaciones de estados peores que la muerte. El número de AVAC representa el valor de la utilidad asociado a un estado de salud determinado multiplicado por los años de vida transcurridos en ese estado (Kind et al 1999).

Los estados de salud de los pacientes antes y después de la cirugía se midieron en el estudio EVAR 1 (EVAR 2005a) con el instrumento EQ-5D. Este instrumento consta de cinco preguntas relacionadas con la movilidad, el cuidado personal, la facilidad para realizar actividades cotidianas, dolor /malestar y ansiedad/depresión. Cada una de las preguntas se define con tres posibles respuestas que definen tres niveles de gravedad. Los estados de salud en el EQ-5D se valoraron para su uso en el ACE por la población general en varios países (Szende et al 2007).

En el segundo capítulo se utiliza un modelo de Markov (Sonnenberg y Beck 1993; Kuntz and Weinstein 2001). Este modelo se caracteriza por un conjunto de estados de salud excluyentes y exhaustivos. La proporción de la cohorte inicial en cada estado de salud cambia en cada periodo de tiempo en función de unas probabilidades de transición. Todas las personas que están en un estado de salud son semejantes en términos de costes acumulados, calidad de vida relacionada con la salud, y prognosis. En una simulación de cohortes, se asume que todos los pacientes tienen las mismas características demográficas y clínicas iniciales. Un modelo de cohorte produce una traza de Markov (“Markov trace”) que muestra el movimiento de la cohorte de pacientes a través de los estados de salud, el AVAC acumulado, y los costes asignados. El modelo se ejecuta para un horizonte temporal finito, por ejemplo 40 años. Si la edad inicial de la cohorte de pacientes es de 60 años, al final del modelo la mayor parte de la cohorte estará muerta. Por tanto, los AVAC acumulados representan la esperanza de

vida de la cohorte ajustada por calidad de vida, y los costes acumulados corresponden a los costes medios incurridos a lo largo de toda la vida de la cohorte.

El modelo en el segundo capítulo supone que la decisión para someterse a la cirugía ya ha sido previamente tomada. En los capítulos tres, cuatro y cinco, se amplía el primer modelo para evaluar un conjunto más amplio de estrategias para pacientes con aneurismas de diferentes tamaños. En concreto, este segundo modelo compara la cirugía inmediata (EVAR o cirugía abierta) versus ninguna intervención quirúrgica o versus retrasar la decisión. Además, este modelo muestra una síntesis de la evidencia sobre la historia natural de AAA con y sin cirugía, con el objetivo de predecir los resultados de una amplia gama de políticas de manejo de pacientes con diagnóstico de aneurisma asintomático. Por otro lado, dada la incertidumbre en estos datos, el modelo pretende ser exploratorio con el objetivo de sugerir nuevas líneas de investigación.

La modelización de la opción de aplazamiento del tratamiento quirúrgica es más complicada que la comparación entre EVAR y cirugía abierta en el segundo capítulo. Estas estrategias son irreversibles, lo que implica que este tipo de análisis de coste-efectividad mantenga una estructura estática. Los costes y beneficios esperados se calculan estimando los costes y beneficios de todos los posibles estados de salud, ponderados por las probabilidades de que ocurran.

Por otro lado, la decisión de esperar es reversible, lo que implica una mayor opción de diferentes decisiones, ya que para cada ciclo del modelo, al paciente se le puede tratar mediante cirugía abierta o endovascular, no seguir ningún tratamiento, o bien, seguir con observación y seguimiento.

En principio, se podría evaluar esta opción a partir de un modelo de Markov convencional, enumerando todas las posibles estrategias y comparándolas al comienzo del primer ciclo. De este modo, se podría comparar la cirugía inmediata *versus* esperar e intervención si el AAA crece  $\frac{1}{2}$  cm *versus* esperar e intervención si el AAA crece 1 cm, etc. Además, se debe tener en cuenta que la relación coste-efectividad de una estrategia puede depender de la esperanza de vida y por lo tanto de la edad del paciente, así como del tamaño del AAA en el momento de decisión clínica del tratamiento. Todo esto implica un gran número de estrategias que sería necesario comparar en cada momento para pacientes con diferentes características basales.

### *Análisis de opciones reales*

Varios autores han observado que el problema de espera vigilada (seguimiento de pacientes con AAA) es un ejemplo de ‘opción real’ (Driffield and Smith 2007; Attema et al 2009). Éste es un método de análisis de decisión que ha adaptado las técnicas matemáticas que originalmente se desarrollaron para valorar las opciones financieras en la toma de decisiones en otros contextos (Myers 1977). La principal ventaja de la utilización del análisis de opción real en el contexto del AAA es que debe definirse por adelantado un número reducido de estrategias. El tercer capítulo es una revisión de los métodos de la teoría de la valoración de opciones. El capítulo cuatro presenta la aplicación del análisis de opciones reales para la opción de espera vigilada. Por último, en el capítulo cinco se realiza un análisis completo del modelo en base a los mejores datos disponibles en la literatura.

Para realizar el análisis de opciones, el problema de decisión debe poseer tres características esenciales: irreversibilidad, posibilidad de demora, e incertidumbre (Palmer y Smith 2000). Todas estas características son aplicables al problema de espera vigilada para cirugía. Por un lado, la cirugía es irreversible, así como la estrategia de no ofrecer cirugía es también en parte irreversible, al menos hasta que la aneurisma comience a ser sintomática o urgente. Por otro lado, la decisión de someterse a cirugía, al menos en principio, podría aplazarse casi indefinidamente. El problema en este sentido radica en la imposibilidad de conocer con certeza el tamaño que puede llegar a desarrollar el aneurisma, debido a la incertidumbre que envuelve estos procesos. En este contexto, es preciso clarificar la definición de incertidumbre. En la literatura se suele encontrar la distinción entre la incertidumbre de primer orden, o variabilidad, y la incertidumbre de segundo orden (Frey y Burmaster 1999). La variabilidad puede considerarse como una propiedad intrínseca que no suele reducirse con más información o con mayor número de estudios. Por ejemplo, en el contexto del AAA, dada una cohorte de pacientes con un tamaño de aneurisma conocido, se considera que existe variabilidad en la futura distribución de tamaños de aneurisma para esa cohorte de pacientes. Incluso si la probabilidad de crecimiento fuese “conocida”, el resultado en el próximo periodo sería aleatorio para cada individuo de la cohorte.

La incertidumbre de segundo orden se debe al desconocimiento del investigador sobre el valor correcto de una variable en el modelo (Frey y Burmaster 1999). Por ejemplo, la

probabilidad de que el AAA crezca puede ser estimada a partir de varios estudios longitudinales pequeños, y por lo tanto sujetos a errores de medición, sesgo de selección, y posiblemente a una población poco representativa de la realidad. A veces, al menos parcialmente, se puede reducir la incertidumbre de segundo orden con un tamaño de muestra mayor o con más estudios.

El objetivo del ACE es informar acerca de la toma de decisiones por medio de la estimación del coste-efectividad medio de las estrategias relevantes, representarlas adecuadamente y cuantificar la incertidumbre que envuelve el problema de decisión. La mayoría de los ACE no tienen en cuenta la incertidumbre de primer orden y aplican únicamente la estimación de la incertidumbre de segundo orden basado en el análisis de sensibilidad probabilístico, por medio de distribuciones probabilísticas para representar los valores medios de los parámetros en el modelo. El modelo en el segundo capítulo es un ejemplo de este método, que se aplica para estimar la probabilidad de que el EVAR sea coste-efectivo (Speigelhalter et al 2004).

Sin embargo, si el seguimiento es una estrategia viable, entonces tanto la variabilidad como la incertidumbre de segundo orden serían relevantes en la toma de decisiones. La opción de esperar permite el cirujano recoger más datos sobre el estado de salud del paciente. En el capítulo cinco se analizan los retos implícitos en el modelo de espera vigilada para analizar la incertidumbre en la toma de decisión.

## Introduction

This thesis is concerned with the economic evaluation of health-care programmes, and in particular the practical application of cost-effectiveness analysis (CEA) to the management of patients with a diagnosed asymptomatic abdominal aortic aneurysm (AAA).

The aim of cost-effectiveness analysis is to determine the optimum or efficient allocation of health-care resources. This of course begs the question as to the definition of efficient, and one of two perspectives is usually offered. In the welfare economics perspective, governments take societal decisions to improve social welfare, or the aggregation of utility across all individuals. The ‘extra-welfarist’ perspective takes a more partial and constrained starting point and aims to maximise expected health, as measured for example by quality-adjusted life years (QALYs), given the budget allocated to health-care. Most practitioners of CEA take this second perspective. Some authors make a distinction between cost-utility analysis, where the objective is to maximise QALYs, and cost-effectiveness analysis, where the objective is to maximise some other measure of health outcome, but in this thesis we follow the taxonomy of Garber and Phelps (1997) and use the term CEA to refer to either type of analysis.

### *Generalisability of CEA*

A current theme of research in the field of health economics is to try and improve the generalisability or transferability of a CEA from one setting so that it is useful to other decision makers (Drummond and Pang 2001; Thompson et al 2006; Manca et al 2007). This thesis takes the perspective of the UK decision-maker, but as it is presented at the University of Granada, it is reasonable to ask to what extent the results are relevant to policy-makers in Spain, or could be made more relevant to them. Chapter 1 uses the theory of the firm to analyse how health care resource use might vary between countries, particularly given differences in relative input prices, and shows how this might affect the generalisability of a CEA.

### *The management of AAA*

AAA develops when the wall of the aorta weakens. Eventually the AAA may rupture, leading to massive internal bleeding. Most AAA are asymptomatic and are detected by chance during clinical investigation for other conditions, although some countries (e.g.

Sweden, UK) have recently implemented systematic screening programmes in men over the age of 60.

Patients with a ruptured AAA have a mortality rate of 80% (Chambers et al 2009). The risk of rupture increases with aneurysm size (Michaels 1992). Because most AAA are asymptomatic, it is difficult to measure the prevalence, but screening studies in the UK have estimated a prevalence of 1.3-12.7% depending on the age group and definition of AAA (Wilmink and Quick 1998).

Clinical guidelines in the UK recommend elective surgery for AAA  $\geq 5.5$ cm in diameter, as well as for AAA  $\geq 4.5$ cm with an increase in size of  $\geq 0.5$ cm in the last 6 months. Current guidelines recommend that patients with asymptomatic AAA  $< 4.5$ cm are followed up with ultrasonography every 6 months, whilst AAA of 4.5 – 5.5cm are followed up every 3 or 6 months (Chambers et al 2009).

There are currently two surgical treatments for AAA: endovascular repair and open repair. Open repair carries a substantial risk of mortality and morbidity. Endovascular repair is associated with lower operative risk, reduced length of stay in hospital and reduced blood loss (EVAR 2005a). However, endovascular repair is associated with greater risk of complications and reinterventions after surgery, and patients are usually recommended to undergo continuing follow-up (EVAR 2005a). Endovascular repair is the only surgical treatment available in patients considered unfit for open surgery (EVAR 2005b).

One of the aims of this thesis is to evaluate these management options from an economic perspective. The conventional approach to evaluating treatments is to compare the expected costs and health benefits in a cost-effectiveness analysis (CEA). The model in Chapter 2 estimates lifetime expected costs and quality-adjusted life years (QALY) for endovascular repair and open repair, for patients who are considered fit for open surgery and anatomically suitable for EVAR. This paper has been published in the British Journal of Surgery (Epstein et al 2008, see Appendix).

QALY capture the impact of treatment on both mortality and morbidity, by assigning to each period of time a value corresponding to health-related quality of life (HRQOL) during that period. The HRQOL value lies on a scale where 1 represents full health and 0 represents death, although negative value for states rated worse than dead are possible.

The number of QALY relating to a health outcome are then expressed as the value given to a particular health state multiplied by the length of time spent in that state (Kind et al 1999). The health states of patients before and after AAA surgery were measured by the EVAR trial 1 (EVAR 2005a) using the EQ-5D, which consists of five questions on mobility, self-care, usual activities, pain and anxiety, each with three levels of response. The health states measured by the EQ-5D have been valued for use in CEA by surveys of the general public in several countries (Szende et al 2007).

The model in Chapter 2 is a Markov model (Sonnenberg and Beck 1993; Kuntz and Weinstein 2001). This is characterised by a set of mutually exclusive and collectively exhaustive health states. At fixed increments of time persons change health state according to a set of transition probabilities. All persons residing in a health state are indistinguishable from one another, in terms of the costs they accrue, their HRQOL and the probability of transit to other health states. In a cohort simulation, all patients are assumed to have identical initial demographic and clinical characteristics. A cohort simulation produces a Markov trace, which shows the movement of the cohort of patients through the health states and the cumulative QALY and costs assigned. The model is run for a finite time horizon, for example, representing 40 years. If the initial age of the cohort is 60 years old, then at the end of the model almost all of the cohort will be dead. The cumulative QALY then represents the quality-adjusted life-expectancy of the cohort, and the cumulative costs represent the mean lifetime costs of the cohort.

The model in Chapter 2 assumes the decision to undergo surgery has already been taken. The remaining chapters extend the first model to evaluate a wider set of management strategies for AAA. Specifically, this second model compares immediate surgery (with EVAR or open repair) *versus* no surgery or delaying the decision. The model brings together the sparse available evidence about natural history in untreated patients with evidence in treated patients to predict outcomes of a wide range of management policies in patients with diagnosed asymptomatic aneurysm. Given the uncertainties in these data, the model is intended to be exploratory and suggest areas for further research.

Modelling the option to delay surgery is more complicated than the comparison between endovascular and open repair in Chapter 2. These strategies are irreversible,

and consequently this Markov model has an essentially static structure. Expected future costs and benefits are calculated by weighting the costs and benefits of all future possible health states by the probability that those states occur, and implies a single decision to be taken at the start of the model. Delay, on the other hand, is reversible. At the start of each period in the watchful waiting strategy, the patient can be treated (with either open repair or endovascular repair), discharged or opt to continue monitoring. This implies a possibly long series of decisions. In principle, this could be evaluated using conventional Markov models by enumerating every possible strategy and comparing them all at the start of the first period. Therefore one might compare immediate surgery *versus* waiting and operating if the AAA grows ½ cm *versus* waiting and operating if the AAA grows 1cm, etc. One should also take into account that the cost-effectiveness of a strategy may depend on remaining life-expectancy and therefore the age of the patient as well as the AAA size at the time a decision is made. This implies a large number of strategies would need to be compared, each time for patients with different baseline characteristics.

#### *Real option analysis*

Several authors have observed that the watchful waiting problem is an example of a 'real option' (Driffield and Smith 2007; Attema et al 2009). This is a method of decision analysis that adapts mathematical techniques originally developed for valuing financial options to decision-making in other contexts (Myers 1977). The main advantage of using real option pricing in this context is that a reduced number of strategies need to be defined upfront. Chapter 3 reviews the methods of option pricing. Chapter 4 introduces the application of real option analysis to the watchful waiting problem for AAA, and Chapter 5 estimates the results of this model using the best available data. Driffield and Smith (2007) first developed a real options model to evaluate watchful waiting, but their measure of how the benefit of surgery evolves over time was rather abstract and not applicable to clinical decision making. The model developed here aims to have a direct clinical application.

An option model has three essential characteristics: irreversibility, deferability and uncertainty (Palmer and Smith 2000). All these characteristics apply to the watchful waiting example. Surgery is irreversible. Discharging the patient is also partly irreversible, at least until the aneurysm becomes symptomatic or urgent. The decision to



undergo surgery is in principle deferrable almost indefinitely. The future size of the aneurysm and health of the patient is uncertain.

It is worthwhile to clarify what is meant by uncertainty in this context. A distinction is usually made in the literature between first-order uncertainty, or variability, and second-order uncertainty (Frey and Burmaster 1999). Variability is a property of nature, and not usually considered irreducible by further information or study. In the AAA context, for example, given any cohort of patients with a known current aneurysm size, the future distribution of aneurysm sizes in that cohort can be considered variability. Even if the probability of growth was thought to be 'known', the outcome in the next period is random for any individual in that cohort. Second-order uncertainty represents partial ignorance about the true value of a variable for any given member of a population (Frey and Burmaster 1999). For example, the probability of AAA growth is estimated from several small longitudinal studies, and therefore AAA growth is subject to measurement error and sampling error and the sample is possibly unrepresentative of the population. Second-order uncertainty is sometimes at least partially reducible with more samples or study.

The aim of CEA is to inform decisions by estimating the mean cost-effectiveness of the relevant strategies, and to properly represent and quantify the uncertainty surrounding the decision. Most applications of CEA ignore first-order uncertainty and aim only to represent second-order uncertainty in the model using probabilistic sensitivity analysis, by assigning probability distributions to estimates of the mean values of the parameters and re-running the model in thousands of simulations (Parmigiani 2002; Spiegelhalter et al 2004). The model in Chapter 2 (Epstein et al 2008) uses this approach, and estimates the probability that EVAR is cost-effective.

However, if watchful waiting is a feasible strategy, then the model should take account of both variability and second-order uncertainty. The option to wait allows further information to be gathered. If the aneurysm grows then the management strategy can be changed conditional on those realised outcomes. Chapter 5 discusses the special challenges and difficulties this implies for undertaking probabilistic sensitivity analysis in a watchful waiting model.

## **Chapter 1: The role of health-care provider behaviour on the internal and external validity of cost-effectiveness analysis**

This paper was submitted for consideration for publication in Health Economics on 14 March 2010 as Epstein D, Martín J, López P, Henriksson M, Levin L. The role of health-care provider behaviour on the internal and external validity of cost-effectiveness analysis (HEC-10-0072). It is currently under review by the editors.

### **Introduction**

Cost-effectiveness analysis (CEA) is usually presented from the perspective of a third-party purchaser of health-care. CEA assumes the aim of this purchaser is to improve allocative efficiency, which in the extra-welfarist framework is usually taken to be to choose the set of treatments or programmes that maximise population health given the limited budget available. There is a large and venerable body of literature that discusses how costs should be calculated in CEA and what types of costs should be included and excluded (for a review, Mogyorosz and Smith 2005). However, the assumptions implicit in CEA about how health-care providers determine resource use and costs have received little attention. Health care providers can also be thought of as decision makers with their own objectives and constraints. One possible framework for examining provider decision-making is the classical micro-economic theory of the firm. It is recognised that while there are many competing economic theories of producer behaviour, this model makes a useful starting place for the analysis and serves as a point of reference.

This analysis has both theoretical and practical implications. It is of theoretical interest because the role of the producer is rarely discussed when considering whether CEA increases economic welfare. It is of practical interest when considering to what extent the results of a CEA in one setting might be transferable to another setting or country, and for the design, reporting and analysis of multinational studies.

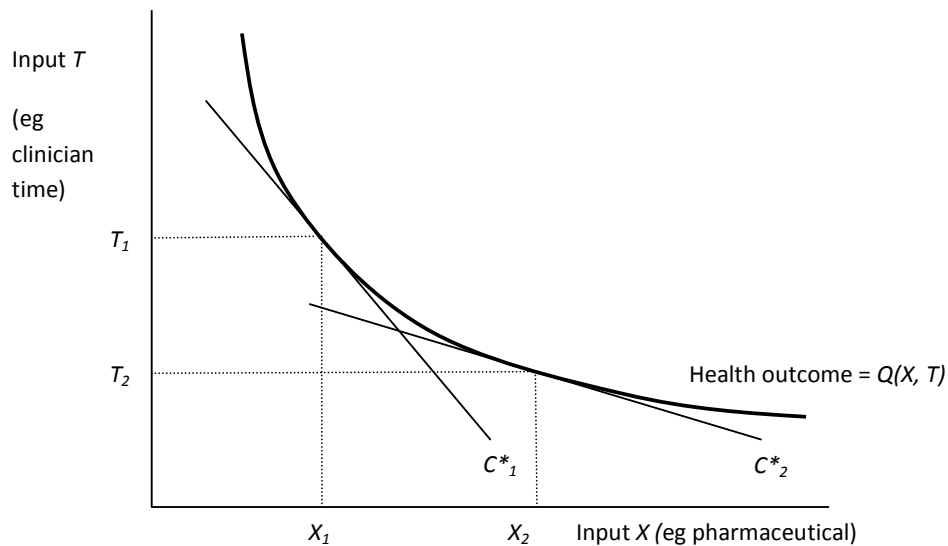
The article is structured as follows. The classical theory of the firm is used to analyse the use of inputs by health-care providers. The assumptions about how health-care providers determine resource use and costs are examined and the consequences for the internal and external validity of CEA are considered. In the conclusion, the limitations

of the model are discussed and the implications of the analysis for the design, reporting and analysis of multinational CEA are reviewed.

### **A hospital production function**

Figure 1 illustrates a hospital production function to treat a particular condition. A hospital stay might require many inputs: investigations, medical and surgical procedures, nursing care etc. Without loss of generalisability, assume there are two health-care inputs:  $X$  and  $T$ . For example, input  $X$  might be “pharmaceuticals” and input  $T$  might be “staff time”. We could imagine a higher-dimensional model which accounts for all key inputs, some of which may be continuous and some categorical. Assume there are several possible ways of treating the condition and obtaining the same outcome. All approaches require some pharmaceuticals and some health-care professional time, but some clinical teams make greater use of specialised drugs while other approaches make more intensive use of other inputs, for example, in operating room time. Each planned combination or vector of inputs  $I=[X=x, T=t]$  represents a ‘treatment’ with a corresponding (expected) outcome of  $Q(I)$ . There may be different combinations of inputs that result in the same outcome or isoquants. Figure 1 shows two of these. In this case  $Q(X_1, T_1) = Q(X_2, T_2)$ . In practice, curve  $Q$  will not be continuous if not all combinations of inputs are clinically feasible. It is assumed that the outcome is a measure of health, such as Quality-Adjusted Life Years or the probability of survival. The distinction between health and health-care (which would be measured in activity, for example DRG admissions) is important and we return to it in the discussion.

**Figure 1. A production function for a health condition**



Suppose that a health care provider has a target response rate ( $Q^*$ ) for the condition and minimises expenditure ( $C$ ) accordingly. The mathematical dual of this problem is that the provider has a fixed expenditure budget and maximises  $Q$  accordingly, with equivalent results. Then the provider will choose  $X$  and  $T$  to satisfy:

$$\text{Min } C = p_X \cdot X + p_T \cdot T$$

$$\text{Subject to } Q(X, T) \geq Q^*$$

The solution  $[X_j, T_j]$  will satisfy the first order conditions, so that the marginal rate of substitution of  $X$  for  $T$  equals relative input prices faced by the provider.

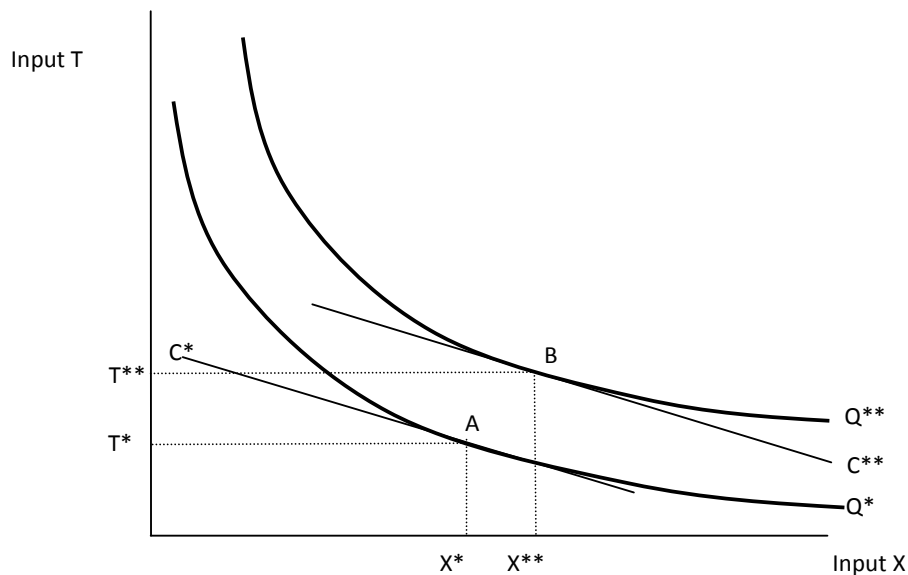
$$(dQ/dX)/(dQ/dT) = p_X / p_T$$

If prices are  $[p_{X1}, p_{T1}]$  (pharmaceutical prices are high relative to wages) the model predicts expenditure will be  $C_1^*$  and resource use  $[X_1, T_1]$ , that is, the ‘time-intensive’ approach will be economically efficient. If relative prices are  $[p_{X2}, p_{T2}]$  the model predicts expenditure will be  $C_2^*$  and resource use  $[X_2, T_2]$ , that is, a more ‘pharmaceutical’ approach will be economically efficient. Expenditure  $C_1^*$  with prices in scenario 1 might be greater or less than  $C_2^*$ , depending on the shape of the production function and prices.

## The internal validity of cost-effectiveness analysis

The previous section established the conditions for ‘economic efficiency’ of a health care provider: Given the prices of health-care inputs, which combination of inputs will minimise expenditure for each possible outcome? The purpose of CEA is to improve ‘allocative efficiency’: what activities should the health-care service undertake so as to maximise health given its limited resources? This section derives the conditions under which the decision rules of CEA are consistent with allocative efficiency in this extra-welfarist sense, taking into account provider behaviour in jointly determining resource use, costs and outcomes.

Figure 2. Cost-effectiveness analysis comparing health care programmes A and B



Consider the case for a provider facing input prices  $[p_{X1}, p_{T1}]$  (Figure 2). There are two economically efficient ‘treatments’ under consideration for some patient group: for example, ‘usual care’ as a combination of inputs  $A = [X^*, T^*]$ , with cost  $C^*$  and outcome  $Q^*$ , and ‘new intervention’ as a combination of inputs  $B = [X^{**}, T^{**}]$ , with cost  $C^{**}$  and outcome  $Q^{**}$ . In this example, the treatments are defined in terms of varying the intensity of the use of some of the factor inputs. An example corresponding to this type of appraisal might be to compare 6 chemotherapy cycles versus 8 cycles. In Figure 2, the inputs are continuous, but the model might be adapted to analyse categorical or binary inputs (eg drug versus no drug) rather than continuous inputs as long as isoquants are concave.

