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ECONOMIC EVALUATION OF PUBLIC HEALTH INTERVENTIONS

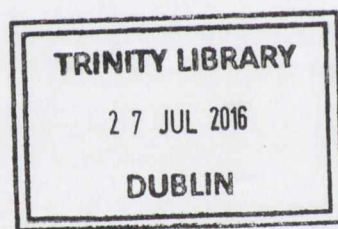
Patrick Moran

Doctor in Philosophy, Health Policy and Management

University of Dublin, Trinity College

Supervisors: Dr Máirín Ryan, Professor Charles Normand, Professor Susan Smith

Submitted to the University of Dublin, Trinity College, October 2015



thesis 10988

DECLARATION

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SUMMARY

This thesis examines the clinical and cost effectiveness of three separate public health interventions that are on the health policy agenda in Ireland and provides information to inform resource allocation at a national level. It also explores the possibility of expanding the role of economic analysis within the public health sector, with the aim of generating a more informed discussion about resource allocation priorities and gradually guiding policymaking towards the long term goal of achieving the mix of interventions that optimises health outcomes within the population.

The Public Health (Availability of Defibrillators) Bill 2013 proposes a national public access defibrillation scheme that would require a range of designated places frequented by the public to provide defibrillators and train staff in their use. This analysis found that the scheme outlined in the Bill is unlikely to be cost effective, with an incremental cost effectiveness ratio (ICER) of €301,204/QALY compared with routine care. A more scaled back version that only included building types with the highest incidence of cardiac arrest would also not be considered cost effective by conventional standards (ICER €95,640/QALY), unless the programme resulted in a 40% increase in the probability that a defibrillator would be used by a member of the public if an arrest occurred in the immediate vicinity. While it is generally assumed that greater awareness of cardiac arrest and the presence of trained staff members would increase the chances that someone would apply a defibrillator before the arrival of emergency medical services, there is currently no evidence to show how much of an increase could reasonably be expected. One of the reasons for the poor cost effectiveness results is the fact that Ireland already has a high number of defibrillators installed on a voluntary basis, and many of these are in places with the highest probability of a cardiac arrest occurring, such as airports and other transport stations.

The national cardiovascular health policy 2010-2019 recommends that a screening programme for atrial fibrillation is implemented for all people aged 65 and over. The results of an economic evaluation found that screening was likely to be cost effective (ICER €23,004/QALY) provided the asymptomatic or minimally symptomatic patients identified through screening had a comparable risk of stroke as those identified through

routine practice. The cost effectiveness of screening could potentially be improved by raising the start age or increasing the screening interval.

The 2015 Programme for Government includes a commitment to extend the upper age limit for mammographic breast screening from 64 to 69 years. The results of a controlled before and after study showed that the current breast screening programme for women aged 50 to 64 was associated with a 16% reduction in breast cancer mortality and an overdiagnosis rate of 19% during active screening. A utility analysis comparing the overall benefits and harms of screening in terms of quality adjusted life years (QALYs) found that despite the level of overdiagnosis screening was associated with a significant net benefit within the screened population. While the existing programme is likely to be cost effective from a societal perspective, the cost per additional QALY gained by extending the upper age limit to 69 years exceeded a willingness to pay threshold of €45,000/QALY. An important consideration in the evaluation of breast screening is the decreasing background trend in breast mortality as a result of improved treatment, which decreases the benefits of earlier detection. If it is assumed that the decreasing trend in breast cancer mortality that was observed prior to the introduction of screening has been maintained since 2007, then the existing programme would not be cost effective from the perspective of the health service (ICER €59,000/QALY).

The use of generalised cost effectiveness analysis (GCEA) to compare competing public health interventions was explored, using the three programmes described above as an example. The feasibility of conducting GCEA within the area of public health is demonstrated in this thesis, which shows that this type of analysis has the potential to provide decision makers with valuable information on the optimal mix of public health interventions, and therefore what they should be striving towards, even if they are not completely free to reallocate all resources in the short term. Further research remains to be done to quantify the relative uncertainty of GCEA results in a way that is relevant and communicable to decision makers, and also in adequately dealing with any interaction that may exist between the costs or effects of different public health interventions.

To my family

ACKNOWLEDGEMENTS

I would like to thank Máirín Ryan, Charles Normand and Susan Smith for their excellent support and guidance over the course of completing this research. Having a supervisory team with such wit, wisdom and experience was of immeasurable benefit.

I would like to thank my employer, the Health Information and Quality Authority (HIQA), for their support over the course of this PhD.

I would like to thank Kathleen Bennett for her help with the statistical analysis for the evaluation of the clinical effectiveness of the Irish breast screening programme.

I would like to thank Conor Teljeur and Patricia Harrington for acting as second reviewers for the analyses of the public access defibrillation and atrial fibrillation screening programmes, and all of the members of the HTA Directorate in HIQA for their help and feedback along the way. I would also like to thank the members of the HTA expert advisory group for both these analyses for their advice and feedback in relation to parameter estimation and interpretation of the results. As well as being described in the relevant section of the main body of the thesis, a detailed summary of the input received from external sources in each of the analyses is also provided in Appendix 1.1.

Finally, I would like to thank my wife, Deirdre O'Neill, for bringing a sparkle to everything we do together, and my parents, Mary and Paddy Moran, two exceptional people to whom I owe a debt of gratitude that I will never be able to repay.

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LIST OF ABBREVIATIONS

AAA	Abdominal aortic aneurysm
ACEP	American College of Emergency Physicians
ADL	Activities of daily living
AED	Automatic external defibrillator
AF	Atrial fibrillation
AHA	American Heart Association
APC	Annual percent change
ASR	Age standardised rate
BA	Before and after study
BCG	Bacillus Calmette-Guerin vaccine
BLS	Basic life support
CBA	Controlled before and after study
CCT	Controlled clinical trial
CDSS	Clinical decision support system
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CI	Confidence interval
CPC	Cerebral performance category
CPI	Consumer price index
CPR	Cardiopulmonary resuscitation
CSO	Central Statistics Office
DNA	Deoxyribonucleic acid
DOAC	Direct oral anticoagulants
DRG	Diagnosis related group
ECG	Electrocardiogram
ED	Emergency department
EMS	Emergency medical services
EORP-AF	EuroObservational Research Programme-Atrial Fibrillation
ERC	European Resuscitation Council
ESC	European Society of Cardiology
ESRI	Economic and Social Research Institute
EU	European union
EVPI	Expected value of perfect information
FDA	US Food and Drug Administration
FIT	Fecal Immunochemical Test
FOBT	Fecal Occult Blood Test
FTE	Full time equivalent
GCEA	Generalised cost effectiveness analysis
GMS	General medical scheme
GP	General practitioner
HIPE	Hospital inpatient enquiry
HIQA	Health Information and Quality Authority
HIV	Human immunodeficiency virus

HPV	Human papillomavirus
HSE	Health Services Executive
HTA	Health technology assessment
ICD	Implantable cardioverter defibrillator
ICER	Incremental cost effectiveness ratio
ICH	Intracranial haemorrhage
ILO	International labour organisation
IMC-CEA	Intervention mixed constrained cost effectiveness analysis
INR	International normalized ratio
IS	Ischaemic stroke
ISPOR	International Society For Pharmacoeconomics and Outcomes Research
IT	Information technology
ITS	Interrupted time series analysis
LYG	Life years gained
NCPE	National Centre for Pharmacoeconomics
NCRI	National Cancer Registry Ireland
NHS	National Health Service
NIHSS	National Institute of Health stroke scale
OAC	Oral anticoagulant
OHCA	Out of hospital cardiac arrest
OHCAR	Out of hospital cardiac arrest register (Ireland)
OR	Odds ratio
PAD	Public access defibrillation
PAP	Papanicolaou test
PCRS	Primary care reimbursement service
PEA	Pulseless electrical activity
PICH	Primary intracerebral haemorrhage
QALY	Quality adjusted life years
QOF	Quality outcomes framework
RCT	Randomised controlled trials
RD	Risk difference
ROSC	Return of spontaneous circulation
RR	Relative risk
SAH	Subarachnoid haemorrhage
SCD	Sudden cardiac death
SE	Standard error
SRR	Standardised rate ratio
TNM	Tumour node metastases
TTR	Time in therapeutic range
UHI	Universal health insurance
US	Ultrasound
VAT	Value added tax
VF	Ventricular fibrillation
WHO	World Health Organisation
WTP	Willingness to pay