Figure 3. ‘Marginal cost’ (or incremental cost-effectiveness ratio (ICER)) and ‘marginal benefit’ (or threshold value of health)

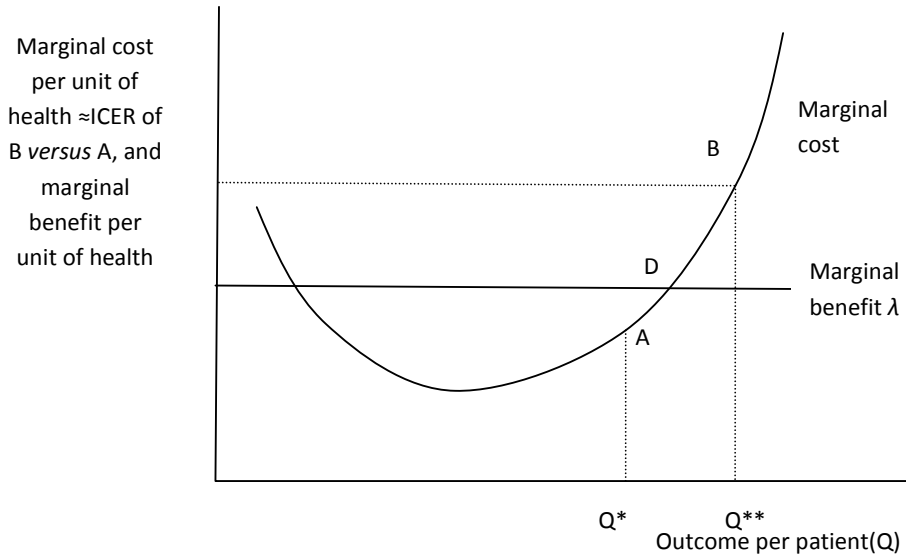


Figure 3 shows the marginal cost function as the change in total cost per patient for a change in health outcome per patient. If all inputs are continuous and the production function is differentiable then this is  $dC/dQ$ . If inputs are only available in discrete packets such as  $A$  and  $B$  then the marginal cost function is approximated by  $(C_B - C_A) / (Q_B - Q_A)$ , that is, the incremental cost effectiveness ratio (ICER) of  $B$  versus  $A$ .

Given these data on the ICERs of the treatments, CEA aims to find the most cost-effective treatment. The health system should only consider offering health-care treatments whose marginal costs are on the upward-sloping segment of the curve, that is, where a more effective treatment has a greater ICER than a less effective treatment. A downward-sloping marginal cost curve indicates that a more effective treatment has a lower ICER than a less effective treatment, that is, the less effective treatment is extendedly dominated (Johannesson and Weinstein 1993). The value that the health service places on health outcomes is represented by constant  $\lambda$ , though this function could be downward sloping with respect to health per patient. CEA in an extra-welfarist perspective usually assumes that this value or function is determined as the reciprocal of the shadow price of the budget constraint (Stinnett and Paltiel 1996, Epstein et al. 2007). In the long-run, the optimum (or cost-effective) treatment is where the

additional costs per patient of increasing health outcome are equal to the additional benefit of that outcome, that is, to adopt the strategy where  $dC/dQ = \lambda$ . If intervention  $D$  could be identified, with outcomes between  $A$  and  $B$ , this would be considered optimal (Figure 3). If  $D$  were not available, the health service would choose to operate at point  $A$  rather than  $B$ , as the marginal cost (that is, the ICER) of obtaining  $Q^{**}$  rather than  $Q^*$  is greater than  $\lambda$ .

The analysis is conducted for the ‘average’ patient and assumes constant returns to scale with respect to the number of patients treated. Note that this is not the same as constant returns to scale with respect to the health outcome. If this were the case, then the marginal cost curve in Figure 3 would be horizontal and all strategies would be equally cost-effective (with the same ICER).

### **The external validity of cost-effectiveness analysis**

Most CEA are designed to inform a decision to adopt a health technology or programme in a specific setting, in terms of time, place, population characteristics or technologies under comparison. However, decision makers often wish to know whether a CEA carried out in one setting might be transferable (or easily adaptable) to another, rather than incur the high fixed cost of initiating a *de-novo* study. In response to these demands, it is increasingly common for investigators or manufacturers to develop a general decision model which can be populated with country-specific parameters as requested, or to conduct large-scale multi-national clinical trials, to try to extend the generalisability of the study across relevant patient groups in several countries and increase the likelihood that the study will be accepted as evidence to support licensing, guidelines and/or reimbursement decisions in multiple jurisdictions.

Some variables of the microeconomic model in the previous section can be considered exogenous. Discount rates and the threshold marginal value of health ( $\lambda$ ) are usually considered to be decisions of the local health system, and (almost) independent of other elements of the model. There are also differences in countries with respect to absolute price levels and currency units, but as long as relative prices are similar, one might adjust for differences in absolute prices using purchasing power parities (Vachris and Thomas 1999). The social tariff used to value health states may differ between countries (Szende et al 2007) but would be unlikely to affect health-care provider decisions.

The microeconomic model predicts that where relative prices differ across countries, this will affect health-care provider decisions about resource use. In this case, populating the model with different unit costs does not take account that resource use might be endogenous. This endogeneity can also create problems for the design of multinational clinical trials. Multicentre RCTs often assume that the clinical treatment effect (as measured by odds ratio for example) is common to all centres and countries. This is usually justified where centres are expected to follow common patient selection criteria and treatment protocols. Yet here is a dilemma. On the one hand the trial protocol might specify that intervention *B* should be compared with control *A*, and specify in detail the combinations of health-care resources that define treatments *A* and *B*. Even if these treatments are economically efficient (ie cost minimising for those respective outcomes) in one of the countries, neither might be economically efficient in another country with different relative prices. On the other hand, allowing each country to define its own version of the intervention and control to suit local conditions might undermine the assumption of common clinical effects.

Therefore there may be a potential trade-off between internal and external validity in the design of multinational clinical trials. This trade-off might become more binding as more diverse countries are included in trials. Even inputs such as aspirin that are relatively low-cost in rich countries may be relatively high-cost in poor countries and may not reflect general practice.

## Conclusions

This article has reviewed the theoretical conditions under which the decision rules for CEA might improve allocative efficiency. In this article, efficiency is defined in an extra-welfarist sense to mean maximising health given a budget constraint. Previous derivations of the decision rules for CEA have taken the average cost per patient of each programme as given. To the authors' knowledge, this is the first such analysis in the CEA literature to take account of the behaviour of health-care providers in jointly determining resource use, costs and health outcomes.

From the microeconomic framework of the theory of the firm, the following conditions are required for CEA to improve allocative efficiency, that is, for internal validity of CEA:



1. Providers are technically efficient, such that it is not possible to produce a given output with less of one input and no more of another.
2. All providers have common technology available
3. There are constant returns to scale with respect to patient numbers
4. Providers are economically efficient, such that it is not possible to produce a given output more cheaply when faced with a given set of input prices.
5. Health-care providers are price-takers in markets for health-care inputs
6. Providers use an indicator of health as their measure of output

The first five of these conditions have been identified by other authors (for example, Drummond et al 2005), though not necessarily from a formal framework. However, to the authors' knowledge, the sixth condition has not been previously identified in the literature, probably because the perspective for the decision rules for CEA is usually that of the third-party purchaser of health-care. Moreover, this condition appears to be a strong assumption. In practice, health-care providers might have multiple objectives or constraints which might question the simple health-maximising model of provider behaviour. Providers may not even measure health gain in a consistent way. In the UK, for example, providers' primary measure of output and unit of reimbursement is the Healthcare Resource Group (a measure of hospital activity derived from the Diagnostic Resource Group classification system) whose reimbursement value may be only weakly correlated with health gain. Therefore the health ministry must use other instruments, such as targets, guidelines and audit, to ensure that healthcare providers offer cost-effective treatments (and withdraw those that are not cost-effective). If providers do not base their resource allocation decisions on health outcomes, it may imply that the resource use and costs of the treatments measured in CEA studies are not those that would maximise health, given the overall health budget constraint. For example, if a provider considered that its objective was to maximise hospital admissions, then in order to increase patient turnover it might discharge patients earlier than a provider whose objective was to maximise health, given similar resources available.

It is often recommended in guidelines for economic evaluation that unit costs used in CEA should reflect opportunity costs or their marginal cost to society, rather than

market prices (for example, Luce and Manning 1996). This recommendation is likely to be motivated by the conditions for allocative efficiency in a welfarist normative framework, which would aim to expand a health care programme if the marginal benefits to society are greater than the marginal cost to society. In an extra-welfarist framework, efficiency is defined in terms of maximising health given the budget constraint faced by the health service. As the health service pays market prices for inputs, this might indicate CEA should estimate actual mean resource use and expenditure per patient, not what resource use and expenditure would have been if input prices reflected marginal social costs and benefits.

There may be a potential trade-off in the design of multinational trials between obtaining high internal and external validity of treatment effects. A CEA estimates two treatment effects; the difference in outcomes ( $Q_B - Q_A$ ) and the difference in costs ( $C_B - C_A$ ). A tightly defined trial protocol would be appropriate where the aim is to measure a common treatment effect for all centres. However, this may mean that the treatments under evaluation are not representative of clinical practice in those centres, or (in the framework presented in this chapter) that the treatments under evaluation are not economically efficient in all the centres. A flexible or pragmatic protocol allows variation between centres and/or countries. The appropriate method of analysis also depends on the degree of variation between centres. A fixed-effect analysis assumes that all centres/countries have a common treatment effect. A random-effects analysis assumes that the treatment effects are similar but not identical in each centre or country, that is, the treatment effects are exchangeable (Drummond et al 2005, Snijders 2005, Higgins et al 2009). If the heterogeneity between studies is very large and cannot be explained by observed covariates then the data cannot be pooled at all and series of stratified analyses must be undertaken separately for each centre or country. Most clinical studies, even multi-national ones, estimate a common treatment effect for the primary health outcome. The framework developed here suggests that this assumption ought to be tested and questioned. Relative prices may vary between countries, for example because not all health care inputs are freely tradeable across national borders. Given that costs depend on prices as well as resource use, it may be implausible to assume in a multinational study that the difference in costs between the treatments is the same in all centres. It may be more plausible to assume that the proportionate increase in cost associated with the treatment ( $C_B/C_A$ ) is similar across centres and countries

even if the absolute increase in cost ( $C_B - C_A$ ) is very heterogenous. This could be implemented if the analysis were undertaken on the logarithm of costs. This analysis would also have the advantage that the logarithm of costs may be closer to a normal distribution than untransformed data (Thompson et al 2006).

The theoretical framework also suggests outcomes and costs will be jointly determined by providers. This lends strength to a recommendation by Manca et al (2007) that CEA should be conducted using bivariate modelling, although this type of analysis usually assumes that costs and outcomes have a bivariate normal distribution which may be unrealistic.

As resource use might be conditional on input prices, any estimation of the costs of treatments in multinational trials should use local input prices if possible and avoid applying the input prices at one location to calculate costs in other countries. This is sometimes done in CEA for various reasons. For example, Grieve et al (2001) carried out a sensitivity analysis to try to identify the whether differences in costs between countries arise mainly because of different use of resources or because of differences in input prices. In other cases, resource use is pooled from different countries in order to 'increase' sample size, or because input prices are not available from some countries. The theoretical model suggests these analyses may be misleading as there will be systematic differences in resource use between countries if relative input prices differ.

Empirical studies of hospital efficiency suggest that few health-care providers produce at a theoretical maximum level of technical efficiency, with considerable unexplained variation (Street and Laudicella 2009). There are likely to be many reasons for this, but one may be that hospitals do not have access to 'common technology' in terms of comparable quality of staff, equipment, management skill etc. Another reason might be varying returns to scale with respect to patient numbers (Vitikainen et al 2009). These considerations mean that hospitals might be able to achieve different health outcomes for similar inputs per patient. The internal validity of a multi-centre RCT could be increased by selecting centres with similar technology, facilities or size etc, though if these centres are not representative of those in the country this might limit the generalisability of the study.

This article has reviewed the theoretical conditions under which the conventional decision rules for CEA can be said to improve efficiency, in an extra-welfarist sense,

taking into account the behaviour of health-care providers. These considerations might be especially important for the design, analysis and reporting of multi-national trials, and for generalising the results of CEA from one setting to another.

## **Chapter 2: The cost-effectiveness of endovascular or open repair in patients with abdominal aortic aneurysm**

This paper has been published as Epstein D, Sculpher M, Manca A, Michaels J, Thompson S, Brown L, Powell J, Buxton M, Greenhalgh R. Modelling the long-term cost-effectiveness of endovascular or open repair for abdominal aortic aneurysm. *British Journal of Surgery* 2008; 95:183-190

### **Introduction**

The standard procedure to repair an abdominal aortic aneurysm (AAA), with a Dacron inlay graft placed at open surgery, was developed in the 1950s. The new, less invasive approach of endovascular aneurysm repair (EVAR) is being evaluated versus the standard open repair in four separate randomised trials (EVAR 2005a; Blankensteijn 2005; Becquemin 2005; Lederle 2005a), two of which now have reported mid-term results, with 351 patients in DREAM and 1082 in EVAR trial 1. The two published trials have shown that EVAR performs better than open repair in some domains - for example, lower operative mortality and shorter hospital stay. However, its cost is higher and the evidence on both long-term mortality and the continuing need for re-interventions and surveillance is uncertain (Bonneux 2005)

Collectively-funded health care systems, like the UK National Health Service (NHS), with limited overall resources, must compare the alternative forms of management available to each group of patients to determine which strategy is likely to be the most cost-effective. Therefore, there is a need to estimate the cost-effectiveness of EVAR relative to open repair. The economic analysis required must appropriately synthesise all the available evidence, extrapolate to obtain estimates of life expectancy, health-related quality of life (HRQoL) and total costs over patients' lifetimes, and provide a framework to explore alternative scenarios. This paper presents the results of a decision-analytic model to compare a strategy of EVAR against open repair.

### **Methods**

#### ***Study question***

The model used compared a strategy of open repair with that of EVAR, for patients with a diagnosed AAA of diameter at least 5.5mm and considered fit for open repair. Patients are

assumed to be men who have their primary AAA procedure at 74 years, the mean age of participants in the EVAR trial 1. The perspective is that of a collectively-funded healthcare system. The measure of health benefit is expected quality-adjusted survival duration. The price year was 2004 (the year the EVAR trial 1 recruitment ended) and all costs were measured in UK pounds. Costs and health benefits in future years were discounted at a rate of 3.5% per year (HM Treasury 2003). In order to model the costs and outcomes as in routine practice, all patients entering the model are assumed to receive their assigned procedure (open repair or EVAR).

### *Structure of the model*

The overall structure is shown in Figure 4 and the data used to estimate transition probabilities, costs and HRQoL (utilities on a scale of 0 (dead) to 1 (good health)) in the model are shown in Table 1 and Table 2. Because the EVAR trial 1 is the largest randomised trial conducted with this patient group, individual patient data from that trial were used to inform much of the analysis. Nevertheless, published information was also available from other sources, including the DREAM trial, population life tables and registry data (GAD 2006; National Statistics 2003; Brady 2001). All parameters estimated from the EVAR trial 1 data were analysed within randomised group using a per-protocol analysis. Full details of the programming code for the Markov model are available from the authors ([www.york.ac.uk/depts/che](http://www.york.ac.uk/depts/che)).

**Table 1: Mean transition probabilities, used as input parameters in the model**

	<i>Open</i>	<i>EVAR</i>	<i>Source</i>
<i>Probability of 30 day mortality</i>			
Mean of all patients	0.050	0.016 (c)	EVAR trial 1
Aged <70 years	0.023	0.007 (c)	EVAR trial 1
Aged >80 years	0.069	0.022 (c)	EVAR trial 1
Conversion during primary admission	0 (a)	0.008	EVAR trial 1
Mortality rate from AAA causes during follow up	1 per 15,000 patient months	6 per 15,000 patient months	EVAR trial 1
Mortality rate from other cardiovascular causes during follow up	Age-dependent (d)	Age-dependent (d)	Population life tables and mortality statistics
Mortality rate from non-cardiovascular causes during follow up	Age-dependent	Age-dependent	Population life tables and mortality statistics
Rate of non-fatal readmission for AAA causes in first 6 months	2 per 1000 patient months (b)	19 per 1000 patient months (b)	EVAR trial 1
Rate of non-fatal strokes and MIs during follow up	Proportional to mortality rate for cardiovascular causes (e)	Proportional to mortality rate for cardiovascular causes (e)	EVAR trial 1

- a. No conversions from open repair to EVAR were undertaken in the EVAR trial 1
- b. The rate of readmissions was greatest in the first 6 months after primary procedure. The rate of readmissions was estimated to decline over time following a Weibull model
- c. Assuming an odds ratio of 0.30 (95%CI 0.13 to 0.67) for all age groups
- d. The risk of cardiovascular mortality in all patients after successful aneurysm repair is assumed to be twice that in the general population (Forbes 2002). In addition the EVAR trial 1 observed 3 times more deaths from cardiovascular causes during the second year of follow up.
- e. The EVAR trial 1 observed on average 0.6 non-fatal cardiovascular events for every fatal event. 50% of cardiovascular events were strokes. It was assumed that 35% of non-fatal strokes were disabling (Prinssen 2005)

**Table 2. Unit costs and HRQoL parameters used in the model**

	<i>Mean value</i>	<i>95% confidence interval</i>	<i>Source</i>
<b>Unit Costs</b>			
EVAR procedure	£10,726	10,100 to 11,300	EVAR trial 1
Open procedure	£9,578	8,600 to 10,100	EVAR trial 1
Conversion to open during primary EVAR	£42,067	0 to 85,000	EVAR trial 1
AAA secondary re-admissions	£5,936	4,500 to 7,300	EVAR trial 1
MI or non-disabling stroke (initial hospitalisation and short-term rehabilitation)	£5,099	4,500 to 5,600	Jones 2003
Disabling stroke (initial hospitalisation and short-term rehabilitation)	£10,555	9,500 to 11,500	Jones 2003
Lifetime annual cost following disabling stroke	£4,003	3,700 to 4,300	Jones 2003
Outpatient visit	£90		Reference costs
CT scan	£104		Reference costs

**Health-related QoL (utility) (a)**

*Utility with no AAA or cardiovascular symptoms*

Age ≤75 years	0.78		Kind 1999
Age > 75 years	0.75		

*Loss of utility compared with general population*

*health for one month following an event*

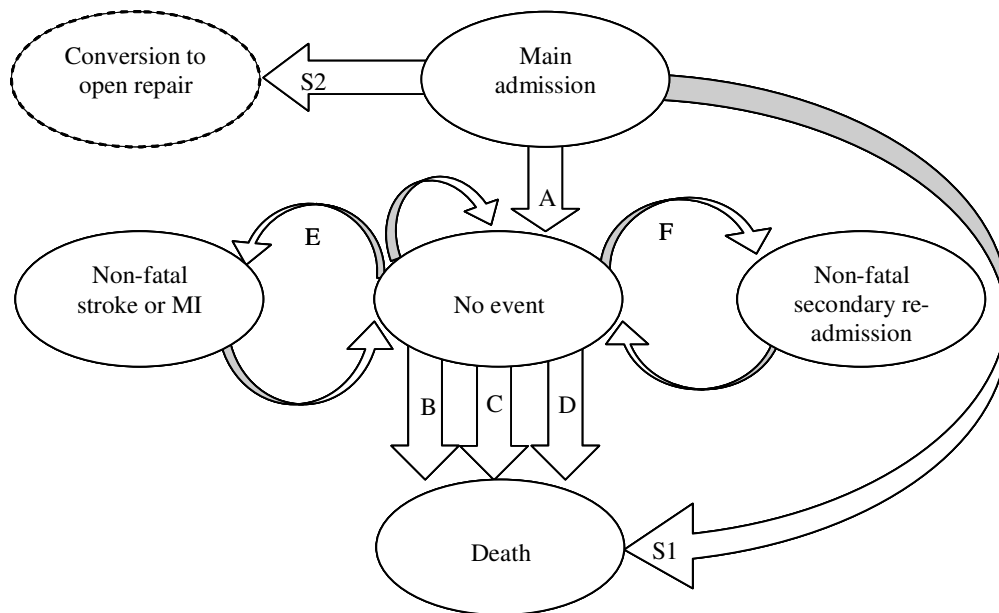
Following an EVAR procedure	0.027	0.007 to 0.061	EVAR trial 1
Following an open procedure or AAA re-intervention	0.094	0.065 to 0.128	EVAR trial 1
Following a non-disabling MI or stroke	0.075	0.047 to 0.109	Lacey 2003



Permanent loss of utility following a disabling stroke	0.50	0.424 to 0.604	Lacey 2003
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a. HRQoL or utility is an index measure of morbidity measured on a scale from 1 (good health) to 0 (death)



**Figure 4: Model structure**

S1: death within 30 days of primary procedure

S2: successful conversion from EVAR to open repair during primary procedure (and enter long term model with same prognosis as open repair). Patients who receive open repair cannot convert

A: successful primary procedure (and enter long term model)

B: death from cardiovascular causes (other than AAA)

C: death from AAA or secondary procedure

D: death from non-cardiovascular cause

E: non-fatal myocardial infarction or stroke

F: non-fatal secondary AAA re-admission

Patients enter the model and have a primary AAA procedure. 25 out of 500 (5%) patients died within 30 days of open repair in the EVAR trial 1 and the odds ratio for EVAR relative to open repair was 0.30 (95% CI 0.13 to 0.67). It was assumed that patients who convert from EVAR to open repair during the primary admission have the same long term prognosis as patients initially undergoing open repair. There was no evidence from the EVAR trial 1 (or any other randomised trial) that the odds ratio for 30-day mortality varied with age or other baseline risk factors (Brown 2007). However, the 30-day mortality rate in the EVAR trial 1 for patients undergoing open repair did vary with age, from 2.2% in patients aged <70 years to 6.9% in patients >80 years. These 'baseline' data were used in scenario analyses to investigate if the cost-effectiveness of EVAR varied with age.

Mortality rates after the primary admission have been estimated as three competing risks: death from an AAA cause, death from a cardiovascular cause other than AAA and death from a non-cardiovascular cause. Patients are also at risk of a non-fatal cardiovascular event (a stroke or a myocardial infarction (MI)) or a re-admission for a secondary AAA procedure.

All patients in the EVAR group, whether they experience adverse events or not, are assumed to require regular specialist hospital outpatient attendances and computed tomography (CT) scans to monitor their aneurysm repair. In the base-case, based on the results of a survey of UK hospitals participating in the EVAR trials, it was assumed that patients require two surveillance visits during the first year and one visit per year thereafter. Patients who have open repair only require one visit in the first year and none thereafter.

#### *Cardiovascular mortality*

Both the EVAR trial 1 and the DREAM trials found that patients with EVAR tended to have a greater risk of cardiovascular mortality (for reasons other than directly caused by the aneurysm or AAA procedure). While this difference between the treatment groups did not reach statistical significance, it nevertheless contributes to the conclusion reached by both trials that the early survival advantage offered by EVAR does not lead to improved overall mortality in the medium term. The cause of this erosion of the early survival advantage after EVAR is unclear. It may be that open surgery precipitates cardiovascular mortality in patients who were already at high risk, or simply a chance finding. In order to evaluate the effects of alternative assumptions about cardiovascular mortality on survival and cost-effectiveness, the increase in cardiovascular hazard associated with the EVAR procedure compared with that after open repair was estimated from the EVAR trial 1 and varied in sensitivity analyses.

### *Death from aneurysm- and procedure-related causes*

The rate of death from aneurysm-related causes used in the base-case analysis was found from the EVAR trial 1 data in the period after the index procedure to be about 0.8 per 1,000 person-years following open repair and 5 per 1,000 person-years following EVAR. By comparison, the EUROSTAR and the RETA registers of patients undergoing EVAR observed a rate of about 8 AAA deaths per 1,000 person-years. Both registers included patients with small aneurysms; EUROSTAR included patients fit and unfit for open surgery and RETA included both current and withdrawn EVAR devices (Torella 2004; Beard 2005; Thomas 2005)

Mortality for non-cardiovascular causes was estimated from age and sex specific population life tables, adjusted to exclude deaths from cardiovascular causes. The rate of non-fatal cardiovascular events and aneurysm related procedures was estimated from EVAR trial 1. Unit costs for EVAR and open repair procedures were estimated from the EVAR trial 1 and include the average costs of in-hospital complications and mortality.

### *Cost-effectiveness analysis*

Standard decision rules were followed for the cost-effectiveness analysis using expected costs and QALYs (Drummond 2005). If the expected costs of one strategy exceed the other, and do not also give an expected gain in health benefits, then this strategy is dominated and the other is the more cost-effective. If both the expected costs and health benefits of one strategy exceed the other, then the incremental cost-effectiveness ratio (ICER) is calculated as the incremental cost per additional QALY generated by the more effective intervention. A probabilistic sensitivity analysis, based on the uncertainty in the parameters of the model, was undertaken to estimate the probability that EVAR is more cost-effective than open repair as a function of the threshold ICER (Speigelhalter 2004).

## **Results**

### *Base-case*

Predictions of survival by the model, and comparison with the EVAR trial data, are shown in Figure 5. The model predicts a persistent reduction in aneurysm-related deaths in the EVAR group at 4 years (3.2% vs 5.3%), while all-cause mortality was similar in the two groups (about 28%). The predicted all-cause survival curves meet at about 2 years; after this, there is a small but persistent divergence due to the greater risk of mortality from aneurysm-related causes in the EVAR group. The estimates for aneurysm-related death in the EVAR trial 1 at 4 years were 4% vs 7%. The model predictions for aneurysm-related deaths are expected to differ from the trial because the latter includes patients who died before a procedure was undertaken and uses an intention-to-treat analysis.

Under base-case assumptions, the model predicted greater lifetime expected costs in the EVAR group (mean difference £3,758, 95% CI £2,439 to £5,183), because of the greater initial cost of the procedure and of monitoring during follow-up (Table 3). The model predicted slightly fewer expected QALYs with EVAR (mean difference -0.020, 95% CI -0.189 to 0.165). This is because the initial survival advantage with the EVAR procedure is eroded by more deaths due to cardiovascular- and aneurysm-related causes over the longer-term. Therefore, based on these expected values, EVAR is dominated by open surgery, and has a probability of only 8% of being cost-effective at a cost-effectiveness threshold of £40,000 per additional QALY.