1. INTRODUCTION

1.1 THE CONCEPTUAL BASIS OF ECONOMIC EVALUATION

All the economic evaluations included in this thesis share a common theoretical framework. This is especially important for later chapters that involve the interpretation of results from different analyses with reference to each other. It is worthwhile at the outset to briefly summarise the core concepts underpinning economic evaluation of health interventions that provide a basis for using this type of information to inform decisions about the allocation of resources, and to consider the type of information and assumptions required for this type of analysis.

While cost effectiveness analysis grew out of a range of different disciplines, the theoretical justification for basing decision making about resource allocation on a comparison of costs and benefits is rooted in welfare economic theory, which provides a normative framework with which to compare the desirability of alternative allocations of societal resources. Central to this theory is the concept of Pareto efficiency. A Pareto efficient improvement is one where at least one person is made better off and no one is made worse off. In reality there are very few examples of changes from which no-one loses out, so the concept of a Pareto improvement can be expanded to include situations where the winners compensate the losers and are still better off (total gains exceed total losses). Extending the point still further is the concept of the potential Pareto improvement, where a change is considered beneficial if the winners could in theory compensate the losers and still be better off, even if this does not happen. While this is not without flaws, the concept of a potential Pareto improvement provides the justification for resource allocation based on cost-benefit analysis. This approach avoids the need to directly compare the welfare of individuals as long as those who benefit could in theory compensate those who lose out, and still be better off.⁽¹⁾

Economic evaluation has been defined as the comparative analysis of alternative courses of action in terms of both their costs and consequences.⁽²⁾ The relationship between costs and benefits is primarily expressed as the incremental cost effectiveness ratio (ICER), or the ratio of the increase in costs to the increase in benefits. In cases where a new health intervention

is both more costly and more effective than the existing standard of care, the ICER is compared to a willingness to pay threshold intended to represent the maximum amount society is willing to pay for a unit of health gain.⁽³⁾ A decision rule that adopts all interventions with an ICER less than a given willingness to pay threshold will be optimal insofar as the set of funded interventions will maximise the aggregate health gain, and this gain will have been achieved at an acceptable cost.⁽⁴⁾

A key consideration, therefore, is how one chooses to measure the costs and consequences of health interventions. In this analysis costs are valued in Euro and consequences in quality adjusted life years (QALYs). QALYs are designed to combine changes in life expectancy and quality of life in a single outcome, which is then used as a basis for comparing interventions across a range of disease areas. Discounting is used to incorporate individuals' time preferences for costs and benefits. The use of QALYs in cost effectiveness analysis is consistent with the assumptions of welfare economics that individuals maximise preference based utility, and that the overall welfare of society is a function of these individual preferences.⁽⁴⁾

However, there are a number of well known limitations in regard to the welfare economics theoretical framework and the methodology used to value costs and benefits. These include the failure to include any information on the desirability of the processes that lead to the utility outcomes or the intentions behind them, or in other words the difficulties associated with 'judging the goodness of states of affairs only by utility information'.^(5;6) Extra-welfarist approaches have been developed that abandon the idea of Pareto improvements by using outcomes other than utility, sources of valuation other than the affected individuals and by allowing outcomes to be weighted according to a range of different factors.⁽⁶⁾ There are also limitations associated with the use of QALYs, for instance the lack of consistency across different utility elicitation methods, and with the use of discounting, which biases against preventative interventions in which the costs are incurred immediately but the benefits don't accrue until much later. While remaining cognisant of the implications these limitations have for how results should be interpreted, it is important to recognise that in the absence of a solution to these intractable problems, welfare economics theory does provide a consistent and widely accepted framework with which to understand the problem and conduct empirical analysis.⁽¹⁾

1.2 ECONOMIC EVALUATION OF HEALTH INTERVENTIONS IN IRELAND

There are two separate agencies with responsibility for carrying out economic evaluations to inform health policy decision making by the Health Service Executive (HSE) and the Department of Health in Ireland. The National Centre for Pharmacoeconomics (NCPE) primarily evaluates the cost effectiveness of new medicines following receipt of an application for reimbursement under the community drugs schemes.⁽⁷⁾ The Health Information and Quality Authority (HIQA) conducts original evaluations of new interventions, including drugs, devices, surgical procedures and public health programmes, that are being considered for introduction at a national level.⁽⁸⁾ HIQA also produces national guidelines for the conduct of economic evaluations. Ireland is somewhat unusual insofar as an explicit willingness to pay (WTP) threshold of €45,000/QALY has been agreed upon for pharmaceuticals. All drugs with ICERs below this threshold are reimbursed, and drugs that have higher ICERs may also be reimbursed in exceptional circumstances.⁽⁹⁾ No such certainty exists in relation to non-drugs interventions, and while the results of cost effectiveness evaluations of these interventions are generally reported against WTP thresholds of €45,000/QALY, there is no guarantee the interventions beneath this threshold will be adopted.

The Irish health service is currently undergoing a period of significant change, which has included the reorganisation of the HSE into a directorate structure and the planned introduction of universal healthcare.⁽¹⁰⁾ This has resulted in the setting up of the Health and Wellbeing Directorate, which has centralised decision making for public health interventions, and the planned creation of a health and wellbeing fund, which will be used to finance these types of programmes. It is envisaged that the basket of services provided using this fund will be largely informed by cost effectiveness analysis, in order to “reflect a continuous commitment to ensuring that public funds provided by the Irish people are used to optimal effect so that our health service can achieve the best health outcomes for available resources.”⁽¹⁰⁾ This includes identifying new treatments as well as opportunities to disinvest in outdated or inappropriate services. The research described in this thesis is designed to address both of these aims, by contributing original, relevant, information with which to inform three national health policy decisions, as well as examining methodological

approaches designed to identify opportunities to replace existing interventions with more cost effective alternatives.

While much progress has been made in relation to the implementation of these changes within the Irish health service, there is uncertainty about how certain elements of the proposed plan will be progressed, particularly in relation to the proposed system of mandatory private health insurance. However, even if there are changes to how universal healthcare is financed, there remains a requirement for high quality, evidence based analyses of the clinical and cost implications of competing interventions, in order to achieve the best outcomes for the limited resources available.

1.3 OUTLINE OF THE THESIS

This thesis describes three separate economic analyses of public health interventions that are either currently in place or under consideration by policymakers within the publicly funded health and social care system in Ireland.

The first is an evaluation of the clinical and cost effectiveness of the national public access defibrillation scheme proposed in the Public Health (Availability of Defibrillators) Bill 2013, which is currently at committee stage in the Irish legislative process.⁽¹¹⁾ This Bill is designed to improve out-of-hospital cardiac arrest (OHCA) outcomes by imposing an obligation on the owners of certain public premises to provide defibrillators that can be used by bystanders before the arrival of emergency medical service (EMS) in the event of a cardiac arrest occurring in the vicinity.

The second public health intervention examined is a national screening programme for atrial fibrillation (AF) for all those aged 65 years and over, which was recommended in the National Cardiovascular Policy 2010-2019.⁽¹²⁾ AF is the most common heart rhythm disorder seen in general practice and a leading cause of stroke. The aim of an AF screening programme is to detect those who are unaware that they have the arrhythmia so they can receive treatment to decrease their risk of stroke or systemic embolism.

The third component of this thesis is an evaluation of the clinical and cost effectiveness of the existing mammographic breast screening programme for women aged 50 to 64 years, as well as an assessment of the cost effectiveness of the planned expansion of the age range to 69 years announced in the 2015 Programme for Government.⁽¹³⁾ Although screening has been considered standard practice in most developed countries for over a decade, evaluating the effect of contemporary population screening programmes on breast cancer mortality and overdiagnosis has proven controversial.⁽¹⁴⁾ This thesis takes advantage of a natural experiment created by the phased introduction of the Irish mammography programme to estimate the overall balance of benefits and harms of screening.