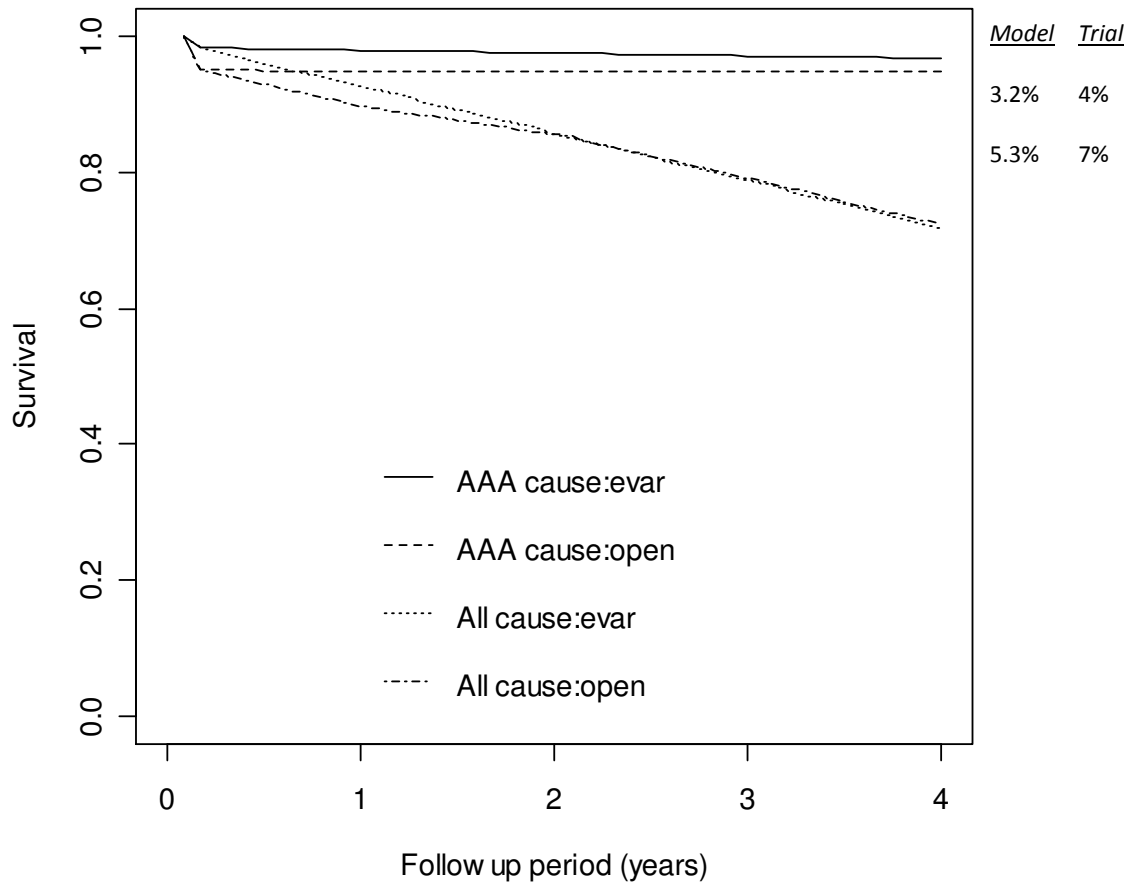
**Table 3: Model estimates of mean costs and QALYs over patients' lifetime under base-case assumptions, and the probability EVAR is cost-effective when the cost-effectiveness threshold per additional QALY is £20,000 and £40,000**

	<i>Mean Cost</i>			<i>Mean</i>		
	<i>£</i>	<i>95% CI</i>		<i>QALYs</i>	<i>95% CI</i>	
EVAR	15,823	14,606	17,418	5.050	3.685	6.172
Open	12,065	10,358	14,144	5.070	3.754	6.123
Difference	3,758	2,439	5,183	-0.020	-0.189	0.165

Probability EVAR is cost-effective:

Assuming a cost-effectiveness threshold of £20,000/QALY	0.01
Assuming a cost-effectiveness threshold of £40,000/QALY	0.08

Figure 5: Model predictions of survival and survival free of aneurysm-related death under base-case assumptions, and comparison to EVAR trial 1 estimates at 4 years



**Secondary analyses**

The base-case assumptions were varied in a series of secondary analyses to reflect alternative sources of evidence and strengths of opinion about some of the key parameters used in the model. The results are shown in

Table 4 in terms of the difference in expected costs and QALYs, the ICER where appropriate and the probability that EVAR is cost-effective at cost-effectiveness thresholds of £20,000 and £40,000 (Rawlins 2004)

Other things being equal, the scenarios which most clearly influenced effectiveness are (i) the relative risk of cardiovascular mortality in these patients compared to the general population (scenario 2); (ii) the relative effect of the treatment strategy on cardiovascular mortality (scenario 3); (iii) the relative risk of AAA death during the follow-up period (scenario 8); and (iv) the probability of death within 30 days of open repair (scenario 9). Scenario 5, in which there is a lower acquisition cost of the EVAR device, reduces the difference in average costs between the strategies but, since it does not affect health benefits nor leads to expected cost savings overall, this scenario did not, on its own, lead to a conclusion that EVAR is cost-effective.

Analyses were also carried out varying the age of the patient at the time of surgery (scenarios 10, 11, 12 and 13). There was no evidence that the odds ratio for operative mortality or all cause mortality varied by age (Brown 2007). However, age was a significant predictor of operative mortality after open repair, and consequently there was a greater absolute difference in the rate of operative mortality between treatment groups among older patients than younger patients. Scenario 13 assumed that the risk of late mortality for non-AAA causes was the same during follow-up after each procedure and therefore the initial benefits of EVAR would be maintained over these patients' lifetimes. Moreover, since elderly patients have a lower life expectancy they will accumulate less health-care costs of follow-up and re-interventions after EVAR. Based on these assumptions, EVAR would have an ICER of £27,000 and would be cost-effective in these patients at a threshold of £30,000 per QALY. However, this analysis is exploratory and more research is needed on all the risk factors, not just age, that might determine procedure-related complications and long-term outcomes.

**Table 4: Results of secondary analyses: difference in mean costs and QALYs and the probability that EVAR is cost-effective when the threshold per additional QALY ( $\lambda$ ) is £20,000 and £40,000**

Scenario	Base-case assumption	Secondary analysis	Difference in		ICER for EVAR vs. Open *	Prob. EVAR is cost-effective†	
			Cost (£)	QALY		$\lambda=20k$	$\lambda=40k$
1	Base-case		3,758	-0.020	EVAR dominated	0.012	0.080
2	Hazard of CV death twice that of the general population	Baseline hazard of CV death is the same as the general population	4,105	0.017	239,000	0.028	0.161
3	Lower rate of CV death following open surgery	Same hazard of CV death following each treatment strategy	3,687	0.087	42,000	0.098	0.481
4	1 CT scan and 1 outpatient visit per year following EVAR	Same cost of monitoring following each treatment strategy	2,613	-0.020	EVAR dominated	0.045	0.145
5	Cost of EVAR device is £4,800	Cost of EVAR device is £3,700	2,669	-0.020	EVAR dominated	0.048	0.147
6	Odds ratio of 30 day mortality from EVAR trial 1 only	Odds ratio from a meta-analysis of DREAM and EVAR trials	3,765	-0.015	EVAR dominated	0.012	0.084



Scenario	Base-case assumption	Secondary analysis	Difference in		ICER for EVAR vs. Open *	Prob. EVAR is cost-effective†	
			Cost (£)	QALY		λ=20k	λ=40k
7	Discount rate of 3.5%	No discounting of costs nor health benefits	4,103	-0.041	EVAR dominated	0.016	0.084
8	Odds ratio of AAA cause mortality during follow-up from EVAR trial 1	No difference between EVAR and open of the rate of AAA death during follow-up	3,859	0.080	48,000	0.076	0.419
9	5% die within 30 days of open repair	8% die within 30 days of open repair	3,795	0.090	42,000	0.147	0.463
10	Age 74 years	Age 66 years	4513	-0.144	EVAR dominated	0.001	0.025
11	Age 74 years	Age 82 years	3072	-0.015	EVAR dominated	0.047	0.138
12	Age 74 years and lower rate of CV death during follow up after open surgery	Age 66 years and no difference in rate of CV deaths after open or EVAR	4468	-0.075	EVAR dominated	0.006	0.068

Scenario	Base-case assumption	Secondary analysis	Difference in		Prob. EVAR is cost-effective†	
			Cost (£)	QALY	ICER for EVAR vs. Open *	$\lambda=20k$ $\lambda=40k$
13	Age 74 years and lower rate of CV death during follow up after open surgery	Age 82 years and no difference in rate of CV deaths after open or EVAR	2960	0.110	27,000	0.262 0.670

\*. “EVAR dominated” means EVAR, on average, costs more and has less QALYs than open repair and is not expected to be cost-effective.

†. The probability EVAR is cost-effective is evaluated at threshold ICERs of £20,000 and £40,000 per additional QALY. The National Institute for Health and Clinical Excellence (NICE) in the UK has not to date funded interventions with an ICER above £40,000. Given the uncertainty in the model parameters, this represents the probability a decision to implement EVAR will be better than open repair.

AAA –abdominal aortic aneurysm

ICER – incremental cost effectiveness ratio (difference in mean cost divided by difference in mean health benefits)

QALY- quality adjusted life year

DREAM trial - Blankensteijn JD et al. 2005

CV- cardiovascular

## Discussion

Decision-analytic models are necessary to inform decision makers by bringing together existing evidence to assess the likely cost-effectiveness of competing forms of patient management. In the absence of long-term results evaluating EVAR compared to open management, the modelling presented here has had to incorporate a range of assumptions to assess cost-effectiveness over the lifetime of the patients. Under base-case assumptions, the early benefit of lower 30-day operative mortality is eroded by mortality from AAA and cardiovascular causes during follow up. Although surgical teams may prefer EVAR because the patient is more likely

to leave their care alive (Curtis 2002), EVAR is unlikely to be considered cost-effective from the perspective of the UK NHS on the basis of endograft performance and costs that applied during the period of recruitment to the EVAR 1 trial. In systems with patient co-payments, patient choice may play an important role in whether EVAR devices are used. In other collectively-funded systems, the costs may differ from those used here, including the price of devices which are ultimately under the control of the manufacturers. However, the clinical effectiveness found in this trial to date, and the most plausible assumptions given clinical uncertainty, are likely to be generalisable, and our results are likely to be directly relevant to other similar health-care systems.

Other authors have considered EVAR cost-effectiveness in this group of patients. Patel *et al* (1999) and Bosch *et al*(2002) both concluded that EVAR was cost-effective, assuming lower rates of renal failure, amputation, stroke and MI compared to open repair. Prinssen (2005) found that, since there was almost no difference in all-cause mortality after one-year of the DREAM trial, EVAR was not cost-effective given its higher cost. This approach assumed that mortality related to non-aneurysm causes during follow-up is greater in patients with EVAR, and cancels out the early aneurysm-related mortality benefit of EVAR. Michaels *et al* (2005) assumed no difference between EVAR and open repair in the rates of mortality or morbidity for non-aneurysm causes, and found that EVAR was more effective than open repair but, because of its high cost, was unlikely to be cost-effective.

Several issues add uncertainty to our modelling exercise. There are plausible scenarios under which EVAR might be cost-effective. For this to be the case, EVAR would have to be both relatively more effective and less costly than the base-case assumptions used here. For example, if the device cost the health service £1,100 less than currently priced and there was no difference in non-aneurysm related cardiovascular mortality between the treatments, then EVAR would be cost-effective (at a threshold of £30,000 per additional QALY). The relative risk of cardiovascular mortality, and a better understanding of its causes in the years following the primary procedure may be informed by results from EVAR 1 and the other on-going trials. In another scenario, EVAR would be more effective if the long term risk of cardiovascular mortality in all patients after successful aneurysm repair were closer to that of the general population: this might be achieved through wider use of statins and anti-platelet drugs at modest additional cost. EVAR would be more effective if there were no difference in the long-term risk of AAA related mortality. This will be informed by continued follow-up of patients in the

EVAR trial . Endografts must be developed that will reduce the need for re-intervention and surveillance, obviating the need for annual CT scans.

EVAR is unlikely to be cost-effective for all patients within collectively-funded healthcare systems based on the assumptions and evidence applied in this study, though it may be cost-effective in a sub-population of elderly patients fit for open surgery under particular assumptions. Older patients have greater risk of operative mortality after open surgery and, since there is no evidence that the odds ratio for EVAR versus open repair, in patients fit for open repair, varies by age, older patients will consequently benefit more from EVAR in terms of absolute risk reduction. However, EVAR will only be cost effective in this group if patients maintain this early survival advantage over open surgery, that is, they do not suffer any excess cardiovascular mortality after EVAR. These scenarios are by nature speculative. Furthermore, it is recognised that endovascular technologies and their clinical applications are evolving rapidly. This indicates that if EVAR is to be available to patients it should continue to be considered a research technology. However, the work undertaken and reported here has outlined the conditions that need to be met for EVAR to be cost-effective and points the direction for further research and development in this important area of endovascular therapy.

## Chapter 3: Cost-effectiveness analysis using real options

### Introduction

Several authors have recognised that the watchful waiting problem is an example of a ‘real option’ (Driffield and Smith 2007; Attema et al 2009; Chambers et al 2009). Real option analysis is the adaptation of mathematical techniques developed for valuing financial options to decision-making in other contexts (Myers 1977). The model developed in Chambers et al (2009) was preliminary work that forms the basis of much of the following chapters of this thesis. The models described here owe much to the theoretical framework originally developed by Driffield and Smith (2007).

The purpose of this chapter is to review the methods of valuing financial and real options. Option pricing models are an application of dynamic programming. The chapter explains the concepts and assumptions underlying dynamic programming and the distinction from Markov models. There is a small literature that has applied real option valuation to problems in health economics. One potentially important aspect of real options analysis applied to health-care programmes is the assumption made about the decision-maker’s attitude to risk. To the author’s knowledge, this has not been previously discussed in the health economics literature. Therefore this chapter also reviews the concept of risk-neutrality, considers how attitudes to risk are incorporated into CEA and models of pricing of financial options, and concludes by discussing the conditions under which methods used to value real options in CEA are consistent with an assumption of risk-neutrality.

### Dynamic programming

The model in Chapter 2 is an example of a Markov model (Sonnenberg and Beck 1993). The attributes of the Markov model can be generalised as follows:

- a. There is a physical system characterised at any stage by a small number of parameters, the state variables
- b. At the start of the first stage, there is a choice of a number of decisions or policies
- c. The effect of a decision is a transformation of the state variables
- d. The past history of the system is of no importance in determining future actions

- e. The purpose of the process is to maximise some function of the state variables

As discussed in the Introduction to this thesis, the watchful waiting problem is complex to model in a conventional Markov framework because it implies a perhaps long series of sequential decisions. There would be a large number of potential strategies if these were all enumerated upfront, as required by assumption (b). The watchful waiting problem can be simplified using dynamic programming. Dynamic programming has all of the five attributes of the Markov model described above, except that (b) is now more general: At each stage of the process, we have a choice of a number of decisions (Bellman 1957). Solving a dynamic programming relies on the principle of optimality: “An optimal policy has the property that whatever the initial state and initial decision are, the remaining decisions must constitute an optimal policy with regard to the state resulting from the first decision” (Bellman 1957). If the problem has a recursive structure and the principle of optimality is assumed to hold, then the dynamic programme can be solved by backward induction. This is the process of reasoning backwards in time to determine the sequence of optimal policies. It proceeds by first considering the last time a decision might be made and choosing what to do in any state at that time. Using this information, one can then determine what to do at the second-to-last time of decision. This process continues backwards until one has determined the optimal policy for every possible state at every point in time. Backward induction is similar to the familiar process of ‘folding back’ a conventional decision tree, except that there are now embedded or downstream decision nodes (Kuntz and Weinstein 2001). Dynamic programming requires an explicit decision rule for determining the optimal policy at each stage, that is, we must specify the decision maker’s threshold value of a QALY in advance in order to calculate expected net benefit in monetary terms.

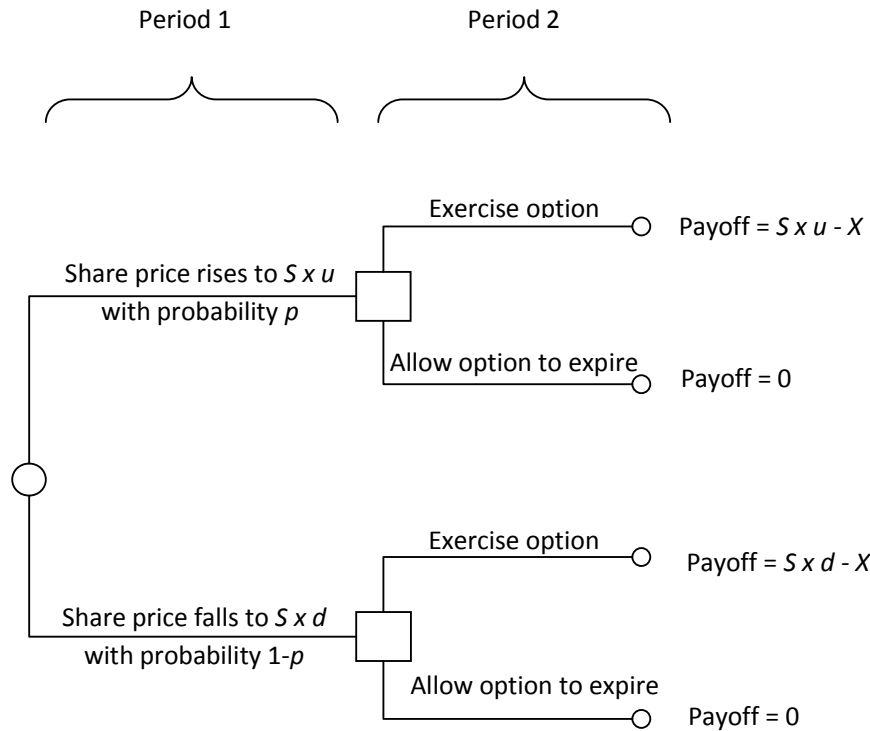
#### Valuation of financial options

An option is a contract between a buyer and a seller that gives the buyer of the option the right, but not the obligation, to buy or to sell a specified asset on or before the option's expiration time, at an agreed price (the strike price). In return for granting the option, the seller collects a payment (the premium) from the buyer. A call option gives the buyer the right to buy the underlying asset at the strike price, and a put option gives the buyer of the option the right to sell the underlying asset at the strike price (Wilmott 1995).

Valuation of financial options is an application of backward induction. Figure 6 shows the buyer's decision problem for exercising a call option in the following period. In a simple, binomial model,  $S$  is the current share price (which takes account of investors' risk-aversion),  $S \times u$  is the price if the share increases in value in the next period, and  $S \times d$  is the price if the share decreases in value ( $u > 1$  and  $d < 1$ ). Variable  $p$  is the probability the share increases in value.  $X$  is the exercise or strike price at which the owner of the call option can purchase the share in the next period. If the share price rises, the option will be exercised, but if it falls the option is worthless and will be allowed to expire. The discount rate per period is  $r$ . At the start of the first period, the expected value of the option is:

$$\text{Expected option value} = (p \times \text{Max}(S \times u - X, 0) + (1-p) \times \text{Max}(S \times d - X, 0)) \div (1+r)$$

Figure 6. The buyer's decision problem for exercising a call option



If the buyer and the seller had the same expectations about the parameters of the decision ( $r$ ,  $p$ ,  $u$  and  $d$ ), and both buyer and seller were risk-neutral, then there would be no market for options: the option would be priced such that its expected value would be equal to the premium for any given strike price. However, an option would have value if the buyer was risk-averse and the seller was risk-neutral. In this case, the call option is a form of insurance against an unfavourable movement in asset prices.

Financial models have been developed to estimate value of an option (and therefore the premium that the option might be offered at) given the degree of risk-adversity held by investors. The price of many types of asset in financial markets is usually lower than its expected value would suggest, as measured for example by future expected cashflows, reflecting the degree of risk in those as-yet unrealized cashflows. One type of model for valuing options is the 'risk-neutral measure' (Cox et al 1979; Wilmott 1995). These models take investors' risk-adversity into account by representing the likelihood of changes in the price of the underlying asset as specially constructed 'risk-neutral probabilities' rather than real-world physical probabilities. Risk-neutral probability



measures are calculated so that all assets have the same expected rate of return. If risk-neutral probability measures are estimated, every asset can be priced at its expected value (acting *as if* investors were risk-neutral), discounted at the risk-free rate.

The seller of the option needs to estimate these ‘risk-neutral’ probabilities of asset price movements up or down, represented as  $p_n$ . If the underlying volatility of the asset is known, then possible values of the asset in the next period ( $u$  and  $d$ ) can be inferred. For no arbitrage to be possible in the share, today’s price must represent its expected value discounted at the risk free rate  $r$ :

$$S = [p_n \times S \times u + (1 - p_n) \times S \times d] \div (1+r)$$

The expression is then rearranged to find  $p_n$ , the ‘risk-neutral’ probability

$$p_n = [(1+r) - d] \div [u - d]$$

The risk-neutral probabilities, rather than the actual probabilities of share movements, are then used to calculate the call option value. For no arbitrage to be possible in the call, today’s price must represent its expected value discounted at the risk free rate:

$$\text{Option value} = (p_n \times \text{Max}(S \times u - X, 0) + (1 - p_n) \times \text{Max}(S \times d - X, 0)) \div (1+r)$$

### Examples of real option analysis in health economics

Real option analysis was originally developed to inform capital budgeting decisions, in situations where the manager can modify the project (for example, expand / cancel) in response to events or further information (Myers 1997). A number of papers have been recently published discussing the extension of real option analysis to various problems in health economics (Palmer and Smith 2000; Driffield and Smith 2007; Eckermann and Willan 2008; Attema et al 2009; Chambers et al 2009).

Palmer and Smith (2000) consider the timing of a decision to invest in a new technology with high initial set up costs and/or a fast rate of product innovation, such as CT scanning or Magnetic Resonance Imaging. Delaying the decision may allow more information to be assembled on the cost-effectiveness of current and possibly future generations of devices. They also suggest that implementing a low-cost, high-utilisation technology might be partly irreversible in the sense that the programme may change perceptions and expectations and therefore have a ‘sunk-cost’ once it is established.

Eckermann and Willan (2008) consider when it might be optimal for Health Technology Assessment (HTA) to delay implementing a new technology in order to wait for further evidence, or to adopt the new technology with further trials in the case of reversible decisions. They find that the option value of delaying a decision can be estimated as the expected value of sample information, and that the optimal policy depends on the costs of reversal, the opportunity cost of delay and the distribution of prior incremental net benefit between the strategies under consideration.

Attema et al (2009) apply real options theory to value stockpiling antivirals as a precautionary measure against a possible influenza outbreak. They model the decision assuming different utility functions: risk-neutrality, risk-aversion and with deviations from expected utility using prospect theory. Uncertainty arises in the problem because of the unknown probability of an outbreak and the uncertain benefits of the drug after an outbreak, about which more information becomes available over time. Delaying the decision is feasible and might have value as it allows time for new information to become available. The authors find that the benefits of stockpiling antivirals are very high and that including an option to wait for further information does not change the decision.

Driffield and Smith (2007) apply real-options theory to the decision to defer treatment for AAA. Much of the conceptual framework in this thesis is based on their work, but differs in two important respects. First, their numerical example is for illustrative purposes, rather than based on secure empirical data. In this thesis, we have attempted to assemble the best available data, although the data for the natural history of untreated AAA are very uncertain. Second, their model structure is a trinomial lattice, where the patient's health status (and, correspondingly, the health benefit associated with surgery) follows a random walk. In each period net benefit is assumed to be able to increase 10%, remain unchanged or decrease 10%, with the probabilities of an upward or downward move governed by a (known) variability parameter. Therefore the number of possible model states increases with the time horizon of the model in a process that is analogous to Brownian motion governing diffusion over time of molecules suspended in a fluid. In this thesis, there are a finite number of model states that represent AAA sizes (measured in 0.5cm bands). The model states therefore have a clear clinical interpretation and the transition probabilities from one aneurysm size to the next are therefore measurable physical phenomena. The model structure is closer to a

conventional CEA decision model than the Driffield and Smith (2007) model, and arguably more likely to be familiar to policy makers.

### Attitude to risk

Decision analysis, including CEA, is usually conducted from the perspective of a rational decision-maker (Nease 1996), that is, the decision maker's preferences are consistent with expected utility theory (see Annex). Expected utility theory does not always accurately describe or predict how people make decisions in real-life, and there are a number of rival theories of actual behaviour, such as prospect theory (Kahneman and Tversky 1979). However, decision analysis is normative, not descriptive – it recommends how a policy-maker should act in order to achieve a given objective.

Risk-aversion, risk-neutrality and risk-seeking are attitudes that are each consistent with rational decision-making. Modelling the decision-maker's attitude to risk is an important element of decision analysis in other fields. Financial assets, for example, are usually valued assuming that investors are risk-averse; indeed, much of the value in options and derivatives arises from differing attitudes to risk on the part of the buyer and seller. CEA on the other hand, particularly in the extra-welfarist approach, usually assumes the decision maker is risk-neutral, because the decision maker is usually the government or a large, well-diversified insurer (Stinnett and Paltiel 1996).

Consequently, the question arises: is a neutral attitude to risk by the decision maker in CEA consistent with real option valuation models?

### *Risk-neutrality*

A risk-neutral decision-maker will aim to maximise expected value (Gafni and Torrance 1984, Wilmott 1995). Value can in principle be measured in any variable with cardinal properties, but CEA in the UK usually assumes the decision-maker aims to maximise expected QALY given the budget constraint (NICE 2008). The monetary value of an additional QALY in most appraisals undertaken by the National Institute for Health and Clinical Excellence (NICE) is usually between £20,000 and £30,000 (Rawlins 2004). If  $V_u$  is the net benefit of a health-care programme  $u \in U$  then the risk-neutral decision maker will choose  $u$  so as to maximise expected value  $V^* = \max_u(V_u)$ . A risk-neutral decision-maker is indifferent between a current certain payoff and future uncertain payoffs with the same expected value, discounted at a risk-free rate. This definition of risk-neutrality is seen to contain three distinct components (Wilmott 1995):

- No quantity effect – utility is proportional to the size of the payoff
- No gambling effect – utility is unaffected by uncertainty about the outcome of the gamble
- No time-preference effect – utility is unaffected by the timing of the payoff, after discounting at the risk-free rate

The definition of the time-preference component shown above differs from that used by Gafni and Torrance (1984). They define a risk-neutral time preference as being utility unaffected by the timing of the payoff. However, this can lead to inconsistent decisions. Under the definition of Gafni and Torrance (1984), if the decision maker were indifferent between a certain payoff of a given size this year or next year, this ignores the possibility for the same sum to be invested and receive a risk-free future profit. Therefore this thesis defines a risk-neutral decision maker to be unaffected by the timing of the payoff, after discounting at the risk-free rate.