A limitation of the prevailing approach to cost effectiveness analysis is that by comparing new interventions to the existing standard of care or other direct comparators within a particular disease area, it lacks the ability to systematically identify potential improvements

in the overall mix of public health interventions currently provided by the state. The final section of the thesis explores the feasibility of taking a broader approach to cost effectiveness analysis, one that emancipates itself from past resource allocation decisions in order to identify what the optimal set of interventions could be if one were free to start again with the benefit of the current best available evidence. This proof of concept analysis combines the three separate economic evaluations in a generalised cost effectiveness analysis of public health interventions in Ireland to examine how they compare to each other, and to explore any relevant conceptual or practical issues in relation to the application of this approach to improving resource allocation within the area of public health.

2. PUBLIC ACCESS DEFIBRILLATION

2.1 BACKGROUND

Cardiac arrest is the sudden cessation of blood circulation due to a malfunction of the electrical system of the heart. Interruption of the blood supply to the brain causes loss of consciousness and respiratory failure. If left untreated, death usually follows within minutes. The definitive treatment for cardiac arrest is defibrillation, which is the delivery of an electric current through the chest wall that momentarily stuns the heart, stopping the abnormal rhythm and helping the heart resume normal electrical activity. However, by the time emergency responders arrive not all patients who have had an out-of-hospital cardiac arrest (OHCA) have a heart rhythm that is amenable to defibrillation. Non-shockable rhythms include asystole (where there is no electrical activity) and pulseless electrical activity (PEA, where electrical activity is observed but no contraction is taking place). Cardiac rhythms that can be successfully reverted to normal sinus rhythm by defibrillation include ventricular fibrillation (VF) and pulseless ventricular tachycardia (pVT). Early intervention is vital, since shockable rhythms eventually deteriorate to asystole if no treatment is received. Cardiopulmonary resuscitation (CPR) can be used to help maintain blood supply to the brain or induce a shockable rhythm prior to defibrillation. OHCA remains a major international health problem, with incidence rates for emergency medical services (EMS) treated cases of approximately 35 per 100,000 population.⁽¹⁵⁾ Despite advances in treatment and improved organisation of services, international survival rates from OHCA have remained relatively consistent at between 7% and 8% for the last 30 years.⁽¹⁶⁾

The aim of public access defibrillation (PAD) is to increase survival from out-of-hospital cardiac arrest by reducing the time from the onset of the arrest to defibrillation. PAD programmes make automatic external defibrillators (AEDs) available to trained volunteers or untrained bystanders for use before the arrival of emergency medical services. AEDs are small, portable devices that analyse the heart rhythm of a person who has experienced a cardiac arrest and deliver an electric shock if it detects a rhythm that can respond to defibrillation.

A number of different approaches to implementing PAD programmes have been described in the literature. These can be broadly separated into three groups:

1. Programmes that involve the provision of static AEDs in public buildings and communal areas that are designed to be used opportunistically by anyone who witnesses an out-of-hospital cardiac arrest.
2. Equipping uniformed first responders, such as the police or fire service, with AEDs and simultaneously dispatching them, along with emergency medical services, to suspected out-of-hospital cardiac arrest events.
3. Community first responder groups run by volunteers that provide AEDs to members who respond to any out-of-hospital cardiac arrest events that occur in their area. These community first responder groups may or may not be linked to emergency medical services' dispatch systems, allowing ambulance dispatch centres to notify them when a suspected cardiac arrest occurs in their area.

There has been considerable support for the establishment of PAD programmes from professional bodies and patient advocacy groups, and many countries have already established some form of PAD programme.⁽¹⁷⁻²⁰⁾ There is, however, a great deal of heterogeneity in the types of interventions that have been chosen, and how these have been structured. Some are national programmes centrally coordinated by government agencies, while others are regional initiatives organised on a voluntary basis. Given the rapid proliferation of these schemes and the significant resources that are required to implement them, it is important that an evidence-based analysis of the effectiveness of different PAD programme configurations is available to inform the ongoing efforts of those in publicly funded health services and the wider society.

Given this high level of heterogeneity, evaluation of the clinical and cost effectiveness of PAD programmes is challenging. The comparability of results is further complicated by differences in the configuration and responsiveness of emergency medical services (EMS) in different areas, and the pre-existing level of AED availability. Historically, the degree of prior AED diffusion was not a major consideration because new programmes were being introduced in settings where there were very few devices available. However, as AEDs have

become more commonplace in society, this issue is becoming increasingly important in the context of public health policymaking, since any pre-existing level of voluntary, ad-hoc deployment of AEDs in high incidence locations may reduce the incremental benefits of a comprehensive publicly-administered programme.

Ireland does not currently have a national PAD programme in place. However there has been widespread diffusion of AEDs on a voluntary basis over the last decade due to the combined efforts of advocacy organisations and community groups, with the support of various sections of the health service. The Irish government is currently considering introducing legislation that would place a legal requirement on the owners of certain designated places to make AEDs publicly available on their premises, register them with a central authority and train staff in their use.⁽¹¹⁾ The aim of this research was to examine the clinical evidence on the effectiveness of different PAD programmes and evaluate the cost effectiveness of the proposed Irish PAD programme based on the mandatory provision of static AEDs in designated building types, compared with the current standard of care involving undirected AED provision on a voluntary basis.

2.2 CLINICAL EFFECTIVENESS OF PUBLIC ACCESS DEFIBRILLATION

2.2.1 INTRODUCTION

A systematic review of public access defibrillation programmes was carried out to identify, appraise and synthesise the best available evidence on the clinical effectiveness and safety of these interventions in the management of out-of-hospital cardiac arrest, to serve as a basis for estimating the likely clinical outcomes associated with the introduction of a public access defibrillation programme in Ireland and identify the key factors that impact these outcomes.

2.2.2 METHODS

A search was performed in Medline, Embase, Scopus, clinical trial registries (Cochrane Registry of Controlled Trials, ClinicalTrials.gov and the ISRCTN register) and the Cochrane Library (Database of Abstracts of Reviews of Effects [DARE], Cochrane Database of Systematic Reviews [CDSR] and the Health Technology assessment [HTA] database) for studies examining the effectiveness of public access defibrillation interventions. Detailed search strings and the number of returned results for each are provided in Appendix 2.1.

Preliminary screening of all returned results was undertaken by a single person to eliminate duplicates and studies that were clearly not relevant. Assessment of the eligibility of studies and data extraction was performed independently by two people according to the inclusion criteria shown in Table 2.1. Disagreements were resolved by discussion.

TABLE 2.1 PAD REVIEW INCLUSION CRITERIA (PICOS)

Population	All out of hospital cardiac arrest patients
Intervention	Any intervention involving AED deployment by non-EMS personnel (including police, fire-fighters or community volunteers) designed to reduce the time to defibrillation in OHCA. Interventions that focus on the provision of AEDs in the homes of individuals who are at high risk of cardiac arrest or in hospitals or other high dependency care facilities are ineligible.
Comparator	Routine emergency medical services care.
Outcomes	Survival to hospital discharge

Study type	Randomised and non-randomised controlled trials, controlled before-and-after studies and observational studies with a concurrent or historical comparison group.
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Study quality was assessed using the EPHPP Quality Assessment Tool for Quantitative Studies.^(21;22) This validated⁽²³⁾ tool assesses both internal and external validity and rates study quality as strong, moderate or weak based on a range of criteria relevant to public health studies, which included assessment of the risk associated with;