#### *Risk-aversion and CEA*

People are commonly risk-averse in major health and financial decisions (as opposed to games such as lotteries and casinos). Risk-aversion is entirely compatible with rational decision making; in these cases, the decision-maker would be maximising expected utility rather than expected value, where utility is non-linear. Although CEA usually adopts a risk-neutral perspective, risk-aversion has been incorporated into CEA in various ways, by applying a non-linear quantity effect, a gambling effect or a time-preference effect to the decision maker's utility function.

Some authors have suggested using a non-linear utility function for the monetary value of a QALY (MVQ) in resource allocation models (Zivin 2001; Al et al 2005; Attema et al 2009). Recent work on estimating the social MVQ (that is, the willingness of the general public to pay for a QALY) has found that it varies inversely with the magnitude of the health gain (Pinto-Prades et al 2009).

Whereas a risk-neutral decision maker is only concerned with expected returns, a risk-averse decision maker might also be concerned with the variability of those returns. In a CEA context, this could be interpreted as a desire for some equality in the distribution of the benefits of health-care as well as the overall expected gains. A risk-averse

decision maker would prefer a technology with a low chance of losses and low chance of gain to a technology with the same expected net benefit but a high chance of losses and gains. Dolan et al (2008) called this parameter ‘aversion to inequality’ in health gain and estimated this from a sample of the general public. These data were then used to calculate weights for the threshold value of a QALY depending on the characteristics of the population and the technology under appraisal.

Another method to take account of risk-aversion is to use a higher discount rate than the risk-free rate. Financial assets are often valued using discounted cash flow analysis (DCF), where the discount rate represents the opportunity cost of capital (the weighted average cost of capital) to the enterprise and reflects the risks of the cashflows.

Therefore a new project must expect to generate at least that average rate of return to be implemented. In CEA, the discount rate is usually an estimate of a risk-free rate. In the UK it is 3.5% per year based on the recommendation of the UK treasury (NICE 2008). In Spain it is 3% per year based on a long-term view of the rate of interest of the Central European Bank (López Bastida et al 2008). Both agencies suggest sensitivity analyses are carried out with discount rates between 0 and 6%. Arguably, as argued above, a 0% discount rate indicates the decision maker is risk-seeking, because the decision maker prefers an investment in the health service with uncertain future benefit to a risk-free return if the money were invested elsewhere.

### Conclusions

Risk-aversion, risk-seeking and risk-neutrality are consistent with rational decision-making. Investors are assumed to be risk-averse by financial asset valuation models. Options can be seen as a form of insurance against an unfavourable movement in asset prices. For the holder of the option, the maximum gain is unlimited, but the maximum loss is the premium paid to buy the option. If investors were risk-neutral, they would not require insurance. They would be indifferent between an option (with a certain future exercise price) and the gamble that the underlying asset would rise or fall in value, and so the option would have no value.

In the health-care context, risk-seeking behaviour would arguably only be seen in relatively rare situations, such as trying a new drug outside its licensed indication, and therefore we exclude this attitude for mainstream health policy-making. Risk-aversion is much more common in health policy. Regulatory authorities set a high hurdle for

licensing new drugs. The burden of proof is on the manufacturer to demonstrate safety and efficacy with a low chance of error, typically 5% in conventional significance tests. Clinicians are often risk-averse, as reflected in the maxim 'first, do no harm'.

Although risk-aversion is common in major health and financial decisions, most CEA assume the decision maker is risk-neutral and despite the few exceptions in the literature there are good reasons for this position. First, CEA takes place after regulatory authorities have licensed a drug, and therefore there is some security that the drug is at least safe and efficacious. Reimbursement or guideline agencies then seek to determine if the drug is cost-effective. Therefore there is less need for CEA to take a risk-averse attitude because this has already been built into the regulatory process. Second, risk-aversion represents an additional constraint on the decision-maker, and the expected value of a risk-neutral decision would always be greater than or equal to the expected value of a decision taken with risk-aversion. Risk-aversion (or a preference for equality of outcomes) therefore comes with an opportunity cost in terms of lower overall health than would be expected by a risk-neutral decision maker (Epstein et al 2007).

These arguments apply to CEA in general. One of the functions of a financial option is to offer a form of insurance, which is valuable if the insured individual is risk-averse. Does this then imply if real option valuation models are used to evaluate health-care programmes, then these decision rules should also assume risk-aversion? Arguably, in the case of access to health-care, the real option to delay surgery does not offer much insurance, because the patient already has entitlement to health-care through the National Health Service. The real option to delay has a more important function in the management of AAA: it allows the clinician more time to obtain further information about the growth of the aneurysm and alter what would otherwise have been an irreversible recommendation to treat or discharge the patient. In financial option valuation models, share prices are assumed to follow a random walk in which no information is available from past share prices. The real option may have value because it increases the information upon which a clinical decision can be made (Driffield and Smith 2007). The current aneurysm size is predictive of future growth rates and the likelihood of aneurysm rupture. Consequently the value of the real option to delay surgery can be positive for risk-neutral, risk-seeking or risk-averse decision makers.

## **Annex : The axioms of expected utility theory**

The axioms of expected utility theory are completeness, transitivity, independence and continuity (Nease 1996). Completeness assumes that an individual has well defined preferences and can decide between two alternatives. For every  $A$  and  $B$  either  $A < B$ ,  $A > B$  or  $A = B$  (this means:  $A$  is worse than  $B$ , better, or equally good) holds. Transitivity assumes that, as an individual decides according to the completeness axiom, the individual also decides consistently. For every  $A$ ,  $B$  and  $C$  with  $A \geq B$  and  $B \geq C$  we must have  $A \geq C$ . Independence also pertains to well-defined preferences and assumes that the preference order of two gambles mixed with a third one maintains the same preference order as when the two are mixed independently. Let  $A$  and  $B$  be two lotteries with  $A \geq B$ , and let  $t$  be a random variable with values between 0 and 1. Then  $tA + (1-t)C \geq tB + (1-t)C$ . Continuity assumes that when there are three lotteries ( $A$ ,  $B$  and  $C$ ) and the individual prefers  $A$  to  $B$  and  $B$  to  $C$ , then there should be a possible combination of  $A$  and  $C$  in which the individual is then indifferent between this mix and the lottery  $B$ . Let  $A$ ,  $B$  and  $C$  be lotteries with  $A > B > C$  then there exists a probability  $p$  such that  $B = pA + (1 - p)C$ .

## **Chapter 4: Dynamic programming applied to the cost-effectiveness analysis of watchful waiting versus immediate surgery for AAA: a simplified, illustrative example of the methodology**

### **Introduction**

An abdominal aortic aneurysm is a dilation of the aorta. The risk of rupture increases with aneurysm size (Michaels 1992), and patients with a ruptured AAA have a mortality rate of 80% (Chambers et al 2009). The normal diameter of the aorta is about 2cm. Current guidelines for the management of asymptomatic AAA recommend that patients are observed until the aneurysm reaches 5.5 cm, after which surgical intervention is considered (Chambers 2009). Under these guidelines, patients with a large aneurysm, anatomically suitable for EVAR and considered fit for open surgery might be offered either EVAR or open surgery; patients considered unfit for open surgery might be offered EVAR or no intervention. The definition of 'fitness' is usually a judgement by the clinician depending on cardiovascular, respiratory and renal status (EVAR 2005a).

The threshold of 5.5cm arose from the design and results of the seminal UK Small Aneurysms Trial (UKSAT 1998). This RCT compared early open surgical repair with a strategy of waiting until the aneurysm grew to 5.5cm, in patients with baseline aneurysm size of between 4cm and 5.5cm. The RCT found no survival advantage for immediate surgery after 6 years of follow up. However, the RCT did not evaluate other feasible management policies that might be relevant to the guideline. These might include operating on larger or smaller aneurysms. Early surgery tends to have immediate operative risks and costs, set against longer term survival benefits, and therefore the optimal management policy may depend on the patient's age.

Endovascular repair may reduce the risk of operative mortality (in patients suitable for EVAR). None of these questions were addressed by the RCT. Furthermore, a publicly funded healthcare system must also evaluate the use of health-care resources, which are not considered explicitly by the current clinical guidelines.

UK SAT did not include patients who were unfit for open repair. The EVAR trial 2 (EVAR 2005b) compared immediate endovascular repair *versus* medical management



in patients with  $AAA \geq 5.5\text{cm}$  and unfit for open repair. Like UKSAT, EVAR trial 2 also found no survival advantage for immediate surgery at 4 years, though found a non-significant advantage for EVAR in aneurysm-related deaths. However, 27% of patients randomised to medical management underwent surgery at some point over the 4 years. These crossovers may have diluted the difference between the randomised groups, and make interpretation of the results of the RCT difficult (Lederle 2005b).

There are, therefore, a number of gaps in the currently available clinical evidence base for the management of AAA. At what aneurysm size should endovascular surgical repair be offered in 'fit' patients? Should endovascular repair be offered at all in 'unfit' patients, and if so, at what aneurysm size?

The aim of this thesis is to evaluate these questions from an economic perspective, and this chapter introduces the analytical framework for the watchful waiting model. The structure of the chapter is as follows. First, we describe the strategies that are being compared. Second, we present a formal treatment of the conceptual framework used to model the watchful waiting strategy. Third, we illustrate the intuition behind the watchful waiting model using a simplified example with two time periods and a reduced number of parameters. In a subsequent chapter, we present the results of the complete long-term model for various patient groups incorporating the best available estimates of parameter values.

## Methods

### *Description of the strategies*

At each consultation with their vascular surgeon, a patient with a diagnosed, asymptomatic, untreated AAA faces four options: no surgery, surgery with EVAR or open repair, or continuing watchful waiting. Surgery is an irreversible treatment. It considerably reduces the risk of aneurysm-related death, but also carries a risk of operative mortality or subsequent complications. It is assumed that a decision to rule out surgery (for whatever reason) is also irreversible. In practice, the patient may be reassessed if the aneurysm later becomes symptomatic, or if their fitness (and hence operative risk) improves, but these scenarios are not included in the current model. A watchful waiting strategy, on the other hand, allows more information on the aneurysm growth rate to be assembled, and preserves the option to commence immediate surgery in the future should the patient's aneurysm size worsen (Driffield and Smith 2007). The

costs of deferral with surveillance are monetary costs (the monitoring costs with computed tomography (CT) and outpatient attendance) but also an important opportunity cost: patients may die from aneurysm rupture while waiting.

As discussed in previous chapters, the watchful waiting problem is complex to model in a conventional Markov framework because it implies a perhaps long series of sequential decisions. Fortunately, the problem can be greatly simplified by using backward induction, a form of dynamic programming (Judd 1998). Backward induction is based on a relatively simple principle: that if a decision has a finite time horizon ( $T$  periods), and given the values (payoffs) attributable to model states and policies during each time period  $t=1, \dots, T+1$ , and given the probabilities of transition between model states under each policy, then we can work backwards to induce the optimal policy for each model state in period  $T$  and each previous period ( $T-1, T-2$ , and so on), until the starting period ( $t=1$ ).

The current model is much influenced by Driffield and Smith (2007). They used backward induction to solve a dynamic programme comparing open surgery with no treatment or deferral. However, the current model builds on this earlier work by using more realistic parameter values and health states that correspond with clinical decision making.

The following section sets out a formal treatment of backward induction, following the notation used by Judd (1998).

#### *Finite-state, finite-horizon dynamic programme*

Let  $X$  be the set  $x_i, i=1, \dots, n$ , of  $n$  states, and  $D=\{u_i | i=1, \dots, m\}$  the set of  $m$  controls for a finite state problem. There are  $T$  periods during which decisions can be made, so that life expectancy is  $T+1$  periods. The  $n=15$  states in the model are the sizes of AAA, represented as categorical variables  $x_1=3$  to  $<3.5\text{cm}$ ,  $x_2=3.5$  to  $<4\text{cm}$  etc, up to  $x_{14}=9.5$  to  $<10\text{cm}$ , plus a 'dead' state. The  $m$  controls are the feasible strategies (e.g. surgery *versus* no surgery *versus* watchful wait) in state  $x$  and time  $t$ . Each control is associated with a transition probability between the states, which can be represented as  $q'_{ij}(u)$ . This is the probability of a transition to state  $x_j$  if the state is  $x_i$  and the control is  $u$  in period  $t$ .

The collection of probabilities specifies the Markov transition matrix at time  $t$  for each  $u$ , denoted  $Q^t(u)$ .

In a finite time horizon dynamic programme we use backward induction to estimate the value function  $V(x,t)$  at each time  $t$ , starting with the terminal value function  $V(x,T+1) = W(x)$ .  $W(x)$  (the terminal valuation),  $x_1$  (the initial state),  $\Pi(x,u,t)$  (the payoffs to the decision maker in period  $t$  for strategy  $u$  and state  $x$ ) and  $\beta$  (the discount factor) are given. Since we have a finite number of states, the value function  $V(x,t)$  at time  $t$  is really just a finite list of values. The Bellman equation breaks a dynamic optimization problem into simpler sub-problems, writing the value of a decision problem at a certain point in time in terms of the payoff from some initial choices and the value of the remaining decision problem which results from those initial choices (Bellman 1957). In this case, the Bellman equation is

$$V(x_i,t) = \max_u [\Pi(x_i,u,t) + \beta \sum_{j=1}^n q_{ij}^t(u) V(x_j,t+1)], \quad i=1,\dots,n, \quad (\text{Equation 4.1})$$

With the terminal condition

$$V(x_i,T+1) = W(x_i), \quad i=1,\dots,n. \quad (\text{Equation 4.2})$$

The value function is the total value of the optimal policy. The optimum policy for each state  $x_i$  at time  $t=1$  is

$$U_i^* = \arg \max_u [\Pi(x_i,u,t) + \beta \sum_{j=1}^n q_{ij}^t(u) V(x_j,t+1)], \quad i=1,\dots,n, \quad (\text{Equation 4.3})$$

We can also define the value function for non-optimal policies (that is, the strategies of immediate endovascular surgery, open surgery or no surgery) using similar notation. If we are at the state  $(x_i,t)$  and we are going to use policy  $U$ , the resulting expected total value equals  $V^U(x_i,t)$  which can be defined recursively by

$$V^U(x_i,t) = \Pi(x_i,u,t) + \beta \sum_{j=1}^n q_{ij}^t(u) V^U(x_j,t+1) \quad (\text{Equation 4.4})$$

Equation 4.4 is simply a recursive way of defining a conventional finite-state, discrete-time Markov model. The structure of the model for watchful waiting differs from the model for the irreversible strategies because of the maximisation step at the start of every period. It follows from the definition of the value functions in Equation 4.1 and Equation 4.4 that  $V^U(x_i,t) \leq V(x_i,t)$  for any given  $t$  and  $x_i$ .

The following section shows the intuition behind the Bellman equation for the AAA example, using a simplified version of the model with a reduced number of parameters and two time periods. This stripped-down model is simple enough to be calculated by hand or in Excel. Chapter 5 goes on to develop the full multi-period model and solve it using the R software package (© The R foundation for statistical computing, 2007).

*Illustrative model of a watchful waiting strategy for AAA*

Figure 7 shows the structure of the model as a decision tree. In this simplified, illustrative version of the model, there are  $T=2$  periods, each period lasting 6 months. There are  $n=4$  states, representing aneurysm sizes plus a dead state:  $X=[x_1:5 \text{ to } <5.5\text{cm}, x_2: 5.5 \text{ to } <6\text{cm}, x_3:6 \text{ to } <6.5\text{cm}, x_4:\text{dead}]$ . Assume that patients have asymptomatic AAA of size  $x_1=5\text{-}5.5$  cm at  $t=1$ . There are  $m=3$  possible strategies being considered:  $U=[u=1:\text{no surgery (irreversible)}, u=2:\text{surgery (irreversible)} \text{ and } u=3:\text{watchful waiting (reversible)}]$ . If surgery is undergone, there is a probability of operative mortality in the period of surgery, but the risk of aneurysm-related death in subsequent periods is very low. If surgery is not undertaken, there is a risk of rupture, or if the aneurysm does not rupture it might grow, with a greater risk of rupture in the following period. Under the watchful waiting strategy, no surgery is undertaken in the first period but the option is retained to undertake surgery in the following period depending on the size of the aneurysm. This differs from the ‘no surgery’ strategy where it is assumed surgery will never be undertaken.

For illustrative purposes, the transition probabilities (the cells of matrix  $Q^t(u)$ ) are as follows (see Figure 7). If surgery is undertaken ( $u=2$ ), then the probability of operative mortality  $q^1_{14}(u=2) = 0.02$  and the probability of aneurysm-related death more than 30 days after surgery  $q^2_{14}(u=2)$  is zero.

If no surgery is undertaken ( $u=1$ ), the probability a 5-5.5cm aneurysm will rupture in 6 months is  $q^1_{14}(u=1) = 0.01$ . The probability a 5.5-6cm aneurysm will rupture in the following 6 months is  $q^2_{24}(u=1) = 0.4$ , and the probability a 6.0-6.5cm aneurysm will rupture in the following 6 months is  $q^2_{34}(u=1) = 0.8$ .

If the AAA does not rupture, it may grow. The probability (conditional on not having ruptured) that it does not grow is  $q^1_{11}(u=1)/(1 - q^1_{14}(u=1)) = 0.71$ , the probability it grows by 0.5cm is  $q^1_{12}(u=1)/(1 - q^1_{14}(u=1)) = 0.28$ , and the probability it grows by 1cm is  $q^1_{13}(u=1)/(1 - q^1_{14}(u=1)) = 0.01$ . These values of the transition probabilities are for convenience and do not represent realistic values, which are estimated in Chapter 5.

It is assumed that the patient is followed up every 6 months in the watchful waiting policy (Brady et al 2004) and patients attend all scheduled follow up visits. In practice, a substantial risk of patient non-compliance would diminish the value of a waiting strategy, though we do not model this scenario. It is assumed that surveillance is discontinued if a decision is made to rule out surgery and then there are no subsequent monetary costs to the health-care service.

In the simplified model there is no mortality for other causes or discount rate  $\beta=0$ , though these parameters will be included in the full model. The full model will use parameters estimated from a review of the literature. It is assumed that CT is a 100% sensitive and specific test.

The cost of surgery is £10,000 for illustrative purposes. The value of one healthy life year is assumed to be £30,000. Net benefit to the health service  $\Pi(x, u, t)$  in any half-year period  $t$  is calculated with the following values

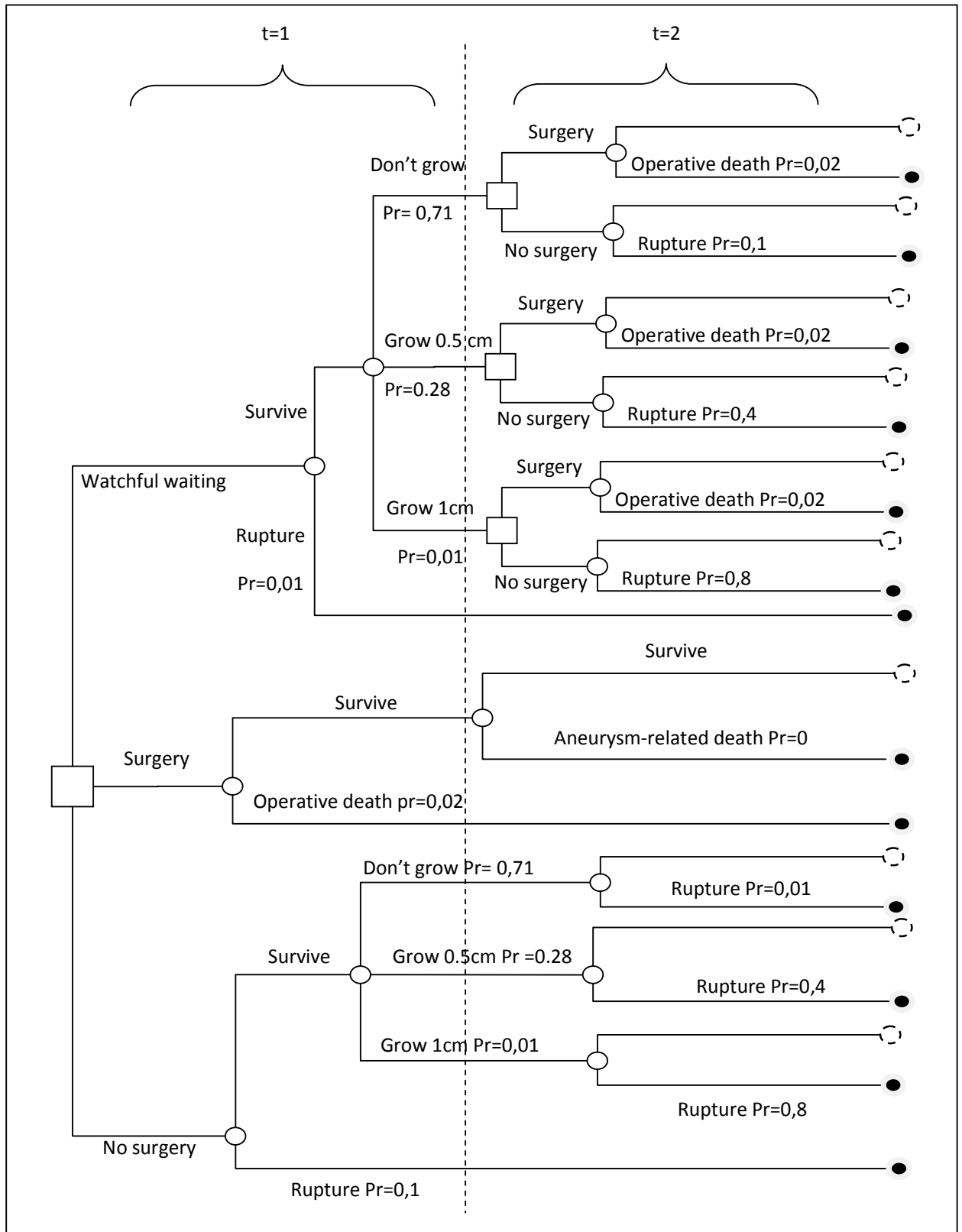
$\Pi = 30,000 \times 0.5 - 10,000 = 5000$  if surgery is undertaken during period  $t$  and patient survives

= -10,000 if surgery is undertaken during period  $t$  and patient dies

= 0 if patient dies or is dead during any other period

=  $30,000 \times 0.5 = 15,000$  if patient survives any other period

Figure 7. Structure of a simplified version of the model



Key: solid black circle – death state, white dashed circle – survive to end of model, white circle – chance node, white square – decision node

### *Probabilistic sensitivity analysis in dynamic programming*

A deterministic analysis estimates the expected net benefit of each of the strategies conditional on point estimates of the mean values of all of the parameters. If  $\theta'$  is a set of point estimates of values of the parameters in the model, then the deterministic results are conditional on those values. The optimal value function can be written  $V(x, t | \theta')$  and the optimal strategy is  $U_i^*(\theta')$ .

However, many of these parameters have been (or could in principle have been) estimated by sampling from a larger population and so there is uncertainty about their mean values. Probabilistic sensitivity analysis (PSA) considers such parameters to be random variables, which can take a range of values defined by a chosen distribution (Speigelhalter et al 2004). PSA has an inherently Bayesian interpretation (Parmigiani 2002). The uncertain random variables  $\theta$  can be thought of as a set of prior inputs to the model with joint multivariate distribution  $p(\theta)$  (Ades and Lu 2003). The output of the model  $V^U(x, t | \theta)$  for strategy  $U$  is then also a random variable conditional on  $\theta$ . The expected net benefit of the optimal strategy is then

$$V(x_i, t | \theta) = \max_u E_{\theta} [V^U(x_i, t | \theta)] \quad (\text{Equation 4.5})$$

PSA is usually implemented using simulation methods such as Monte-Carlo Markov Chain (MCMC). Formally it can be described in three steps (Parmigiani 2002):

1. Draw  $\theta^1, \dots, \theta^K$  from  $p(\theta)$ , perhaps using MCMC
2. For each  $k = 1, \dots, K$ , compute the model  $V_k^U = V^U(x = x_i, t = 1 | \theta^k)$  for strategy  $U$
3. Summarise the overall variability in  $V_k^U$  due to imperfect knowledge of the parameters, for example, using cost-effectiveness acceptability curves (Van Hout 1994)

This approach is valid when estimating the net benefits of irreversible policies, that is, if a decision is only made at time  $t=1$ , rather than in each period of the model. In this case, the optimal strategy  $U_i^*(\theta)$  at time  $t=1$  for initial state  $x_i$  can be calculated by

$$U_i^*(\theta) = \arg \max_u E_{\theta} [V^U(x_i, t=1 | \theta)] \quad (\text{Equation 4.6})$$

The acceptability curve shows the probability  $Pr(U_i = U_i^* | \theta)$  that strategy  $U$  is the most cost-effective given initial model state  $x_i$  at  $t=1$ . This is approximated in a PSA by

calculating the proportion of  $K$  simulations in which strategy  $U$  has the highest net benefit from the set  $D$  of competing strategies.

It is not necessarily the case that the optimal strategy  $U_i^*(\theta)$  is the same as the strategy with the highest probability of being cost-effective.  $U_i^*(\theta)$  is the strategy with the maximum expected net benefit, calculated from the mean of the posterior distribution of net benefit  $E_\theta[V^U(\theta)]$  for each strategy (Equation 4.6), whereas  $Pr(U_i = U_i^* | \theta)$  is approximated from the quantiles of the posterior distribution of net benefit  $V^U(\theta)$ . The distinction is perhaps analogous to the distinction between the mean and the median of a random variable. Whether or not the strategy with the highest mean net benefit  $E_\theta[V^U(\theta)]$  is the same strategy that maximises net benefit in the greatest proportion of the  $K$  simulations depends on the dependence of  $V^U$  on individual components of  $\theta^k$  and the dependence among the states  $x$  in the decision model (Fenwick et al 2001). In general, the selection of the optimal strategy should be based on the mean rather than the quantiles of  $V^U$  because the objective is to maximise total health of the population subject to a budget constraint, and total health is the product of the mean health per patient times the number of patients in the population, and similarly total costs are mean costs per patient times the number of patients.

It is straightforward to apply PSA to estimate the probability that the irreversible strategies (surgical repair or no treatment) are cost-effective, for different values of a QALY. These results do not take account that the option to delay the decision for at least one period may be more cost-effective than any of these irreversible treatments. Unfortunately, PSA does not seem readily transferable to dynamic programming methods, at least as they are applied in this thesis. Equation 4.5 and 4.6 can be computed easily by Monte-Carlo methods because the value function defining the value of a policy  $U$  for irreversible strategies is linear in the unknown function  $V^U(x_i, t)$ , as shown by its definition in Equation 4.4. This means the expectation in Equation 4.5 only needs to be calculated once for each strategy, at time  $t=1$ . In dynamic programming the value of the optimal policy  $V(x_i, t)$  is calculated by the Bellman equation (Equation 4.1). This has a recursive maximisation step and is therefore non-linear in  $V$ . If we did not take this into account, we would be calculating  $\max_u V(x_i, t | \theta^k)$  at each period  $t$  for Monte-Carlo simulation  $k$  and not  $\max_u E_\theta[V(x_i, t | \theta^k)]$ . In effect, we would be calculating the net benefit at each period of the model as if we knew the values of the uncertain parameters, and this would over-estimate the value of the optimal policy in the



PSA. It appears that we can only estimate the mean value of the option to continue surveillance using deterministic methods, and we cannot estimate the posterior distribution or confidence interval of the value of the option using conventional PSA methods.

This is left as a problem for further research. In Chapter 5, we use PSA to estimate the probability that aneurysm repair or no surgery is cost-effective, without taking account of the option to delay. We then use deterministic methods to estimate the mean value of the option for watchful waiting, that is, based on point estimates of the mean values of the parameters of the model.

### Results of the illustrative model

Given the point estimates of the parameters of the simplified model (Figure 7), the net benefit for each strategy at time  $t=1$  for a patient with aneurysm of 5 to 5.5cm is:

Immediate surgery	£19,400.00
No surgery	£23,665.50
Watchful waiting	£23,680.80

If watchful waiting were not offered as an option, then no surgery would be the most cost-effective strategy. However, watchful waiting has a greater net benefit, without considering the cost of the CT. The value of the option for watchful waiting is  $£23,680.80 - £23,665.50 = £15.30$ . This is because if the aneurysm does not grow, or grows by only 0.5cm, no surgery continues to be the best option in period 2, but if the aneurysm grows by 1cm, it is cost-effective to change the strategy and undertake surgery. The option to wait therefore has value because it allows the patient the flexibility to change the strategy depending on the result of the CT in the following period.

However, the value of the option is low in this case. If the cost of CT were greater than £15.30, it would not be cost-effective to continue surveillance, and more efficient to never offer surgery.

### Conclusion

This chapter has described the methods of dynamic programming, and illustrated the basic approach applied to a watchful waiting strategy for AAA using a simplified

version the model. The subsequent chapter will undertake a more complete analysis of the management options for AAA using the best parameter estimates available.

## **Chapter 5: Immediate repair *versus* watchful waiting for the management of abdominal aortic aneurysms: results of cost-effectiveness analysis using dynamic programming**

Most of the data and methods in this chapter have been published as: Chambers D, Epstein D, Walker S, Fayter D, Paton F, Wright K, Michaels J, Thomas S, Sculpher M, Woolacott N. Endovascular stents for abdominal aortic aneurysms: a systematic review and economic model. *Health Technology Assessment* 2009; 13(48):1-214

### **Introduction**

There has recently been considerable attention by policy makers in the UK on the comparison between endovascular and open repair for patients who are fit for open repair and anatomically suitable for EVAR, with the publication of the EVAR 1 trial (EVAR 2005a) and an appraisal by the National Institute for Health and Clinical Excellence (NICE 2009). Based on the EVAR trials (see Chapter 2), EVAR does not appear cost-effective (EVAR 2005a; Epstein et al 2008; Chambers et al 2009).

However, the NICE committee received evidence from clinical experts that current generations of EVAR devices are more effective, with fewer complications and lower length of stay in hospital than found in the EVAR trials, and this advice led to a recommendation by NICE in favour of EVAR (NICE 2009). Even so, there remain a number of gaps in the evidence base concerning the broader management of these patients; in particular, when might watchful waiting be most effective and cost-effective?

The purpose of this chapter is to compare the cost-effectiveness of the management options for AAA for these two groups of patients for whom the evidence base from RCTs is currently weak or equivocal. Decision modelling is carried out using dynamic programming to evaluate the option for watchful waiting. By definition, there is considerable uncertainty around the parameters to inform this model. Therefore the model is intended to explore the optimum strategies given the evidence available, rather than provide definitive statements, and indicate promising further areas for research and investigation.

## Methods

### *Treatment strategies and patient groups*

For patients who are fit for open repair, there are four treatment options: endovascular repair, open repair, no treatment, and watchful waiting. Open repair is not considered for patients who are assessed as unfit according to the criteria of the EVAR trials (EVAR 2005a). Because one of the aims of the model is to assess whether the recommendation to offer surgery at an aneurysm  $\geq 5.5$ cm is cost-effective (UKSAT 1998), the model will evaluate the strategies across a range of aneurysm sizes at the time of the decision, from 3cm to 8cm (in intervals of 0.5cm). Patients in the base-case are 74 years old at the initiation of the model (EVAR 2005a). The model is also evaluated for younger patients, aged 60 years, and older patients, aged 85 years.

### **Model structure**

The model structure is a Markov model for the irreversible strategies: surgery (endovascular repair *versus* open repair) *versus* no surgery. A dynamic programme is used to model the watchful waiting strategy. The basic model structure is described in Chambers et al 2009 and in Chapter 4 of this thesis. The cycle length of the model is 6 months, and the time horizon is 10 years for a patient aged 85 and 35 years for a patient aged 65 at baseline. Health benefits are measured in QALYs, and costs are those of the UK National Health Service in 2008. The discount rate is 0.035 per year and is the same for costs and health benefits (NICE 2008). In a sensitivity analysis, we apply model inputs relevant to the Spanish NHS.

The dynamic programming model is not able to separately estimate costs and QALYs. Instead, the results are expressed in terms of net benefit. The net benefit  $\Pi(x,u,t)$  in period  $t$  for strategy  $u$  and state  $x$  is defined as:

$$\Pi(x,u,t) = H(u,t) * \lambda * 0.5 - C(u,t)$$

Where  $H$  is the HRQoL index (measured by EQ5D) and  $C$  are the costs of strategy  $u$  in period  $t$ , and  $\lambda$  is the value of a QALY. The base-case assumes the value of a QALY is £20,000 (NICE 2008). Other values are used as sensitivity analyses.

## *Parameters*

### *Rupture rate for untreated patients*

Table 5 shows rupture rates obtained from a recent review of the literature. Full details of the search strategies are available elsewhere (Chambers et al 2009). It is difficult to measure the risk of rupture of an AAA in an untreated patient because patients with large AAA are usually operated on. The EVAR trial 2 RCT compared EVAR with no surgery in patients considered unfit for open repair (EVAR 2005b). Powell et al (2008) conducted a review of the literature and compared the results with estimated rupture rates in the EVAR trial 2. Powell et al (2008) found that the patients with large aneurysms (>6 cm) in the EVAR trial 2 had a lower untreated risk of rupture than patients in the other studies, and concluded that this might be due to patients being selected in the RCT to be anatomically suitable for EVAR. For patients with aneurysm <6 cm they found that the rupture rate in EVAR trial 2 was similar to other published estimates. However, neither study measured AAA diameter after the start of the study. This limits the usefulness of these data to model a watchful waiting strategy.

In the base-case decision model, we use the data from Michaels (1992) to estimate rupture rates, as this was the only study that reports these data for both small and large aneurysm sizes. Standard errors were not reported although there is likely to be considerable uncertainty as sample sizes were small. Rupture rates are converted to probabilities assuming a constant hazard over the 6 month period. In the base-case rupture is assumed to be fatal.

Powell et al (2001) and Brown et al (2003) found that rupture rates tended to be greater in women for a given aneurysm size, though Powell et al (2001) found the result non significant (hazard ratio women v men 1.21 (95% ci 0.77 – 1.90)

**Table 5.** Estimates of rupture rates for different sizes of untreated aneurysm: results from review of the literature

	AAA diameter cm	Rupture rate /year
<b>Studies of patients considered fit for open surgery</b>		
	<4	0
Limet 1991 (Case series based on last observed AAA diameter)	4-5	n/a
	≥5	0.22
	3-3.9	0.005
	4-4.9	0.010
	5-5.9	0.050
Michaels 1992 (Meta-analysis, based on last observed AAA diameter)	6-6.9	0.090
	7-7.9	0.125
	8-8.9	0.250
	9-9.9	0.500
	≥10	0.900
	3-3.9	0.000
Reed 1997 (Case series, based on last observed AAA diameter)	4-4.9	0.010
	5-5.9	0.110
	≥6	0.260
UK SAT 1998 (Surveillance arm of RCT)	4-5.5	0.010
	3-4.4	0.000
Kim 2007 (MASS trial, based on baseline AAA diameter)	4.5-5.4	0.009
	≥5.5	0.063
<b>Studies of patients refusing or unfit for open repair</b>		
Powell 2008 (meta-analysis of 5 studies, based on baseline AAA diameter) †	5.0-5.9	0.103
	≥6	0.270
	5.5-5.9	0.097
Powell 2008 (EVAR 2 trial, based on baseline AAA diameter)	≥6	0.174
<b>Studies with patients both fit and unfit for open repair</b>		
Brown 2003 (Canadian cohort, men)	5.0 -5.9	0.010
	≥6	0.141
Brown 2003 (Canadian cohort, women)	5.0 –5.9	0.039
	≥6	0.223
	3 – 3.9	0.003
Brown 1999 (UKSAT randomised and unrandomised, based on last observed or estimated AAA diameter)	4- 4.9	0.015
	5- 5.9	0.065

† The 5 studies used in the Powell (2008) review were: Jones 1998, Powell 1999, Conway 2001, Lederle 2002, Ariz 2004

#### *Expansion rate of untreated aneurysm*

Table 6 shows the estimates of the expansion rate of untreated aneurysm from a recent literature review (Chambers et al 2009). The base-case decision model used the mean expansion rate from Michaels et al (1992), as these data were available for a wide range of aneurysm sizes and appeared to be consistent with estimates from the other sources.

**Table 6:** Expansion rate of untreated aneurysm, results of review of the literature

	<i>AAA diameter cm</i>	<i>Median expansion rate cm/yr</i>	<i>Variability</i>
Limet 1991 (Case series based on last observed AAA diameter)	<4	0.53	n/a
	4-5	0.69	n/a
	>5	0.74	n/a
Michaels 1992 (Meta-analysis, based on last observed AAA diameter)			No increase (%)
	3-3.9	0.28	53
	4-4.9	0.60	22
	5-5.9	0.68	19
	6-6.9	0.96	5
	7-7.9	1.26	0
Reed 1997 (Case series)	All	0.21	n/a
UK SAT 1998 (Surveillance arm of RCT)	4-5.5	0.33	IQR 0.2-0.53 cm
Kim 2007 (MASS trial, based on baseline AAA diameter)			Rate of expansion to next size in 3 months
	3-4.4	n/a	0.025
	4.5-5.4	n/a	0.087
	>5.5	n/a	n/a

The decision model requires estimates of the probability of changing from one ‘state’ or aneurysm size to another. The  $n=15$  states in the full decision model are the sizes of AAA, represented as categorical variables  $x_1=3$  to  $<3.5$ cm,  $x_2=3.5$  to  $<4$ cm etc, up to  $x_{14}=9.5$  to  $<10$ cm, plus a ‘dead’ state. Given a patient has not died during the cycle, we calculate the transition probabilities of growth from one aneurysm size to another in 6 months by assuming growth takes a normal distribution truncated at zero, that is, it is not possible for the aneurysm to shrink. Michaels (1992) does not give the standard deviations (SD) of the expansion rates, but does estimate the mean expansion over one year and the probability of no increase during the year. We assume that ‘no growth’ is a change in aneurysm size of less than 0.25cm. Under these assumptions the data in Michaels (1992) is consistent with a standard deviation for the expansion rate of approximately 0.45cm/year for all aneurysm sizes at the start of the period. For example, Michaels (1992) found that the expansion rate for aneurysms of 4-4.9cm was 0.6cm/year and after 1 year, 22% had grown by less than 0.25cm. If growth per year  $g$  follows a distribution  $g \sim \text{Normal}(\text{mean}=0.6\text{cm}, \text{SD}=0.45\text{cm})$ , then  $\Pr(g \leq 0.25\text{cm}) = 0.22$ .

Assuming a normal distribution for AAA growth truncated at zero, the estimated 6 month transition probabilities are shown in Table 7. We assume that ‘no growth’ is a change in aneurysm size of less than 0.25cm, a change of between 0.25 – 0.75cm corresponds to growth in AAA to the next 0.5cm interval, and a change of  $\geq 0.75$ cm corresponds to growth in AAA by two intervals.

**Table 7.** Estimated transition probabilities of AAA expansion in a six month cycle, assuming a truncated normal distribution for aneurysm growth. Estimates based on data from Michaels (1992)

<i>Aneurysm size at start of 6 month cycle, cm</i>	<i><math>\leq 0.25</math> cm growth</i>	<i>0.25- 0.75cm growth</i>	<i><math>&gt;0.75</math> cm growth</i>
3-3.4	0.69	0.30	0.00
3.5-3.9	0.69	0.30	0.00
4-4.4	0.41	0.57	0.02
4.5-4.9	0.41	0.57	0.02
5-5.4	0.34	0.62	0.03
5.5-5.9	0.34	0.62	0.03
6-6.4	0.15	0.73	0.12
6.5-6.9	0.15	0.73	0.12
$>7$	0.05	0.66	0.30

### *Operative mortality*

A recent systematic review and meta-analysis (Chambers et al 2009) found 3 RCTs (EVAR 2005a; Blankensteijn et al 2002; Cuypers et al 2001) that had compared operative mortality for EVAR versus open repair. The EVAR trial was the largest trial with the greatest weight in the meta-analysis. The EVAR trial 1 estimated that in patients considered fit for open surgery, 30 day mortality after endovascular repair was  $9/532 = 0.017$  and  $25/518=0.048$  after open repair (EVAR 2005a). The EVAR trial 2 found that operative mortality after elective endovascular repair in patients considered unfit for open surgery was  $10/147 = 0.068$ (EVAR 2005b). Operative mortality after endovascular repair might also depend on other factors such as age and comorbidities (Buth et al 2002; Brown et al2007), this scenario is not modelled.

The odds ratio for 30 day mortality from EVAR trial 1 was 0.37(95% CI 0.19 – 0.73), and this was similar to estimates from other trials (Chambers et al 2009). This 30 day mortality odds ratio was used in the previous model (Epstein et al 2008), presented in Chapter 2. However, the cycle length in the current model is 6 months, not 30 days. The hazard ratio for aneurysm death for EVAR *versus* open repair in the first six months in



EVAR trial 1 was 0.42 (95% CI 0.21-0.82) (EVAR 2005a), because there were some procedure-related deaths after 30 days. This estimate is used in the base-case model.

#### *Other cause mortality*

There is a strong association between aneurysm size and other-cause mortality, thought to mainly be related to cardiovascular disease. Some studies find that these risks continue after aneurysm repair (Peppelenbosch et al 2004). Based on data from the EUROSTAR patient register, it is assumed that patients with aneurysm of 5-5.4cm have a 20% greater risk of mortality than the general population, patients with an aneurysm of 5.5-5.9cm have a 34% greater risk, patients with an aneurysm of 6-6.4cm have 54% greater risk and patients with an aneurysm of 6.5 cm or more have 76% greater risk (Chambers et al 2009). Patients who are unfit for open surgery independently have 49% greater risk of other causes of death (Chambers et al 2009).

The Gompertz function is used to model mortality risks by age in the general population. In the Gompertz function, mortality hazards  $h(x)$  at age  $x$  (where  $x \geq 40$ ) are given by:

$$h(x) = R \exp(a x), \text{ where } R \text{ and } a \text{ are parameters.}$$

Taking logs,

$$\log(h(x)) = \log(R) + a x$$

This was fitted by ordinary least squares regression to UK life table hazards for 2006-2008 (ONS 2009). The coefficients are shown in Table 8.

**Table 8. Results of regression of log(life table hazards) versus age in years in the general population aged 40 years or over**

<i>Men</i>	<i>Mean coefficient</i>	<i>SE</i>	<i>95% CI</i>
Age ( $a$ )	0.0946	0.00067	0.0932 to 0.0959
Constant ( $\log R$ )	-10.257	0.046	-10.349 to -10.165
<i>Women</i>	<i>Mean coefficient</i>	<i>SE</i>	<i>95% CI</i>
Age ( $a$ )	0.101	0.00067	0.0999 to 0.1027
Constant ( $\log R$ )	-11.109	0.046	-11.203 to -11.017

Epstein et al (2008) (Chapter 2) assumed the rate of other causes of mortality was slightly greater after EVAR than open repair up to 4 years after surgery, based on the finding of the EVAR trial 1 that there was no difference in survival at 4 years (EVAR 2005a). In this model, it is assumed that the rate of other-cause mortality is the same for all strategies. There are three justifications for this change. First, given that the excess mortality was estimated based on very small numbers of events, the difference is highly uncertain. Second, we do not know the rate of non-aneurysm cause mortality with no treatment, and any assumption of a difference between treated and untreated patients would be speculative. Third, including excess mortality after EVAR for a limited time period would require using 'tunnel states' in the model. Although it is feasible to include time-dependent transition probabilities in a dynamic programme, it makes the analysis more complex (as there would be more states).

#### *Aneurysm-related mortality after surgical repair*

Surgical repair greatly reduces the risk of aneurysm related death, but does not entirely eliminate it, and the risk may depend on aneurysm size at the time of surgery. Data from the EUROSTAR register indicate that the mean rate of aneurysm related death for later devices (implanted after year 2000) was 0.001 per 6 months in aneurysms less than 5.5cm, 0.002 per 6 months in aneurysms 5.5-6.4cm and 0.012 per 6 months in aneurysms over 6.5cm (Peppelenbosch et al 2004, Chambers et al 2009).

The EVAR trial 1 found that the rate after endovascular repair was slightly greater than after open repair (hazard ratio EVAR v open repair 1.15, 95% CI 0.39-3.41)(EVAR 2005a). We use these estimates in the base-case model. This estimate differs from the relative risk used in the previous model (Epstein et al 2008) that used a hazard ratio for late aneurysm deaths for EVAR versus open repair of 2.46 (95% CI 0.48 -12.7). This latter estimate was based on deaths between 30 days and 4 years after surgery and may have over-estimated the long term relative risk which appears from the 4-year data to be highest in the months immediately after AAA repair.

#### *Health service costs*

Health service costs are expressed in 2008 prices. The EVAR trial 1 found that the cost of the endovascular procedure was £10,800 at 2003-04 prices, and the cost of open repair was £9,200, a difference of £1,600 (SE 607) (EVAR 2005a). NHS pay and price inflation was 14% from 2003-04 to 2007-08 (Curtis 2009). The rate of reintervention was 6.9 per 100 years in the EVAR group and 2.4 per 100 years in the open repair

group, a hazard ratio of 2.7(95%CI 1.8-4.1)(EVAR 2005a). Assuming a reintervention costs £1,320 (FZ27C: Endoscopic or Intermediate General Abdominal Procedures 19 years and over without CC)(DH 2009) then the mean cost of reinterventions per 6 months is  $6.9/100*0.5*1320 = £45$  after endovascular repair and 2.7 (95%CI 1.8-4.1) times lower after open repair. The cost of CT is £110 and a follow up outpatient attendance is £139(DH 2009). Based on a survey of 23 UK hospitals in 2004(EVAR 2005a), and uncertainty about the long-term performance of endovascular devices, it was assumed that patients require one CT per year after endovascular repair, but not after open repair.

There are assumed to be no costs to a policy never to treat the patient (or, at least, any costs are equal across all strategies). The cost of CT is not included in the payoffs for the watchful wait strategy, because watchful waiting is reversible. The option only needs to be kept open for one period. At the start of the next period, following a CT, physical examination and discussion with the clinician, the option to delay should be reevaluated based on the patient's current fitness, age and aneurysm size. The aim is to estimate whether the keeping the option for surveillance has positive value (compared with the alternatives) for one period. Continuing surveillance will be cost-effective if this option value is greater than the cost of one CT examination.

#### *Health-related quality of life*

The EVAR trial 1 measured health-related quality of life (HRQOL) using the EQ-5D weighted index score, which values health states on a scale where 1 represents full health and zero represent a health state considered by the general population to be equivalent to death (Kind et al 1999). This is often referred to as 'utility' in the health economics literature, although the operational research literature sometimes uses the term 'utility' to refer to the value function  $V$  (Judd 1999).

The EVAR trial 1 found that mean HRQOL measured by the EQ-5D index was about 0.75 (SD 0.25) one year after surgery. This was similar to HRQOL at baseline and is similar to the mean HRQOL in the general population of a similar age distribution (Kind et al 1999). Patients have lower HRQOL after open repair than EVAR in the 3 months following surgery (mean difference 0.05 (SE 0.02) (EVAR 2005a)). In the base-case model we assume patients have lower HRQOL after open repair for the first cycle following surgery and then return to normal HRQOL for their age. Given the results of EVAR trial 1, we assume patients with untreated asymptomatic AAA have normal

HRQOL for their age while under surveillance, although there is some evidence from other sources that patients with diagnosed untreated aneurysm suffer anxiety (Brady et al 2004).

#### *Model inputs for the Spanish Health Service*

The value of a QALY is conventionally assumed to be €30,000 in the Spanish health economics literature (Sacristan et al 2002). The recommended discount rate is 0.03/year (Lopez et al 2008). Cariols et al (2008) estimated the costs of the initial endovascular procedure including prosthesis to be €15,035 and open surgery to be €12,692. The cost of admissions for reintervention was €1,293. The mean cost of CT is €102 (Llanos et al 2007) and an outpatient visit is €114 (BOJA 2005).

#### *Estimates of distributions of uncertain parameters for PSA*

Few of the studies estimating rupture rates conditional on aneurysm size reported standard errors, so a formal evidence synthesis of these data could not be undertaken. Some estimate of the variability around the mean can be seen by examining the mean rupture rates between studies for aneurysms of 5-5.9cm, which varied from 0.01/year to 0.22/year across the studies, with 0.05/year as our base-case (Table 5). We assume the probability the rupture rate is half the base-case is 0.26, the probability that it is same as the base-case is 0.63, the probability that it is twice as great is 0.1, and the probability that it is four times the base-case is 0.01. For the expansion rate (Table 6), one study reported the inter-quartile range (UKSAT 1998), but this is an estimate of the variability in the population and not the uncertainty in the mean. For AAA of 5-5.9cm, one study reported an expansion rate of 0.33cm/year and two reported an expansion rate of between 0.68-0.74cm/year (base case). We assume the probability the expansion rate is as the base-case is 0.85, the probability it is half the base-case is 0.1 and the probability it is twice the base-case is 0.05. These distributions have been chosen for these parameters because they are broadly in keeping with the variation in the estimated means across the studies and in each case the expected value is equal to the base-case.

Other uncertain parameters for this model are the hazard ratios for early aneurysm-related deaths, late aneurysm-related deaths and reinterventions of EVAR versus open repair estimated from the EVAR trial 1 (EVAR 2005a) which we assume follow log-normal distributions. If variable  $X \sim \text{LogNormal}(\mu, \sigma^2)$ , and given the lower and upper

percentiles of the 95% CI for  $X$  in  $[q_{0.025}, q_{0.975}]$ , then  $\mu = \log(q_{.975} * q_{0.025})/2$  and  $\sigma = \log(q_{.975}/q_{0.025})/4$ .

The analysis was carried out in R version 2.6.1 (© The R foundation for statistical computing, 2007). 1,000 Monte-Carlo iterations of the model were undertaken for each scenario for the PSA. Each scenario took about 5 minutes to run on the University of York data analysis server cluster.

## Results

### *Base-case results in patients aged 74 years who are fit for open repair*

Table 9 presents the results of the probabilistic model, showing the probability that either EVAR, open repair or no treatment is the most cost-effective strategy for a patient aged 74 years, at a value of £20,000 per QALY and £30,000 per QALY under base-case assumptions. These results do not account for the possibility that delaying the decision for six months might be the optimum policy.

The treatment that has the lowest error probability (or highest probability of being cost-effective) is not necessarily the same as the treatment with the greatest mean net benefit (Fenwick et al 2001). Therefore the treatment that has the greatest mean net benefit is highlighted (in **bold** script), averaged over all of the simulations of the model.

The PSA results estimated in the first 3 columns of Table 9 do not take account that it might be more cost-effective to wait six months rather than make an immediate and irreversible decision for or against surgery. The value of the ‘option’ to continue surveillance (rather than one of the other three strategies) is calculated as the difference between the net benefit of the watchful waiting strategy less the maximum net benefit of the other three strategies, and is always greater than or equal to zero. Table 5.5 presents the value of the option to continue surveillance, given point estimates of the mean values of the uncertain parameters in the deterministic model.

If the value of a QALY is £20,000, open surgery is the most cost-effective strategy if the aneurysm is >4.5cm without taking account of the option to wait. However, if the aneurysm is between 4 and 5.5cm, there is considerable decision uncertainty about whether to operate or not. The value of the option to continue waiting is £240 for aneurysms of 4 – 4.5cm. If the cost of a CT is £110 then it appears cost-effective to continue surveillance for aneurysms of 4- 4.5cm.

If the value of a QALY is £30,000, endovascular surgery is the most cost-effective strategy if the aneurysm is >4.0cm without taking account of the option to wait, a lower threshold diameter for surgery than in the previous case. However, if the aneurysm is between 4 and 4.5cm, there is considerable decision uncertainty about whether to operate or not. The value of the option to continue waiting is greater than £110 (the cost of one CT) for aneurysms of 3 – 4.5cm and it appears cost-effective to continue surveillance up to 4.5cm and to operate at this size.