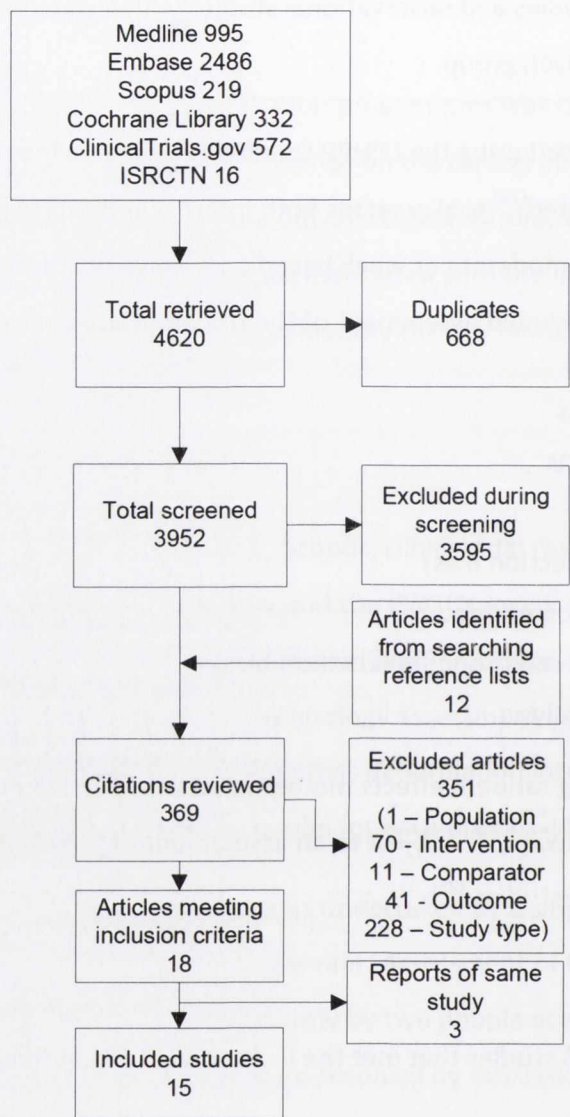
- selection bias
- allocation bias
- confounding
- blinding (detection bias)
- data collection methods
- withdrawals and dropouts (attrition bias)
- statistical analysis

Evidence synthesis using random effects meta-analysis was carried out using Review Manager (RevMan) software,⁽²⁴⁾ subject to an assessment of the clinical and statistical heterogeneity between studies.⁽²⁵⁾

2.2.3 RESULTS

The search identified 15 studies that met the inclusion criteria. A flowchart of the results is shown in Figure 2.1.

FIGURE 2.1 FLOWCHART OF PUBLIC ACCESS DEFIBRILLATION SEARCH RESULTS



Three distinct types of programmes were identified, involving 1) static AED deployment in public areas; 2) mobile AEDs carried by police first responders; and 3) mobile AEDs carried by fire-fighter first responders. Some studies used a combination of these interventions. Details of the PAD intervention, quality appraisal results and a summary of the extracted data for all included studies are shown in Table 2.2

TABLE 2.2 TYPE OF INTERVENTION, QUALITY APPRAISAL AND OUTCOME DATA FOR EACH INCLUDED STUDY

AED Intervention	Study (Country)	Study Design & Quality	Cases		Survival to discharge, n (%)		RR (95% CI)
			Int	Ctrl	Int	Ctrl	
Static AEDs in public places	Hallstrom 2004 ⁽²⁶⁾ (USA)	RCT, Strong	128	107	30 (23)	15 (14)	1.67 (0.95, 2.94)
Fire-fighter first responders	Smith 2001 ⁽²⁷⁾ (Australia)	CCT - Moderate	161	268	6 (4)	11 (4)	0.91 (0.34, 2.41)
	Sweeney 1998 ⁽²⁸⁾ (USA)	Crossover trial- Moderate	110	133	5 (5)	7 (5)	0.86 (0.28, 2.65)
	Kellermann 1993 ⁽²⁹⁾ (USA)	Crossover trial- Moderate	447	432	40 (9)	27 (6)	1.43 (0.89, 2.29)
	Shuster 1993 ⁽³⁰⁾ (Canada)	BA - Weak	140	147	8 (6)	4 (3)	2.10 (0.65, 6.82)
Police first responders	Sayre 2005 ⁽³¹⁾ (USA)	CCT- Strong	154	427	11 (7)	16 (4)	1.91 (0.90, 4.02)
	Myerberg 2002 ⁽³²⁾ (USA)	BA - Weak	420	318	32 (8)	19 (6)	1.28 (0.74, 2.21)
	Groh 2001 ⁽³³⁾ (USA)	BA - Weak	388	472	21 (5)	20 (4)	1.28 (0.70, 2.23)
	Mosesso 1998 ⁽³⁴⁾ (USA)	BA - Weak	132	80	18 (14)	5 (6)	2.18 (0.84, 5.65)
Mixed: Static AEDs in public places + Fire-fighter first responders	Saner 2013 ⁽³⁵⁾ (Switzerland)	BA - Weak	238	46	18 (8)	0 (0)	7.28 (0.45, 118.65)
	Hollenberg 2009 ⁽³⁶⁾ (Sweden)	BA -Weak	863	657	59* (7)	29* (4)	1.55 (1.00, 2.39)
Mixed: Volunteer first responders + Police first responders	Moore 2008 ⁽³⁷⁾ (Northern Ireland)	BA - Weak	330	279	7 (2)	11 (4)	0.54 (0.21, 1.37)