**Table 9. Results of the base-case model for a patient aged 74 years and fit for open surgery**

	If the value of a QALY is £20,000				If the value of a QALY is £30,000			
	Probability that the treatment is cost-effective			Value of option to wait	Probability that the treatment is cost-effective			Value of option to wait
	evar	open	none	£	evar	open	none	£
3-	0	0	<b>1</b>	3.95	0.011	0.005	<b>0.984</b>	120.47
3.5-	0.005	0.012	<b>0.983</b>	33.84	0.085	0.032	<b>0.883</b>	659.78
4-	0.043	0.086	<b>0.871</b>	240.33	<b>0.519</b>	0.184	0.297	1108.91
4.5-	0.241	<b>0.443</b>	0.316	54.57	<b>0.719</b>	0.252	0.029	0
5-	0.231	<b>0.469</b>	0.300	0	<b>0.713</b>	0.258	0.029	0
5.5-	0.234	<b>0.591</b>	0.175	0	<b>0.698</b>	0.275	0.027	0
6-	0.344	<b>0.635</b>	0.021	0	<b>0.707</b>	0.293	0.000	0
6.5-	0.265	<b>0.570</b>	0.165	0	<b>0.509</b>	0.471	0.020	0
7-	0.349	<b>0.631</b>	0.020	0	<b>0.524</b>	0.476	0.000	0
7.5-	0.358	<b>0.642</b>	0	0	<b>0.524</b>	0.476	0.000	0
8-	0.358	<b>0.642</b>	0	0	<b>0.524</b>	0.476	0.000	0
8.5-	0.358	<b>0.642</b>	0	0	<b>0.524</b>	0.476	0.000	0
9-	0.358	<b>0.642</b>	0	0	<b>0.524</b>	0.476	0.000	0
9.5-	0.358	<b>0.642</b>	0	0	<b>0.524</b>	0.476	0.000	0

#### *Univariate and multivariate sensitivity analyses*

Table 10 shows the results of a sensitivity analysis assuming the parameters of the model are the same as those estimated by Epstein et al (2008). Under this scenario, endovascular repair had a lower relative risk of early AAA and procedure related mortality *versus* open repair than the base-case, but higher relative risks of late AAA mortality and higher relative costs of re-interventions and post-surgery surveillance. In this case, EVAR is not likely to be cost-effective if the value of a QALY is £30,000 or less.

**Table 10. Results of model assuming the parameters used in Epstein et al (2008)**

	<i>If the value of a QALY is £20,000</i>				<i>If the value of a QALY is £30,000</i>			
	Probability that the treatment is cost-effective			Value of option to wait	Probability that the treatment is cost-effective			Value of option to wait
	evar	open	none	£	evar	open	none	£
3-	0.000	0.000	<b>1.000</b>	1.39	0.003	0.003	<b>0.994</b>	78.37
3.5-	0.000	0.009	<b>0.991</b>	16.79	0.022	0.043	<b>0.935</b>	365.87
4-	0.002	0.113	<b>0.885</b>	134.11	0.048	0.449	<b>0.503</b>	1982.17
4.5-	0.008	0.446	<b>0.546</b>	577.48	0.227	<b>0.566</b>	0.207	0
5-	0.046	<b>0.656</b>	0.298	0	0.324	<b>0.651</b>	0.025	0
5.5-	0.044	<b>0.679</b>	0.277	0	0.330	<b>0.645</b>	0.025	0
6-	0.049	<b>0.842</b>	0.109	0	0.328	<b>0.659</b>	0.013	0
6.5-	0.120	<b>0.643</b>	0.237	0	0.351	<b>0.627</b>	0.022	0
7-	0.135	<b>0.791</b>	0.074	0	0.361	<b>0.639</b>	0.000	0
7.5-	0.168	<b>0.819</b>	0.013	0	0.361	<b>0.639</b>	0.000	0
8-	0.173	<b>0.827</b>	0.000	0	0.361	<b>0.639</b>	0.000	0
8.5-	0.173	<b>0.827</b>	0.000	0	0.361	<b>0.639</b>	0.000	0
9-	0.173	<b>0.827</b>	0.000	0	0.361	<b>0.639</b>	0.000	0
9.5-	0.173	<b>0.827</b>	0.000	0	0.361	<b>0.639</b>	0.000	0

Assuming: Mean hazard ratio for early AAA mortality (EVAR v open)=0.30; Mean hazard ratio for late AAA mortality (EVAR v open)= 2.46; Cost of re-intervention = £5936; Mean hazard ratio for reintervention (EVAR v open) = 9.5; Annual cost of surveillance after EVAR = £249; No difference in all cause mortality between EVAR and open

Table 11 shows the results if the rupture rate with untreated aneurysm is twice the base-case. Under this scenario, aneurysm repair is more likely to be cost-effective at smaller aneurysm sizes, compared to the base-case (4cm at £20,000 per QALY, 3.5cm at £30,000 per QALY) (not taking account of the option to wait) and surveillance is expected to be cost-effective for aneurysms less than 4.5cm.



**Table 11. Results of the model if the rupture rate with untreated aneurysm is twice the base-case**

	<i>Value of a QALY is £20,000</i>				<i>Value of a QALY is £30,000</i>			
	Probability that the treatment is cost-effective			Value of option to wait	Probability that the treatment is cost-effective			Value of option to wait
	evar	open	none	£	evar	open	none	£
3-	0.006	0.026	<b>0.968</b>	116.69	0.113	0.044	<b>0.843</b>	890.38
3.5-	0.046	0.099	<b>0.855</b>	672.94	<b>0.495</b>	0.202	0.303	2152.39
4-	0.252	<b>0.441</b>	0.307	920.82	<b>0.698</b>	0.283	0.019	297.08
4.5-	0.362	<b>0.619</b>	0.019	0	<b>0.713</b>	0.287	0.000	0
5-	0.349	<b>0.632</b>	0.019	0	<b>0.703</b>	0.297	0.000	0
5.5-	0.340	<b>0.651</b>	0.009	0	<b>0.684</b>	0.316	0.000	0
6-	0.340	<b>0.660</b>	0.000	0	<b>0.676</b>	0.324	0.000	0
6.5-	0.363	<b>0.637</b>	0.000	0	<b>0.513</b>	0.487	0.000	0
7-	0.363	<b>0.637</b>	0.000	0	<b>0.513</b>	0.487	0.000	0
7.5-	0.363	<b>0.637</b>	0.000	0	<b>0.513</b>	0.487	0.000	0
8-	0.363	<b>0.637</b>	0.000	0	<b>0.513</b>	0.487	0.000	0
8.5-	0.363	<b>0.637</b>	0.000	0	<b>0.513</b>	0.487	0.000	0
9-	0.363	<b>0.637</b>	0.000	0	<b>0.513</b>	0.487	0.000	0
9.5-	0.363	<b>0.637</b>	0.000	0	<b>0.513</b>	0.487	0.000	0

Table 12 shows the results if the growth rate of an untreated aneurysm is twice the base-case. Under this scenario, aneurysm repair is more likely to be cost-effective at smaller aneurysm sizes, compared to the base-case (4cm at £20,000 per QALY, 3.5cm at £30,000 per QALY) (not taking account of the option to wait). Surveillance is expected to be cost-effective for aneurysms less than 4.5cm at £20,000 per QALY and for aneurysms less than 4cm at £30,000 per QALY

**Table 12. Results of the model if the growth rate of an untreated aneurysm is twice the base-case**

	<i>Value of a QALY is £20,000</i>				<i>Value of a QALY is £30,000</i>			
	Probability that the treatment is cost-effective			Value of option to wait	Probability that the treatment is cost-effective			Value of option to wait
	evar	open	none	£	evar	open	none	£
3-	0.002	0.020	<b>0.978</b>	647.85	0.072	0.111	<b>0.817</b>	3582.90
3.5-	0.036	0.279	<b>0.685</b>	2054.93	<b>0.503</b>	0.212	0.285	1731.73
4-	0.245	<b>0.517</b>	0.238	190.58	<b>0.680</b>	0.229	0.091	0
4.5-	0.333	<b>0.572</b>	0.095	0	<b>0.721</b>	0.251	0.028	0
5-	0.316	<b>0.589</b>	0.095	0	<b>0.716</b>	0.256	0.028	0
5.5-	0.321	<b>0.627</b>	0.052	0	<b>0.691</b>	0.282	0.027	0
6-	0.332	<b>0.639</b>	0.029	0	<b>0.705</b>	0.295	0.000	0
6.5-	0.358	<b>0.613</b>	0.029	0	<b>0.506</b>	0.475	0.019	0
7-	0.358	<b>0.617</b>	0.025	0	<b>0.522</b>	0.478	0.000	0
7.5-	0.366	<b>0.634</b>	0.000	0	<b>0.522</b>	0.478	0.000	0
8-	0.366	<b>0.634</b>	0.000	0	<b>0.522</b>	0.478	0.000	0
8.5-	0.366	<b>0.634</b>	0.000	0	<b>0.522</b>	0.478	0.000	0
9-	0.366	<b>0.634</b>	0.000	0	<b>0.522</b>	0.478	0.000	0
9.5-	0.366	<b>0.634</b>	0.000	0	<b>0.522</b>	0.478	0.000	0

Table 13 aims to compare the decision model results with those in the UK SAT study. UK SAT (1998) found that the growth rate and rupture rate for small aneurysms (4-5.5cm) were lower than those estimated by than Michaels (1992)(see Table 2). The population was also younger (mean age 69 years) and with higher other –cause mortality than the base-case model. If these parameters are used in the decision model, other variables equal, then at £20,000 per QALY, open repair is cost-effective for aneurysms greater than 5cm, without the option to defer, but deferral is the more cost-effective option if the aneurysm is 4.5-5.5cm. At £30,000 per QALY, endovascular repair is cost-effective for aneurysms greater than 4.5cm, without the option to defer, but deferral is the more cost-effective option if the aneurysm is 3.5-5.5cm.

**Table 13. Results of the model if the growth rate and rupture rate of small (4-5.5cm) untreated aneurysms are lower than the base-case**

	<i>Value of a QALY is £20,000</i>				<i>Value of a QALY is £30,000</i>			
	Probability that the treatment is cost-effective			Value of option to wait	Probability that the treatment is cost-effective			Value of option to wait
	evar	open	none	£	evar	open	none	£
3-	0.000	0.001	<b>0.999</b>	2.81	0.003	0.003	<b>0.994</b>	53.32
3.5-	0.002	0.012	<b>0.986</b>	19.29	0.036	0.011	<b>0.953</b>	210.38
4-	0.020	0.025	<b>0.955</b>	103.29	0.086	0.036	<b>0.878</b>	836.18
4.5-	0.058	0.082	<b>0.860</b>	563.11	<b>0.497</b>	0.179	0.324	2300.01
5-	0.287	<b>0.415</b>	0.298	1587.18	<b>0.711</b>	0.264	0.025	700.50
5.5-	0.386	<b>0.588</b>	0.026	0	<b>0.701</b>	0.277	0.022	0
6-	0.381	<b>0.593</b>	0.026	0	<b>0.714</b>	0.286	0.000	0
6.5-	0.387	<b>0.588</b>	0.025	0	<b>0.534</b>	0.466	0.000	0
7-	0.387	<b>0.600</b>	0.013	0	<b>0.534</b>	0.466	0.000	0
7.5-	0.397	<b>0.603</b>	0.000	0	<b>0.534</b>	0.466	0.000	0
8-	0.397	<b>0.603</b>	0.000	0	<b>0.534</b>	0.466	0.000	0
8.5-	0.397	<b>0.603</b>	0.000	0	<b>0.534</b>	0.466	0.000	0
9-	0.397	<b>0.603</b>	0.000	0	<b>0.534</b>	0.466	0.000	0
9.5-	0.397	<b>0.603</b>	0.000	0	<b>0.534</b>	0.466	0.000	0

Assuming: Mean rupture rate and growth rate for aneurysms of 4-5.5cm are as UK SAT (1998) (Tables 2 and 3); age = 69 years; other cause mortality for patients with small aneurysms is 1.2 times that of the general population

If costs and the discount rate for Spain are used in the model, then at €20,000 per QALY results are similar to the base-case at £20,000 per QALY (

Table 14). At €30,000 per QALY, endovascular repair is cost-effective for aneurysms of 4-6.5cm but open repair is cost-effective for larger aneurysms. This is because the cost of the EVAR device has been estimated to be greater in Spain than the UK, and so the decision is more marginal than in the UK. The greater long term risks of aneurysm-related death for very large aneurysms after endovascular repair change the decision in favour of open repair, though with a high degree of uncertainty.

**Table 14. Results with Spanish NHS costs and discount rate**

	<i>If the value of a QALY is €20,000</i>				<i>If the value of a QALY is €30,000</i>			
	Probability that the treatment is cost-effective			Value of option to wait	Probability that the treatment is cost-effective			Value of option to wait
	evar	open	none	€	evar	open	None	€
3-	0.000	0.001	<b>0.999</b>	3.14	0.008	0.018	<b>0.974</b>	156.94
3.5-	0.000	0.026	<b>0.974</b>	30.15	0.059	0.056	<b>0.885</b>	825.95
4-	0.022	0.108	<b>0.870</b>	240.73	<b>0.361</b>	0.315	0.324	1335.90
4.5-	0.137	<b>0.562</b>	0.301	0	<b>0.474</b>	0.470	0.056	0
5-	0.129	<b>0.582</b>	0.289	0	<b>0.493</b>	0.482	0.025	0
5.5-	0.132	<b>0.694</b>	0.174	0	<b>0.487</b>	0.488	0.025	0
6-	0.163	<b>0.811</b>	0.026	0	<b>0.490</b>	0.510	0.000	0
6.5-	0.203	<b>0.610</b>	0.187	0	0.415	<b>0.564</b>	0.021	0
7-	0.248	<b>0.728</b>	0.024	0	0.425	<b>0.575</b>	0.000	0
7.5-	0.248	<b>0.742</b>	0.010	0	0.425	<b>0.575</b>	0.000	0
8-	0.257	<b>0.743</b>	0.000	0	0.425	<b>0.575</b>	0.000	0
8.5-	0.257	<b>0.743</b>	0.000	0	0.425	<b>0.575</b>	0.000	0
9-	0.257	<b>0.743</b>	0.000	0	0.425	<b>0.575</b>	0.000	0
9.5-	0.257	<b>0.743</b>	0.000	0	0.425	<b>0.575</b>	0.000	0

**Subgroups**

Table 15 shows the results of the model in patients unfit for open surgery. Open surgery has a very low probability of being cost-effective, indicating face validity for this model. If the value of a QALY is £20,000 it is cost-effective to operate with endovascular repair when the aneurysm is 5.5cm or larger, though there is still considerable decision uncertainty when the aneurysm is up to 7.5cm in diameter. There is little value of continuing surveillance for aneurysms up to 5 cm. This is because the competing risks of other cause mortality are relatively high in this group.

If the aneurysm is 6.5-7cm at the time of the decision, the model indicates there may be value in continuing surveillance rather than operating. This is because the risks of graft rupture and other aneurysm-related mortality after endovascular repair are assumed to increase with aneurysm size at the time of operation, and this increases the decision uncertainty that EVAR is cost-effective. At very large aneurysm sizes (>7cm) the risks of rupture if untreated once more outweigh the risks of complications after surgery.

If the value of a QALY is £30,000, it is cost-effective to operate with endovascular repair when the aneurysm is 4.5cm or larger with less decision uncertainty. Surveillance may be cost-effective for aneurysms of 4-4.5cm.

**Table 15. Results of the model in patients unfit for open surgery**

	Value of a QALY is £20,000				Value of a QALY is £30,000			
	Probability that the treatment is cost-effective			Value of option to wait £	Probability that the treatment is cost-effective			Value of option to wait £
	evar	open	none		evar	Open	None	
3-	0.000	0.000	<b>1.000</b>	0	0.000	0.000	<b>1.000</b>	12.94
3.5-	0.001	0.001	<b>0.998</b>	0.04	0.013	0.002	<b>0.985</b>	74.16
4-	0.043	0.004	<b>0.953</b>	2.32	0.131	0.007	<b>0.862</b>	430.43
4.5-	0.122	0.012	<b>0.866</b>	23.07	<b>0.676</b>	0.019	0.305	0
5-	0.130	0.050	<b>0.820</b>	137.49	<b>0.675</b>	0.020	0.305	0
5.5-	<b>0.583</b>	0.062	0.355	0	<b>0.734</b>	0.026	0.240	0
6-	<b>0.582</b>	0.065	0.353	0	<b>0.948</b>	0.029	0.023	0
6.5-	<b>0.551</b>	0.095	0.354	919.16	<b>0.696</b>	0.063	0.241	0
7-	<b>0.616</b>	0.103	0.281	0	<b>0.904</b>	0.073	0.023	0
7.5-	<b>0.616</b>	0.105	0.279	0	<b>0.926</b>	0.074	0.000	0
8-	<b>0.823</b>	0.148	0.029	0	<b>0.926</b>	0.074	0.000	0
8.5-	<b>0.849</b>	0.151	0.000	0	<b>0.926</b>	0.074	0.000	0
9-	<b>0.849</b>	0.151	0.000	0	<b>0.926</b>	0.074	0.000	0
9.5-	<b>0.849</b>	0.151	0.000	0	<b>0.926</b>	0.074	0.000	0

Assuming operative mortality after endovascular repair of 0.068(EVAR 2005b) and all cause mortality is 1.49 times the rate for patients fit for open repair (Brady 2004)

Table 16 shows the results of the model in patients aged over 85 years at the time of the decision and considered fit for either open surgery or endovascular repair. At £20,000 per QALY, aneurysm repair (with open surgery) is likely to be cost-effective if the aneurysm is between 6 – 6.5cm or greater than 7.5cm. For aneurysm of 6.5-8cm, it is likely to be cost-effective to wait if the risk of late aneurysm-related death after surgery increases with aneurysm size at the time of surgery. It is unlikely that surveillance is cost-effective for smaller aneurysms.

At £30,000 per QALY, aneurysm repair (with endovascular repair) is on average cost-effective if the aneurysm  $\geq$ 4.5cm. For aneurysms of 4-4.5cm and 6.5-7cm, it seems cost-effective to continue surveillance. With these input parameters, open repair has the highest probability of being cost-effective out of the three treatments for aneurysms  $\geq$ 6.5cm, but is not the optimum treatment based on a comparison of mean net benefits.



Results for patients aged 60 years were very similar to those for 74 years and are not shown.

**Table 16. Results of the model for patients aged 85 years.**

	<i>Value of a QALY is £20,000</i>				<i>Value of a QALY is £30,000</i>			
	Probability that the treatment is cost-effective			Value of option to wait	Probability that the treatment is cost-effective			Value of option to wait
	evar	open	none	£	evar	open	None	£
3-	0.000	0.000	<b>1.000</b>	0	0.000	0.000	<b>1.000</b>	1.27
3.5-	0.000	0.000	<b>1.000</b>	0	0.025	0.021	<b>0.954</b>	15.31
4-	0.016	0.028	<b>0.956</b>	0.07	0.086	0.070	<b>0.844</b>	646.36
4.5-	0.030	0.108	<b>0.862</b>	1.45	<b>0.441</b>	0.308	0.251	0
5-	0.028	0.306	<b>0.666</b>	17.08	<b>0.583</b>	0.337	0.080	0
5.5-	0.029	0.456	<b>0.515</b>	0	<b>0.609</b>	0.372	0.019	0
6-	0.131	<b>0.524</b>	0.345	0	<b>0.597</b>	0.384	0.019	0
6.5-	0.035	0.196	<b>0.769</b>	946.82	<b>0.342</b>	0.357	0.301	263.63
7-	0.179	<b>0.477</b>	0.344	477.73	<b>0.377</b>	0.428	0.195	0
7.5-	0.196	<b>0.531</b>	0.273	182.38	<b>0.489</b>	0.493	0.018	0
8-	0.196	<b>0.542</b>	0.262	0	<b>0.499</b>	0.501	0.000	0
8.5-	0.196	<b>0.644</b>	0.160	0	<b>0.499</b>	0.501	0.000	0
9-	0.268	<b>0.732</b>	0.000	0	<b>0.499</b>	0.501	0.000	0
9.5-	0.268	<b>0.732</b>	0.000	0	<b>0.499</b>	0.501	0.000	0

## Conclusion

### *Principal findings*

This chapter has presented a decision model comparing endovascular repair, open repair, no treatment and the option to wait for patients with different aneurysm sizes. The principal results and univariate sensitivity analyses are summarised in

Table 17. In the base-case model for patients aged 74 years and fit for open surgery, and at a value of £20,000 per QALY, open repair is cost-effective for aneurysms  $\geq 4.5$ cm but surveillance may be cost-effective at smaller aneurysm sizes. At a value of £30,000 per QALY, endovascular repair is the most cost-effective treatment for aneurysms  $\geq 4$ cm if delaying the decision is not an option, but continued surveillance is more cost-effective if the aneurysm is  $< 4.5$ cm. These thresholds vary by up to  $\pm 1.0$ cm in other scenarios for this patient group.

For patients unfit for open surgery, the risk of operative mortality after endovascular repair is much higher than fit patients (0.068 *versus* 0.017) and other cause mortality is greater. In these patients, endovascular repair is predicted by the model to be cost-effective at a value of £20,000 per QALY for aneurysms  $\geq 5.5$ cm. For AAA  $\geq 6.5$ cm the optimum policy is complex because some studies have shown that risks of late mortality after EVAR appear to increase in patients with large aneurysm at the time of surgery, independently of other risk factors (Peppelenbosch et al 2004, Chambers et al 2009). Given these data, the model predicts that at £20,000 per QALY, delaying the decision may be more cost-effective for patients with aneurysms in the range 6.5-7cm. This is because the additional risk of late mortality after EVAR partly offsets the additional risk of rupture in patients with large aneurysms, reducing the expected benefit of AAA repair. At £30,000 per QALY, this constraint does not seem binding and EVAR is cost-effective in all unfit patients with AAA  $\geq 4.5$ cm.

For patients aged 85 years who are still considered fit for open surgery, their relatively short remaining life expectancy means there is less time for the benefits of surgery to be realised relative to no treatment, and the threshold aneurysm size for operating is higher (6cm at a value of £20,000 per QALY). As with patients who are unfit for open surgery, the possibility that there is a higher risk of late mortality after AAA repair in patients with large aneurysms means that it may be cost-effective to delay the decision for patients with aneurysms in the range 6.5-7.5cm.

**Table 17. Summary of the results of the dynamic programme**

Scenario	Table	Value of a QALY is £20,000			Range of aneurysm sizes for which surveillance is cost-effective (cm)‡	Value of a QALY is £30,000			Range of aneurysm sizes for which surveillance is cost-effective (cm)‡
		Evar	Open	None		Evar	Open	None	
Basecase	5	-	≥4.5	<4.5	4-4.5	≥4	-	<4	<4.5
Greater late AAA mortality and reinterventions after EVAR†	6	-	≥5	<5	4- 5	-	≥4.5	<4.5	3.5-4.5
Greater risk of rupture of untreated AAA	7	-	≥4	<4	<4.5	≥3.5	-	<3.5	<4.5
Faster growth of untreated AAA	8	-	≥4	<4	<4.5	≥3.5	-	<3.5	<4
Lower risk of rupture and slower growth of small aneurysms <5.5cm‡	9	-	≥5	<5	4.5-5.5	≥4.5	-	<4.5	3.5-5.5
Unit costs and discount rate in Spain	10	-	≥4.5	<4.5	4-4.5	4-6.5	≥6.5	<4	<4.5
Unfit for open surgery	11	≥5.5	-	<5.5	5-5.5 and 6.5-7	≥4.5	-	4-4.5	4-4.5
Aged 85 years	12	-	6-6.5 and ≥7	<6 and 6.5-7	6.5-8	≥4.5	-	<4.5	4-4.5 and 6.5-7

†Parameters from Epstein et al (2008)‡Parameters from UK SAT (1998) ◇ The columns labelled

“EVAR”, “Open” and “none” shows the range of aneurysm sizes (in cm) for which EVAR, open repair or no treatment is most likely to be cost-effective, not taking into account the option to delay the decision.

‡The column labelled "Range of aneurysm sizes for which surveillance is cost-effective (cm)" shows the results of the option to delay the decision.

### *Comparison with RCTs and published decision models*

The predictions from some of the scenarios in this model can be compared with the results of RCTs. The EVAR trial 2 compared endovascular repair (n=166) to no intervention (n=172) in patients considered unfit for open surgery (EVAR 2005b). The median aneurysm diameter in the RCT was 6.4cm (IQR 6.0-7.4cm). The RCT found no difference in survival after 4 years, and concluded that endovascular repair was ineffective in this patient group. The decision model finds that endovascular repair is the most cost-effective treatment on average for patients with aneurysms 5.5-6.5cm at value of £20,000 per QALY, which is considered conventional in the NHS in the UK. However, there is considerable decision uncertainty, as the probability that endovascular repair is the most cost-effective treatment is only slightly greater than 50% (Table 9). Moreover, 20% of patients in the RCT overall did not adhere to their allocated treatment, and this may dilute the results of the trial. It may be the case that some of these patients assigned to no treatment broke the trial protocol and underwent surgery if the aneurysm grew in size, in effect following a policy of watchful waiting. This is difficult to verify as most patients gave a reason of 'patient preference' or gave no reason when asked why they underwent AAA repair. The decision model suggests that, at value of £20,000 per QALY, delaying the decision is more cost-effective than either surgery or no surgery for patients with aneurysms 6.5-7cm. However, for a large proportion of these patients, delaying the decision would never result in treatment given their co-morbidities and high rate of other-cause mortality.

It is difficult to conclude whether or not the results of the decision model and EVAR trial 2 are compatible. The decision model suggests EVAR is cost-effective in unfit patients with AAA of 5.5-6.5cm. The RCT did not stratify results by baseline AAA size. If such a post-hoc analysis were undertaken it might help validate (or reject) the validity of the parameters of the base-case model, though the trial was not powered for subgroup analysis.

UK SAT (1998) compared early elective open surgery (n=563) with continued surveillance until the aneurysm reached 5.5cm (n=527) in patients with an AAA of 4 – 5.5cm and fit for open surgery. The RCT found no difference in survival at 6 years and concluded that surveillance should be continued for patients with small AAA until the aneurysm reaches 5.5cm. The parameters of the UK SAT trial varied in several ways from those of the base-case in the decision model. The mean estimated rupture rate of

small (4 – 5.5cm) untreated aneurysms was 0.01/year, whereas Michaels (1992) estimated that the rupture rate was 0.01/year in aneurysms of 4-5cm and 0.05/year in aneurysms of 5-6cm (Table 5). The estimated mean expansion rate of small aneurysms was 0.33cm/year whereas Michaels estimated the expansion rate is 0.60cm/year for aneurysms of 4-5cm and 0.68cm/year for aneurysms of 5-6cm. The population was younger (mean 69 years) than the EVAR 1 population (mean 74 years). About 2/3 of patients in both arms survived at least 6 years, which is lower than would be expected in the general population of that age (GAD 2009), indicating greater other –cause mortality.

If these parameter values are used in the decision model the results are broadly in line with those of the UK SAT trial. Surveillance is cost-effective up to an aneurysm size of 5.5cm at a value of a QALY of either £20,000 or £30,000. These results are conditional on a low estimated expansion rate and rupture rate for aneurysms of <5.5cm, and a relatively high expansion and rupture rate for larger aneurysms. Endovascular repair was not available in UK SAT, but the results of this model suggest it would have been cost-effective for aneurysms  $\geq 5.5$ cm at £30,000 per QALY.

Chambers et al (2009) conducted a systematic review to identify economic evaluations comparing endovascular *versus* open repair in patients fit for open surgery. Bosch et al (1999) and Patel et al (2002) are based on now rather dated inputs that were obtained from observational studies. Epstein et al (2008) used data from the EVAR trial 1 RCT but some different input parameters to those shown here, in general representing a more pessimistic view of the long term effectiveness of endovascular repair and the costs of reinterventions. In the base-case of the current model, endovascular repair is more cost-effective than open repair at £30,000 per QALY but open repair is more cost-effective at £20,000 per QALY. If the parameters from Epstein et al (2008) are used in the current decision model then results are consistent between the two models. Cairols et al (2008) adapted the model published in Epstein et al (2008) for the Spanish NHS. As before, if the parameters from Cairols et al (2008) are used in the current decision model then similar results are obtained for patients with aneurysms 5.5-6.5cm, that is, that EVAR would be cost-effective in Spain compared to open repair at €30,000 per QALY but open repair would be more cost-effective at €20,000 per QALY, and with high decision uncertainty.

Michaels et al (2005) compared endovascular repair *versus* no treatment (but not watchful waiting) in patients unfit for open repair with large aneurysm  $\geq 5.5$ cm. The study found that endovascular repair was expected to be cost-effective with an ICER of less than £10,000 per QALY. However, Michaels et al (2005) assumed 30-day operative mortality after endovascular repair would be the same in the unfit population as in a fit population. Consistent with Michaels et al (2005), the current decision model finds that endovascular repair is more cost-effective than no treatment in unfit patients with aneurysm  $\geq 5.5$ cm, but the current model also find that delaying the decision might be more cost-effective at £20,000 per QALY than either treatment or no treatment in patients with aneurysms of 6.5-7 cm.

Chambers et al (2009) include an analysis of endovascular repair, open repair, no treatment or continued surveillance as one of the models in a recent appraisal by the National Institute for Clinical Excellence (NICE 2009). This model was similar to the current model and based on similar data but contained several errors. The main errors were (i) incorrect specification of the Bellman equation (ii) incorrect calculation of the transition probabilities from one aneurysm size to the next with no treatment (iii) incorrect interpretation of the output of the dynamic programme. Of these, the last is instructive because it illuminates an important aspect of a dynamic programme.

Chambers et al (2009) suggested that the optimal policy for each possible health state  $x$  in current periods ( $t=1$ ) and future periods ( $t>1$ ) could be inferred from a single run of the model. For example, if current age is 60 years at  $t=1$ , Chambers et al assumed one can infer what the optimal policies would be at age 60 ½ years, 61 years etc by looking forward along the predicted optimal path at  $t=2$ ,  $t=3$  etc. This is incorrect because the optimal policy at any given time is conditional on being alive at that time, the actual health state at that time and the actual policy undertaken in the preceding period. Therefore to know the optimal policy for any given aneurysm size at age 61 years, one must run the model again for a person aged 61 at  $t=1$  who has an untreated aneurysm.

Given the difficulty in estimating the parameters of the model, the watchful waiting analysis is intended to be indicative and exploratory. Nevertheless, the parameters represent the best evidence that could be found from the literature. In the final chapter of this thesis, we discuss the strengths and limitations of the model in more detail and suggest areas of further development.

## Capítulo 6: Conclusiones

### *Pacientes que pueden someterse a la cirugía abierta*

Esta tesis ha investigado la relación coste-efectividad de un amplio conjunto de estrategias para el manejo de AAA. Se presentaron dos modelos de decisión. En el primer modelo descrito en el segundo capítulo se comparó el tratamiento endovascular frente a la cirugía abierta en pacientes que ha decidido la decisión de someterse a cirugía. Este análisis concluyó que la cirugía abierta es más coste-efectiva asumiendo una disposición a pagar de 20.000£ por AVAC, aunque con una incertidumbre considerable, y que el tratamiento endovascular podría ser coste-efectivo en ciertos escenarios.

En el segundo modelo, desarrollado en los capítulos tres, cuatro y cinco, se compararon otras estrategias para pacientes con diferentes tamaños de aneurisma, la no cirugía (tratamiento conservador) y la opción de esperar a tomar una decisión definitiva. Para el caso base, y asumiendo una disposición a pagar de 20.000£ por AVAC, la opción de espera vigilada sería coste-efectiva para pacientes que pueden someterse a cirugía abierta con un tamaño de aneurisma entre 4 – 4,5cm. Mientras que la cirugía abierta se mostró coste-efectiva para pacientes con una aneurisma  $\geq 4,5$ cm.

La práctica clínica en el Reino Unido recomienda la intervención quirúrgica cuando el tamaño de la aneurisma alcanza el límite de 5,5cm de diámetro, o cuando es  $\geq 4.5$ cm, siempre que haya aumentado de tamaño en  $\geq 0.5$ cm durante los últimos 6 meses. En pacientes asintomáticos con una aneurisma menor de 4.5 cm, se aplica un seguimiento con tomografía computerizada (TC) o ecografía cada seis meses. Mientras que para pacientes con AAA entre 4,5 y 5,5cm, el seguimiento sería cada tres o seis meses (Chambers et al 2009).

Los resultados de este análisis difieren a los de la práctica clínica en el Reino Unido en dos aspectos. En primer lugar, el análisis sugiere que los pacientes con una aneurisma menor de 4 cm deben ser dados de alta en lugar de realizarles un programa de seguimiento. La razón fundamental es que según el modelo, el beneficio esperado de realizar cirugía en este grupo de pacientes es muy pequeño, y dado el pronóstico de tasa de crecimiento para tratar un AAA de 4 cm o menos, el valor de esta última opción

sería menor que los coste de la TC. Estas diferencias pueden ser debidas a que los médicos pueden considerar que el riesgo de crecimiento de la aneurisma es mayor que el estimado en el estudio. No hay que olvidar que el modelo asume que los decisores son neutrales al riesgo. Si los médicos fuesen aversos al riesgo, no estarían dispuestos a cargar con la responsabilidad de un paciente, incluso aunque la probabilidad de crecimiento de aneurisma fuese baja. También, las guías de práctica clínica no consideran explícitamente los costes de seguimiento de la TC o ecografía junto con los beneficios.

En segundo lugar, el modelo estimó, para el caso base, que la cirugía es recomendable para un AAA  $\geq 4,5$  cm. Sin embargo, la práctica clínica actual recomienda basándose en los resultados del ECA UKSAT, la cirugía para un AAA  $\geq 5,5$  cm o más. Una de las razones de esta diferencia puede ser que las tasas de ruptura de AAA de 4.5 a 5.5cm fueran más bajas en promedio en el ECA UKSAT (1% por año) que las estimaciones utilizadas en este modelo (1% por año para un AAA de 4,5 a 5 cm, y 5% por año para el AAA, de 5 a 5,5 cm). Si las tasas de UKSAT se utilizasen en el modelo, los resultados serían más coherentes con la práctica clínica actual.

### **Pacientes que no pueden someterse a la cirugía abierta**

Asumiendo una disposición a pagar de 20.000£ por AVAC, para pacientes que no pueden someterse a cirugía abierta y con AAA de tamaño comprendido entre 5,5 a 6,5cm, el modelo estima que el tratamiento endovascular es coste-efectivo. En cambio para pacientes con un tamaño de AAA de 5 a 5,5cm, se indica el seguimiento como el tratamiento a seguir. Ninguna intervención sería coste-efectiva en pacientes con AAA menor de 5cm.

### *Fortalezas y limitaciones de los análisis*

Los modelos de decisión se basan en los riesgos relativos (“hazard ratios”) estimados en un ensayo clínico aleatorio que realiza una comparación de la efectividad de la cirugía endovascular versus cirugía abierta (EVAR 2005a). Esta metodología debe asegurar que las comparaciones entre esas estrategias son validas. Sin embargo, hay una continua innovación en las prótesis y técnicas endovasculares, por lo que podría darse que los resultados del ensayo clínico no fuesen transferibles a la práctica clínica actual, especialmente con respecto a las estimaciones de tasas de re-intervenciones y los costes. Algunos expertos aseguran que actualmente algunas de las complicaciones (“type 2



endoleak”) debidas a la prótesis no son importantes y que como consecuencia hoy día existen menos re-intervenciones (Chambers et al 2009). El seguimiento a los diez años de los ensayos EVAR 1 y EVAR 2 se publicarán en 2010, con lo que proporcionará evidencia adicional sobre la incidencia y consecuencias de las complicaciones relacionadas con la prótesis. Además, aunque no existen datos experimentales para verificarlo, los procedimientos quirúrgicos y las prótesis han mejorado en los últimos años, por lo que algunos expertos aseguran que la estancia en hospital y UCI durante el tratamiento EVAR se está reduciendo. Sin embargo, los estudios EVAR son los únicos ensayos clínicos aleatorios a largo plazo que analizan el uso de recursos y las tasas de reintervención. El EVAR es actualmente una práctica habitual en pacientes de menor riesgo quirúrgico que lo era hace unos años y este cambio en la casuística puede haber contribuido a una reducción aparente en la duración de la estancia hospitalaria, la UCI y la tasa de reintervención.

El segundo modelo de decisión no recoge datos comparativos aleatorios sobre la eficacia de la cirugía versus no intervención quirúrgica. En su lugar, los datos de tasas de ruptura y crecimiento de AAA, se obtienen de estudios observacionales, por lo que puede que no sean comparables los grupos poblaciones en el modelo. Las guías técnicas de evaluación económica, recomiendan, para modelos de decisión que comparan tratamientos sanitarios, el uso de los riesgos relativos procedentes de ensayos clínicos (NICE 2008; López et al 2008). En principio, sería posible elaborar un modelo de decisión basado en estimaciones de riesgos relativos para la mortalidad por AAA de los ensayos clínicos UKSAT o EVAR 2. Sin embargo, no se realizó porque en ambos ensayos clínicos los riesgos relativos cambian en el tiempo, es decir, inicialmente la tasa de mortalidad era mayor después de la cirugía inmediata (por la mortalidad debida a la intervención), pero con el tiempo la tasa aumenta con un aplazamiento de la cirugía (debido a la ruptura en pacientes con AAA sin tratamiento). Por tanto, resulta difícil extrapolar los datos de un ensayo clínico cuando los riesgos relativos no son constantes en tiempo, lo que plantea un reto cuando no se tienen datos más allá del seguimiento del ensayo clínico. El programa dinámico extrapola las tasas de mortalidad de AAA mediante la modelización del proceso clínico subyacente (en términos de crecimiento y tasa de ruptura de AAA) que lleva a los pacientes y cirujanos a tomar la decisión de llevar a cabo la intervención.

Los resultados del modelo son bastantes similares a los del ensayo UKSAT (UKSAT 1998), cuando se utilizan los parámetros de este ensayo en el modelo de decisión. Esta conclusión da validez interna a la estructura del modelo. Sin embargo, plantea la cuestión acerca de qué conjunto de estimaciones de parámetros es el más representativo para usar en el modelo. Para el caso base, el modelo se actualizó a partir de los datos sobre la historia natural del AAA del estudio de Michaels (1992), porque los valores de estos parámetros se situaban en el centro del rango de los demás estudios y porque además eran los únicos datos disponibles en la literatura sobre la historia natural del AAA de gran tamaño ( $\geq 6$  cm).

Por el momento no existen recomendaciones en el Reino Unido para el manejo de pacientes con AAA que no puedan someterse a cirugía abierta, no obstante el ensayo clínico (EVAR 2005b) no encontró mejor supervivencia después del tratamiento endovascular versus no cirugía. Sin embargo, los resultados del modelo sugirieron que podía haber más probabilidad de beneficio en salud para los con AAA de 5,5 a 6,5cm, que aquellos con AAA de mayor tamaño (6.5 a 7.0cm).

El modelo no incluyó todas las opciones para el tratamiento de AAA. Por ejemplo, muchos pacientes pueden tener una o más comorbilidades, en particular enfermedades cardiovasculares, y factores de riesgo como el tabaquismo. Una hipótesis clínica es que seleccionar a los pacientes que se encuentran en mejor estado físico puede ser más efectivo y coste-efectivo que la cirugía en todos (EVAR 2005b). En el modelo se suponía que el seguimiento con ecografía se realizaba cada seis meses, aunque en la práctica clínica el seguimiento depende del tamaño del aneurisma y otros factores de riesgo (Brady et al 2004).

El análisis se realizó desde la perspectiva del sistema nacional de salud (SNS). El objeto general del análisis coste-efectividad es maximizar la salud de la población, dado el presupuesto total del sistema de salud. Dado que este presupuesto proviene del gobierno, en el modelo solo se incluyeron los costes del sistema público. No obstante, se debe tener en cuenta que puede haber costes incurridos por los pacientes, como la pérdida de productividad laboral, o costes soportados por otras organizaciones. Algunas agencias de evaluación de tecnologías sanitarias en España y otros países como Suecia, toman una perspectiva de la sociedad, y recomiendan la inclusión de estos costes en los análisis basales (López et al 2008).

En este trabajo, como en la mayoría de análisis de coste-efectividad, se asume que el decisor es neutral al riesgo. Sin embargo, con algunas excepciones (Zivin 2001, Al et al 2005, Attema et al 2009), esta hipótesis es raramente examinada en la literatura. En el capítulo 3 se examinó este supuesto concluyéndose que la actitud neutral al riesgo es justificada y compatible con la valoración de opciones reales.

El caso base se realizó bajo la perspectiva del sistema de salud británico, pero el análisis de sensibilidad realizado en el capítulo 5, evaluó el modelo tomando los parámetros correspondientes al sistema sanitario español. Estos resultados son similares al análisis del caso-base para los pacientes con aneurisma de tamaño menor de 6,5 cm. Para pacientes con AAA  $\geq$  6,5cm, el caso base concluyó que EVAR es coste-efectivo para el Reino Unido para una disposición a pagar de 30.000€ por AVAC, mientras en España la cirugía abierta es más coste-efectivo en este grupo. Esto se debe a que hay una mayor diferencia de coste de procedimiento en España que en el Reino Unido, debido principalmente a un precio más alto de la prótesis.. El marco teórico presentado en el capítulo 1 demuestra que es necesario tener precaución cuando se intenta adaptar un modelo de un país a otro, particularmente cuando los precios relativos de los recursos son diferentes. Por ejemplo, la tasa de re-intervención por complicaciones de la prótesis puede ser diferente en España que el Reino Unido.

#### *Líneas futuras de investigación*

El análisis coste-efectividad se utiliza cada vez con mayor frecuencia como herramienta de ayuda en la toma de decisiones sobre política de salud, en varios países. Por lo tanto la metodología debe ser robusta, transparente y con un amplio apoyo de los académicos, políticos y otros participantes en el proceso. La programación dinámica es un método comúnmente utilizado en economía, ciencias ambientales y en investigación operativa, aunque todavía hay pocos ejemplos en ACE. Una razón puede ser que el ACE suele obtener estimaciones de la efectividad relativa de los tratamientos de ensayos clínicos. Los programas dinámicos requieren estimaciones de parámetros mucho más detallados, y frecuentemente no es posible utilizar los resultados de los ECAs (por ejemplo, expresados como “odds ratio” o riesgos relativos) directamente en el modelo.

Esta es la principal limitación para considerar estos métodos como evidencia aceptable en la toma de decisiones. Probablemente, estos modelos se presentarían mejor como experimentales, por ejemplo, para generar hipótesis que podría ser confirmado en un

ensayo clínico. En esta aplicación, para el caso base se concluyó que sería coste-efectivo operar con un  $AAA \geq 4,5\text{cm}$ . Los ensayos clínicos aleatorios (ECA) se están llevando a cabo para comparar el tratamiento endovascular frente al seguimiento de pacientes con una aneurisma de reducido tamaño (Ouriel et al 2009). También se encontró que el tratamiento endovascular podría ser coste-efectivo para pacientes con AAA 5.5-6.5cm. Posiblemente, esta hipótesis podría ser comprobada con un nuevo análisis de los datos del estudio EVAR 2, estratificado por tamaño inicial de AAA.

El modelo de programación dinámica en ACE puede ser un método más apropiado cuando no hay ensayos clínicos relevantes, o si el ensayo clínico disponible tiene una baja tasa de adherencia al protocolo del estudio, tal y como ocurre en el ensayo EVAR 2. En este caso, es difícil interpretar los resultados del ensayo porque los cruces de pacientes entre un tratamiento y otro tienden a diluir el efecto del tratamiento, y por lo tanto, la validez externa del ensayo, ya que la tasa de pacientes que cambian de un tratamiento a otro y la captación tardía de los pacientes a tratamiento quirúrgico puede variar en función del ámbito en el que se realice el estudio.

Se ha planificado más trabajo basado en este modelo para analizar los resultados del ensayo EVAR 2 a largo plazo, que se realizará en colaboración con investigadores y médicos de la Universidad de York y la Imperial College de Londres.

Existen muchos ejemplos de otros problemas clínicos con una estructura recursiva, en los que las decisiones son secuenciales. Por ejemplo, para pacientes con enfermedades crónicas como psoriasis o artritis reumatoide, los médicos pueden ofrecerles un fármaco para un periodo inicial limitado de tres meses. Si responden al fármaco, continúan con el tratamiento, y en caso contrario, pueden ofrecerles otro fármaco o ninguno. En este ejemplo, el problema es estimar la secuencia óptima (más coste-efectiva) de fármacos. Si los datos se pueden obtener de la eficacia relativa de los fármacos suministrados en la secuencia, la programación dinámica sería una metodología ideal para analizar este problema.

Desde una perspectiva metodológica, una limitación del modelo de programación dinámica es la dificultad de estimar un intervalo de confianza para la opción de aplazar la cirugía, aplicando el método habitual de simulación de Monte-Carlo para realizar análisis de sensibilidad probabilístico. Un programa dinámico tiene una estructura similar a la del modelo de Markov, a la que se le añaden nodos de decisión intermedios

a lo largo del seguimiento del modelo. Si se hubiera aplicado el método de análisis de sensibilidad probabilístico, se habría estimado el beneficio neto en cada ciclo del modelo como si se conociese los valores de los parámetros para tomar decisiones en el futuro, y se habría sobreestimado el valor de la política óptima. Precisamente, la estimación correcta de la incertidumbre es un área que precisa de más investigación.

## Chapter 6: Conclusions

### Patients who are fit for open surgery

This thesis has investigated the cost-effectiveness of a wide range of strategies for the management of AAA. Two decision models have been presented. The first model, in Chapter 2, compared open repair and endovascular repair in patients who have already taken the decision to undergo surgery. This analysis concluded that open repair was more cost-effective, but that there was considerable uncertainty and endovascular repair might be cost-effective in certain scenarios.

The analysis in Chapters 3, 4 and 5 compared a wider range of strategies for patients with different aneurysm sizes, including no treatment and the option to delay making a definitive decision. Under base case assumptions at £20,000 per QALY, watchful waiting seems cost-effective for patients with aneurysms of 4 to 4.5cm who are fit for open surgery. Open repair is cost-effective for aneurysms  $\geq 4.5$ cm.

Clinical guidelines in the UK recommend elective surgery for AAA  $\geq 5.5$ cm in diameter, as well as for AAA  $\geq 4.5$ cm with an increase in size of  $\geq 0.5$ cm in the last 6 months. The UK guidelines recommend that patients with asymptomatic AAA  $< 4.5$ cm are followed up with CT or ultrasonography every 6 months, whilst AAA of 4.5 –  $< 5.5$ cm are followed up every 3 or 6 months (Chambers et al 2009).

The results of this analysis differ from current UK guidelines in two ways. First, it suggests that patients with aneurysms  $< 4$ cm should be discharged rather than placed on a watchful waiting programme. The model estimates that the expected benefits of surgery in this group are small, and given the predicted growth rate for untreated small AAA, the value of the option to continue surveillance would be less than the costs of CT. There may be several reasons for these differences between the conclusions of the model and current guidelines for the management of AAA. Clinicians may consider that the risks of AAA growth are in fact greater than estimated in this study. The model assumes decision makers are risk-neutral; if clinicians are risk-averse they would not wish to discharge a patient with even a fairly low chance of future AAA growth. Current guidelines do not explicitly consider the costs of follow up with CT or ultrasonography alongside the benefits.

Second, the base-case model suggests that AAA repair should be considered for aneurysms  $\geq 4.5$ cm. Current guidelines were based on the results of the UKSAT RCT, which concluded that surgery should be recommended for AAA  $\geq 5.5$ cm. One reason for this difference may be that rupture rates for AAA of 4.5 to 5.5cm were lower on average in the UKSAT trial (at 1% per year) than the estimates used in this model (1% per year for AAA of 4.5 to 5cm and 5% per year for AAA of 5 to 5.5cm). If the UKSAT estimates of rupture rates are used in the model then the results are more consistent with current guidelines.

### **Patients who are unfit for open surgery**

At £20,000 per QALY, for patients who are unfit for open surgery, the model predicts that endovascular repair is cost-effective for patients with AAA of 5.5-6.5cm. Watchful waiting is cost-effective for AAA of 5-5.5cm. No surgery is cost-effective for AAA less than 5cm. For AAA  $\geq 6.5$ cm the optimum policy is complex because some studies have shown that risks of late mortality after EVAR appear to increase in patients with large aneurysm at the time of surgery, independently of other risk factors (Peppelenbosch et al 2004, Chambers et al 2009). At £30,000 per QALY, EVAR is cost-effective in AAA  $\geq 4.5$ cm, and watchful waiting is cost-effective in patients with AAA of 4-4.5cm.

### **Strengths and weaknesses of the watchful waiting model**

The decision model uses relative risks (hazard ratios) from a RCT to compare endovascular *versus* open repair (EVAR 2005a). This should ensure that comparisons of outcomes between these interventions are valid because the trial controls for observed and unobserved confounders. However, there is continual innovation in medical devices and endovascular techniques, and it has been suggested that the RCT results are not generalisable to current practice, particularly with regard to estimates of re-intervention rates and costs. Some experts have suggested that some of the complications of the endovascular device (type-2 endoleaks) are minor and surgeons are now less inclined to re-operate than during the EVAR trials (Chambers et al 2009). Furthermore, procedures and devices have improved over the past few years and the length of stay and use of ITU during an EVAR admission is claimed to be falling. However, the EVAR trials remain the only long-term randomised studies of resource use and reintervention rates. EVAR is now commonly used in patients of lower operative risk than a few years ago,

and this change in case-mix may also have contributed to an apparent reduction in length of stay, ITU and reintervention rates observed anecdotally and in case-series. 8-year randomised follow up from the EVAR trials found that reintervention rates and late aneurysm-related mortality continue to be greater in the long term after EVAR than open repair (EVAR 2010).

The decision model does not make use of randomised comparative data on the effectiveness of surgery *versus* no surgery. Data for the rupture rate and growth rate of untreated aneurysms are obtained from observational studies, while operative and late mortality after surgery are obtained from the surgery arm of the RCTs. Therefore the estimates of relative risks may be confounded. It is in general recommended that decision models comparing health-care treatments use relative risks estimated from RCTs (NICE 2008; Lopéz et al 2008). In principle, it might be possible to construct a decision model based on estimates of hazard ratios for aneurysm-related mortality and other parameters from the UKSAT trial or EVAR trial 2. This was not done in this case because in both trials the hazard ratios are time-dependent; that is, mortality is initially higher following ‘early surgery’ (reflecting operative mortality) but later mortality is greater for ‘delayed surgery’ (reflecting rupture in untreated aneurysms). Furthermore, the crossovers in the EVAR trial 2 may be due to growth in the aneurysm, reflecting loss of clinical equipoise over time. Both these factors pose a challenge for extrapolating mortality rates beyond the trial follow up, which is central to constructing a long-term decision model. The dynamic programme extrapolates the AAA mortality rates by modelling the assumed underlying clinical process (in terms of AAA growth and rupture rate) that leads to patients and surgeons deciding to undergo surgery.

The decision model can be interpreted as giving broadly similar results to UK SAT if parameter estimates from that RCT are used as inputs to the model. This provides some face validation for the model structure. It also raises the question of which set of parameter estimates are most representative. In the base-case, estimates of the natural history of untreated aneurysms are taken from Michaels (1992) because these seemed to be roughly in the centre of the range across all the studies, and because these were the only estimates available of the natural history in large aneurysms ( $\geq 6$ cm).

There are no formal guidelines in the UK for patients who are unfit for open repair, though the EVAR 2 trial did not find any benefit for endovascular surgery *versus* no



surgery in patients with  $AAA \geq 5.5\text{cm}$  (EVAR 2005b). The results of the model suggest there is more likely to be benefit for patients with AAA of 5.5 to 6.5cm than those with AAA of 6.5 to 7.0cm.

The model does not analyse all of the possible management strategies. For example, many patients with AAA have one or more comorbid conditions, particularly cardiovascular disease, and adverse lifestyle factors such as smoking. It has been suggested that trying to select fitter patients or improve their fitness would be more effective and cost-effective than AAA surgery (EVAR 2005b). It was assumed in the model that surveillance would occur every 6 months, whereas in practice a graduated policy is used where patients with larger AAA sizes, and therefore most at risk, are followed at more frequent intervals (Brady et al 2004).

This decision model is analysed from the perspective of a publicly-funded NHS. The overall aim of cost-effectiveness analysis is to maximise total health given a budget constraint. As the budget constraint is fixed by government for the NHS, only costs and liabilities accrued by the NHS are included. However, there may be other important costs borne by patients and other organisations, such as lost productivity from work and normal activities that are not included in the model. Some health technology assessment agencies in other countries (e.g. Spain, Sweden) take a societal perspective and recommend that these costs are included in their base-case (López et al 2008).

This CEA has assumed the decision-maker is risk-neutral, in common with most cost-effectiveness studies. However, with a few exceptions (Zivin 2001; Al et al 2005; Attema et al 2009) this assumption is rarely examined in the literature. In Chapter 3 the implications of the attitude of the decision-maker to risk was discussed, and concluded that risk neutrality is a justifiable position to adopt and is compatible with real option models.

The base-case CEA is carried out for the UK NHS. As a sensitivity analysis in Chapter 5, we evaluated the model using parameters corresponding to the Spanish NHS. This gives similar results to the base-case analysis for patients with aneurysms less than 6.5cm. For aneurysms greater than 6.5cm, the sensitivity analysis finds that open repair is more cost-effective than EVAR at both €20,000 and €30,000 per QALY. This is because the Spanish data indicate a greater difference in costs between the procedures than the UK data, mainly because of a higher stent price. Consequently the risk of late

aneurysm death after endovascular repair for larger aneurysms, combined with the higher cost of the procedure, switches the decision against EVAR. The theoretical framework presented in Chapter 1 shows that caution is needed when attempting to adapt a CEA from one country to another, particularly if relative prices of inputs are different. In this case, it cannot necessarily be assumed that health-care resource use for a given health state will be similar across countries. For example, re-interventions in Spain for AAA or graft-related complications may not be at the same rate as the UK.

### **Further research**

CEA is increasingly being used to support health policy-making in several countries. Therefore the methods used in CEA must be robust, transparent and be broadly supported by academics, policy-makers and other participants in the process. Dynamic programming is a commonly used analytic method in economics, environmental science and operational research, though as yet there are few examples in CEA. One reason for this may be that CEA usually obtains estimates of the relative effectiveness of treatments from RCTs. Dynamic programmes typically require much more detailed parameter estimates, and it is not usually possible to use the results of RCTs expressed as odds ratios or hazard ratios directly in the model.

This is a major limitation on whether a CEA based on a dynamic programme populated with data from non-randomised studies would be considered acceptable evidence for health policy making. Such models would probably be best presented as exploratory, for example, generating hypotheses that could be tested in an RCT. In this application, we found that it is cost-effective to treat AAA at a size of 4.5cm. RCTs are currently underway to evaluate endovascular repair versus surveillance in patients with small aneurysms (Ouriel et al 2009). We also found that endovascular repair might be cost-effective for patients with AAA 5.5-6.5cm. This hypothesis perhaps could be tested by re-analysis of the data from the EVAR trial 2, stratifying by baseline AAA size.

The dynamic programming model may be an acceptable method of analysis when there are no relevant RCTs, or where the available RCTs have high rates of crossover from one arm to another. This was observed in the EVAR trial 2 (EVAR 2005b). In this case, interpretation of the trial is problematic because the crossovers tend to dilute any treatment effect, and the results of the trial are difficult to generalise to clinical practice where the rate of 'crossover' or delayed uptake of surgery may vary from one setting to

another. Cost-effectiveness decision modelling using longer-term follow up data from the EVAR trials (EVAR 2010) incorporating the methods outlined in this thesis will be carried out in collaboration with the University of York and Imperial College, London.

There are many examples of other problems in health economics with a recursive structure where sequential decisions have to be made. Patients with chronic diseases such as psoriasis and rheumatoid arthritis may be offered a drug for a trial period, typically 3 months. If they respond to the drug they will continue using it, but if they do not, the drug may be withdrawn and the patient trialled on another drug. The problem is to determine the optimum (most cost-effective) sequence of drugs. If data can be obtained on the relative effectiveness of drugs used in sequence then dynamic programming could be used to tackle this problem.

One limitation of the model from a methodological perspective is that it appears to be difficult to estimate a confidence interval for the value of an option to delay by applying the usual method of Monte-Carlo simulation to undertake probabilistic sensitivity analysis. A dynamic programme has a similar structure to a Markov model, but with the addition of embedded or downstream decision nodes. Probabilistic sensitivity analysis would estimate the net benefit at each period of the model as if we knew the values of the uncertain parameters used to make future decisions, and this would over-estimate the value of the optimal policy. Estimating the effect of parameter uncertainty on the option value in CEA may be an area of further methodological research.

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**Appendix. Epstein et al. Modelling the long-term cost-effectiveness of endovascular or open repair for abdominal aortic aneurysm. *British Journal of Surgery* 2008; 95:183-190**

# Modelling the long-term cost-effectiveness of endovascular or open repair for abdominal aortic aneurysm

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**Background:** Recent randomized trials have shown that endovascular abdominal aortic aneurysm repair (EVAR) has a 3 per cent aneurysm-related survival benefit in patients fit for open surgery, but it also has uncertain long-term outcomes and higher costs. This study assessed the cost-effectiveness of EVAR.

**Methods:** A decision model was constructed to estimate the lifetime costs and quality-adjusted life years (QALYs) with EVAR and open repair in men aged 74 years. The model includes the risks of death from aneurysm, other cardiovascular and non-cardiovascular causes, secondary reinterventions and non-fatal cardiovascular events. Data were taken largely from the EVAR trial 1 and supplemented from other sources.

**Results:** Under the base-case (primary) assumptions, EVAR cost £3800 (95 per cent confidence interval (c.i.) £2400 to £5200) more per patient than open repair but produced fewer lifetime QALYs (mean -0.020 (95 per cent c.i. -0.189 to 0.165)). These results were sensitive to alternative model assumptions.

**Conclusion:** EVAR is unlikely to be cost-effective on the basis of existing devices, costs and evidence, but there remains considerable uncertainty.

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## Introduction

The standard procedure to repair an abdominal aortic aneurysm (AAA) using a Dacron inlay graft placed at open surgery was developed in the 1950s. The new, less invasive approach of endovascular aneurysm repair (EVAR) is being compared with the standard open repair in four separate randomized trials<sup>1-4</sup>, two of which have reported mid-term results: 1082 patients in EVAR trial 1 (EVAR 1)<sup>1</sup> and 351 in the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial<sup>2</sup>. In the two published trials, EVAR performed better than open repair in some domains, for example with lower operative mortality and shorter hospital stay. However, its cost is higher and the evidence on both long-term mortality and the continuing need for reinterventions and surveillance is uncertain<sup>1,2,5</sup>.

Collectively-funded healthcare systems, such as the UK National Health Service, with limited overall resources, must compare the alternative forms of management available to each group of patients to determine the most cost-effective. Therefore it is necessary to estimate the cost-effectiveness of EVAR relative to open repair. The economic analysis should synthesize all the available evidence, extrapolate to obtain estimates of life expectancy, health-related quality of life and total costs over patients' lifetimes, and provide a framework in which to explore alternative scenarios. This paper presents the results of a decision-analytic model to compare a strategy of EVAR against open aneurysm repair.

## Methods

### Study question

The model compared a strategy of open repair with that of EVAR for AAA of at least 5.5 cm in diameter in patients

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**Table 1** Mean transition probabilities, used as input parameters in the model

	Open repair	EVAR	Source
Probability of 30-day mortality			
All patients	0.050	0.016*	EVAR 1 <sup>1</sup>
Patients aged < 70 years	0.023	0.007*	EVAR 1 <sup>1</sup>
Patients aged > 80 years	0.069	0.022*	EVAR 1 <sup>1</sup>
Conversion during primary admission	0†	0.008	EVAR 1 <sup>1</sup>
Mortality rate from AAA-related causes during follow-up	1 per 15 000 patient months	6 per 15 000 patient months	EVAR 1 <sup>1</sup>
Mortality rate from other cardiovascular causes during follow-up	Age-dependent‡	Age-dependent‡	Population life-tables and mortality statistics <sup>7,8</sup>
Mortality rate from non-cardiovascular causes during follow-up	Age-dependent	Age-dependent	Population life-tables and mortality statistics <sup>7,8</sup>
Rate of non-fatal readmission for AAA causes in first 6 months	2 per 1000 patient months	19 per 1000 patient months§	EVAR 1 <sup>1</sup>
Rate of non-fatal strokes and MIs during follow-up	Proportional to mortality rate for cardiovascular causes#	Proportional to mortality rate for cardiovascular causes#	EVAR 1 <sup>1</sup>

\*Assuming an odds ratio of 0.30 (95 per cent confidence interval 0.13 to 0.67) for all age groups. †There were no conversions from open repair to EVAR in the EVAR trial 1. ‡The risk of cardiovascular mortality in all patients after successful aneurysm repair is assumed to be twice that in the general population<sup>9</sup>. In addition, the EVAR trial 1 observed three times more deaths from cardiovascular causes during the second year of follow-up. §The rate of readmissions was greatest in the first 6 months after primary procedure. The rate of readmissions was estimated to decline over time following a Weibull model. #The EVAR trial 1 observed a mean 0.6 non-fatal cardiovascular events for every fatal event; 50 per cent of cardiovascular events were strokes. It was assumed that 35 per cent of non-fatal strokes were disabling<sup>10</sup>. EVAR, endovascular abdominal aortic aneurysm repair; AAA, abdominal aortic aneurysm; MI, myocardial infarction.

**Table 2** Unit costs and health-related quality of life parameters used in the model

	Value	Source
Unit costs (£)		
EVAR procedure	10 726 (10 100, 11 300)	EVAR 1 <sup>1</sup>
Open procedure	9 578 (8600, 10 100)	EVAR 1 <sup>1</sup>
Conversion to open repair during primary EVAR	42 067 (0, 85 000)	EVAR 1 <sup>1</sup>
AAA secondary readmissions	5 936 (4500, 7300)	EVAR 1 <sup>1</sup>
MI or non-disabling stroke (initial hospitalization and short-term rehabilitation)	5 099 (4500, 5600)	Jones 2003 <sup>10</sup>
Disabling stroke (initial hospitalization and short-term rehabilitation)	10 555 (9500, 11 500)	Jones 2003 <sup>10</sup>
Lifetime annual cost after disabling stroke	4 003 (3700, 4300)	Jones 2003 <sup>11</sup>
Outpatient visit	90	Reference costs <sup>11</sup>
Computed tomography	104	Reference costs <sup>11</sup>
HRQoL (utility)*		
Utility with no AAA or cardiovascular symptoms		
Age ≤ 75 years	0.78	Kind 1999 <sup>12</sup>
Age > 75 years	0.75	
Loss of utility compared with general population health for 1 month after an event		
After an EVAR procedure	0.027 (0.007, 0.061)	EVAR trial 1 <sup>1</sup>
After an open procedure or AAA reintervention	0.094 (0.065, 0.128)	EVAR trial 1 <sup>1</sup>
After a non-disabling MI or stroke	0.075 (0.047, 0.109)	Lacey 2003 <sup>13</sup>
Permanent loss of utility following a disabling stroke	0.500 (0.424, 0.604)	Lacey 2003 <sup>13</sup>

Values in parentheses are 95 per cent confidence intervals. \*Health-related quality of life (HRQoL) or utility is an index measure of morbidity measured on a scale from 1 (good health) to 0 (death). EVAR, endovascular abdominal aortic aneurysm repair; AAA, abdominal aortic aneurysm; MI, myocardial infarction.

All patients in the EVAR group, whether they experienced adverse events or not, were assumed to require regular specialist hospital outpatient attendances and computed tomography (CT) to monitor their aneurysm repair. In the base case, it was assumed that patients

required two surveillance visits during the first year and one per year thereafter, based on a survey of UK hospitals who participated in the EVAR trials<sup>1</sup>. Patients who had open repair required only one visit in the first year and none thereafter.



### Cardiovascular mortality

Both EVAR 1 and the DREAM trial found that patients having EVAR tended to have a greater risk of cardiovascular mortality (for reasons other than directly caused by the aneurysm or AAA procedure). Although this difference between the treatment groups was not significant, it nevertheless contributed to the conclusion of both trials that the early survival advantage of EVAR does not lead to improved overall mortality in the medium term<sup>1,2</sup>. The cause of this erosion of the early survival advantage after EVAR is unclear. It may be that open surgery precipitates cardiovascular mortality in patients who were already at high risk, or it could simply be a chance finding. In order to evaluate the effects of alternative assumptions about cardiovascular mortality on survival and cost-effectiveness, the increase in cardiovascular hazard associated with EVAR compared with that after open repair was estimated from EVAR 1 and varied in sensitivity analyses.

### Death from aneurysm- and procedure-related causes

The rate of death from aneurysm-related causes used in the base-case analysis was found from EVAR 1 to be about 0.8 per 1000 person years following open repair and 5.0 per 1000 person years following EVAR. By comparison, the EUROSTAR (EUROpean collaborators on Stent-graft Techniques for abdominal aortic Aneurysm Repair) and RETA (UK Registry of Endovascular Repair of Aneurysms) registries of patients undergoing EVAR observed rates of about eight AAA deaths per 1000 person years. Both registers included patients with small aneurysms; EUROSTAR included patients fit and unfit for open surgery, and RETA included both current and withdrawn EVAR devices<sup>14-16</sup>.

Mortality from non-cardiovascular causes was estimated from age- and sex-specific population life-tables<sup>7</sup>, adjusted to exclude deaths from cardiovascular causes<sup>8</sup>. The rate of non-fatal cardiovascular events and aneurysm-related procedures was estimated from EVAR 1. Unit costs for EVAR and open repair procedures were estimated from EVAR 1 and included the average costs of in-hospital complications and mortality<sup>1</sup>.

### Cost-effectiveness analysis

The analysis of cost-effectiveness followed standard decision rules using expected costs and quality-adjusted life years (QALYs)<sup>18</sup>. If the expected costs of one strategy exceeded the other without the expected gain in health

benefits, then this strategy was dominated and the other was deemed the more cost-effective. If both the expected costs and health benefits of one strategy exceeded the other, then the incremental cost-effectiveness ratio (ICER) was calculated as the incremental cost per additional QALY generated by the more effective intervention. A probabilistic sensitivity analysis, based on the uncertainty in the parameters of the model, was undertaken to estimate the probability that EVAR is more cost-effective than open repair as a function of the threshold ICER<sup>19</sup>.

## Results

### Base case

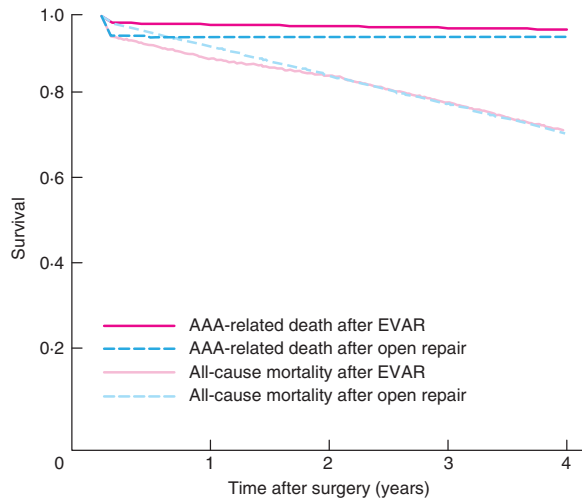
*Fig. 2* shows survival predictions by the model and comparison with the EVAR trial data. The model predicted a persistent reduction in aneurysm-related deaths in the EVAR group compared with the open repair group at 4 years (3.2 *versus* 5.3 per cent respectively), although all-cause mortality was similar in the two groups (about 28 per cent). The predicted all-cause survival curves meet at about 2 years; after this, there is a small but persistent divergence due to the greater risk of mortality from aneurysm-related causes in the EVAR group. The estimates for aneurysm-related death in EVAR 1 at 4 years were 4 *versus* 7 per cent. The model predictions for aneurysm-related deaths are expected to differ from the trial because the latter included patients who died before a procedure was undertaken and used an intention-to-treat analysis.

Under base-case assumptions, the model predicted greater lifetime expected costs in the EVAR group (mean difference £3758 (95 per cent c.i. £2439 to £5183)), because of the greater initial cost of the procedure and monitoring during follow-up (*Table 3*). The model predicted slightly fewer expected QALYs with EVAR (mean difference -0.020 (95 per cent c.i. -0.189 to 0.165)). This was because the initial survival advantage with EVAR was eroded by more deaths due to cardiovascular- and

**Table 3** Model estimates of mean costs and QALYs over patients' lifetime under base-case assumptions

	Cost (£)	QALYs
EVAR	15 823 (14 606, 17 418)	5.050 (3.685, 6.172)
Open repair	12 065 (10 358, 14 144)	5.070 (3.754, 6.123)
Difference	3758 (2439, 5183)	-0.020 (-0.189, 0.165)

Values are estimated mean (95 per cent confidence interval). The probability that EVAR is cost-effective, assuming a cost-effectiveness threshold of £20 000 per QALY, is 0.01; assuming a cost-effectiveness threshold of £40 000 per QALY, it is 0.08. QALY, quality-adjusted life year; EVAR, endovascular abdominal aortic aneurysm repair.



**Fig. 2** Model predictions of survival and survival free from aneurysm-related death under base-case assumptions. Comparison with Endovascular Aneurysm Repair (EVAR) 1<sup>1</sup> mortality estimates at 4 years gives 3.2 per cent (model) *versus* 4.0 per cent (trial) for death from AAA-related cause after EVAR; 5.3 *versus* 7 per cent for death from AAA-related cause after open repair; 28.0 per cent (model and trial) for all-cause mortality after both EVAR and open repair. AAA, abdominal aortic aneurysm

aneurysm-related causes over the longer term. Therefore, based on these expected values, EVAR was dominated by open surgery and had a probability of only 8 per cent of being cost-effective at a cost-effectiveness threshold of £40 000 per additional QALY.

**Secondary analyses**

The base-case assumptions were varied in a series of secondary analyses to reflect alternative sources of evidence and strengths of opinion about some of the key parameters used in the model (Table 4).

Other things being equal, the scenarios that most clearly influenced effectiveness were the relative risk of cardiovascular mortality in the trial patients compared with the general population (scenario 2), the relative effect of the treatment strategy on cardiovascular mortality (scenario 3), the relative risk of AAA death over the long term (scenario 8) and the probability of death within 30 days of open repair (scenario 9). Scenario 5, in which there is a lower acquisition cost of the EVAR device, reduced the difference in average costs between the strategies but, since it does not affect health benefits or lead to expected cost savings overall, this scenario did not, on its own, suggest that EVAR is cost-effective.

Analyses were also carried out varying the age of the patient at the time of surgery (scenarios 10–13). There was no evidence that the odds ratio for operative mortality or all-cause mortality varied by age<sup>17</sup>. However, age was a significant predictor of operative mortality after open repair. Scenario 13 assumed that the risk of late mortality for non-AAA causes was the same during follow-up after each procedure and therefore the initial benefits of EVAR would be maintained over these patients’ lifetimes. Moreover, since elderly patients have a lower life expectancy they will accumulate fewer healthcare costs of follow-up and reintervention after EVAR. Based on these assumptions, EVAR would have an ICER of £27 000 and would be cost-effective in these patients at a threshold of £30 000 per QALY. However, this analysis was exploratory and more research is needed on all the risk factors, not just age, that might determine procedure-related complications and long-term outcomes.

**Discussion**

Based on the assumptions and evidence applied in this study, EVAR is unlikely to be cost-effective for all patients within collectively funded healthcare systems.

Decision-analytical models are necessary to inform decision makers by bringing together existing evidence to assess the likely cost-effectiveness of competing forms of patient management. In the absence of long-term results evaluating EVAR compared with open AAA management, the modelling presented here had to incorporate a range of assumptions to assess cost-effectiveness over the lifetime of the patients. Under base-case assumptions, the early benefit of lower 30-day operative mortality was eroded by mortality from AAA and cardiovascular causes during follow-up. Although surgical teams may prefer EVAR because the patient is more likely to leave their care alive<sup>21</sup>, EVAR is unlikely to be considered cost-effective from the perspective of the National Health Service on the basis of endograft performance and the costs that applied during recruitment to EVAR 1. In systems with patient co-payments, patient choice may play an important role in the decision to use EVAR devices. In other collectively funded systems, the costs may differ from those used here, including the price of devices, which are ultimately under the control of the manufacturers. However, the clinical effectiveness found in this trial to date, and the most plausible assumptions given clinical uncertainty, are likely to be generalizable, and the present results are likely to be directly relevant to other similar healthcare systems.

Other authors have considered EVAR cost-effectiveness in this group of patients<sup>22–26</sup>. Patel and colleagues<sup>24</sup>

**Table 4** Results of secondary analyses: difference in mean costs and QALYs, and the probability that EVAR is cost-effective when the threshold per additional QALY is £20 000 and £40 000

Scenario	Base-case assumption	Secondary analysis	Difference in cost (£)	Difference in QALYs	ICER for EVAR versus open*	Probability EVAR is cost-effective†	
						$\lambda = £20\,000$	$\lambda = £40\,000$
1	Base case		3758	-0.020	EVAR dominated	0.012	0.080
2	Hazard of cardiovascular death is twice that of the general population	Baseline hazard of cardiovascular death is the same as the general population	4105	0.017	239 000	0.028	0.161
3	Lower rate of cardiovascular death following open surgery	Same hazard of cardiovascular death following each treatment strategy	3687	0.087	42 000	0.098	0.481
4	1 CT and 1 outpatient visit per year after EVAR	Same cost of monitoring following each treatment strategy	2613	-0.020	EVAR dominated	0.045	0.145
5	Cost of EVAR device is £4800	Cost of EVAR device is £3700	2669	-0.020	EVAR dominated	0.048	0.147
6	Odds ratio of 30-day mortality from EVAR 1 only	Odds ratio from a meta-analysis of DREAM <sup>2</sup> and EVAR trials	3765	-0.015	EVAR dominated	0.012	0.084
7	Discount rate of 3.5%	No discounting of costs nor health benefits	4103	-0.041	EVAR dominated	0.016	0.084
8	Odds ratio of AAA-related death during follow-up from EVAR 1	No difference between EVAR and open repair of the long-term rate of AAA-related death	3859	0.080	48 000	0.076	0.419
9	5% die within 30 days of open repair	8% die within 30 days of open repair	3795	0.090	42 000	0.147	0.463
10	Age 74 years	Age 66 years	4513	-0.144	EVAR dominated	0.001	0.025
11	Age 74 years	Age 82 years	3072	-0.015	EVAR dominated	0.047	0.138
12	Age 74 years and lower long-term rate of cardiovascular death after open surgery	Age 66 years and no difference in rate of cardiovascular death after open repair or EVAR	4468	-0.075	EVAR dominated	0.006	0.068
13	Age 74 years and lower long-term rate of cardiovascular death after open surgery	Age 82 years and no difference in rate of cardiovascular death after open repair or EVAR	2960	0.110	27 000	0.262	0.670

\*'EVAR dominated' means EVAR, on average, costs more and has fewer QALYs than open repair and is not expected to be cost-effective. †The probability EVAR is cost-effective is evaluated at threshold ICERs ( $\lambda$ ) of £20 000 and £40 000 per additional QALY<sup>20</sup>. The National Institute for Health and Clinical Excellence in the UK has not to date funded interventions with an ICER above £40 000. Given the uncertainty in the model parameters, this represents the probability that a decision to implement EVAR will be better than open repair. QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio (difference in mean cost divided by difference in mean health benefits); EVAR, endovascular abdominal aortic aneurysm repair; CT, computed tomography; AAA, abdominal aortic aneurysm.

and Bosch and colleagues<sup>25</sup> both concluded that EVAR was cost-effective, assuming lower rates of renal failure, amputation, stroke and myocardial infarction than open repair. Prinssen<sup>23</sup> found that, since there was almost no difference in all-cause mortality after 1 year of the DREAM trial, EVAR was not cost-effective given its higher cost. This approach assumed that mortality related to non-aneurysm causes during follow-up is greater in patients with EVAR, and cancels out the early benefit in aneurysm-related mortality of EVAR. Michaels and colleagues<sup>26</sup>

assumed no difference between EVAR and open repair in the rates of mortality or morbidity for non-aneurysm causes, and found that EVAR was more effective than open repair but, because of its high cost, was unlikely to be cost-effective.

Several factors add uncertainty to the present modelling exercise. There are plausible scenarios under which EVAR might be cost-effective. For this to be the case, EVAR would have to be both relatively more effective and less costly than the base-case assumptions used here. For

example, if the device cost the health service £1100 less than the current price and there was no difference in non-aneurysm-related cardiovascular mortality between the treatments, then EVAR would be cost-effective (at a threshold of £30 000 per additional QALY). The relative risk of cardiovascular mortality, and a better understanding of its causes in the years after the primary procedure, may be informed by late results from EVAR 1 and the other ongoing trials<sup>1–4</sup>. In another scenario, EVAR would be more effective if the long-term risk of cardiovascular mortality in all patients after successful aneurysm repair was closer to that of the general population: this might be achieved through wider use of statins and antiplatelet drugs at modest additional cost. EVAR would be more effective if there were no difference in the long-term risk of AAA-related mortality. This will be informed by continued follow-up of patients in the EVAR trials. Endografts must be developed that will reduce the need for reintervention and surveillance, obviating the need for annual CT.

EVAR may be cost-effective in a subpopulation of elderly patients fit for open surgery under particular assumptions. Older patients have greater risk of operative mortality after open surgery and, since there is no evidence that the odds ratio for mortality after EVAR in patients fit for open repair vary by age, older patients should benefit more from EVAR in terms of absolute risk reduction. However, EVAR will be cost-effective in this group only if patients maintain this early survival advantage over open surgery, that is, they do not suffer any excess cardiovascular mortality after EVAR. These scenarios are by nature speculative. Furthermore, endovascular technologies and their clinical applications are evolving rapidly. This indicates that EVAR should continue to be considered a research technology. However, the work undertaken and reported here has outlined the necessary conditions for EVAR to be cost-effective and points the direction for further research and development in this important area of endovascular therapy.

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