Mixed: Static AEDs in public places + AEDs added to EMS	Cappato 2006 ⁽³⁸⁾ (Italy)	BA - Weak	702	692	31 (4)	10 (1)	3.06 (1.51, 6.18)
Mixed: Police first responders + Fire-fighter first responders	Van Alem 2003 ⁽³⁹⁾ (Netherlands)	Crossover trial - Moderate	243	226	44 (18)	33 (15)	1.24 (0.82, 1.87)
Mixed Intervention: Fire-fighter first responders + AEDs added to EMS	Stiell 1999 ⁽⁴⁰⁾ (Canada)	BA - Moderate	1641	4690	85 (5)	183 (4)	1.33 (1.03, 1.71)

Key: AED – automated cardiac defibrillator; EMS – Emergency Medical Services; Int - intervention; Ctrl – control; RR – Relative Risk; * - Survival at one month post-discharge, RCT – Randomised Controlled Trial, CCT – Controlled Clinical Trial, BA - Before and after comparison,

2.2.3.1 PUBLICLY-ACCESSIBLE STATIC AED PROGRAMMES

One study⁽²⁶⁾ examining the effect of making AEDs available in public places was identified. Two studies^(35;36) combined the placement of AEDs in public venues with equipping fire-fighter first responders with AEDs, so they are discussed separately.

The Public Access Defibrillation (PAD, Hallstrom 2004) trial was a community-based randomised controlled trial that allocated 993 community groups to either a CPR-plus-AED or CPR-only response system.⁽²⁶⁾ Residential and public areas were eligible if they could expect an average of one witnessed event every two years, based on OHCA records or the presence of at least 250 adults aged more than 50 years for more than 16 hours per day at that location. Volunteer responders from these communities were trained in either CPR or CPR-plus-AED. Patients with cardiac arrest due to trauma, drug overdose or other non-cardiac cause were excluded from the analysis.

The authors reported the results of the trial as the absolute number of outcome events in both groups, rather than as a rate based on the total number of presumed or definite cardiac arrests. The rationale for this approach was that more definite cardiac arrests were likely to be recorded in the intervention group, since volunteers with AED training were considered more likely to intervene, and AED electrocardiograms would facilitate better diagnosis of cardiac arrests. However, changing standard effect size calculation methods to adjust for a perceived bias that cannot be accurately measured increases the risk of a type I error from overcompensation. Furthermore, the assumption that volunteers were more likely to respond to an event in the treatment groups does not appear to be supported by the data; resuscitation was attempted in 88 of 97 public OHCA events in the control group and 123 of 139 public OHCA events in the treatment group (RR 1.03, 95% CI 0.94 to 1.12). The potential for bias arising from OHCA events in the treatment group being more likely to receive bystander intervention is minimal, since it is very unlikely that the rate of EMS resuscitation differed for comparable events. For this to have an effect on the denominator, witnessed events with no bystander intervention would have to have a higher chance of not receiving an EMS resuscitation attempt. EMS resuscitation is generally attempted on everyone with non-traumatic cardiac arrest, other than those with obvious signs of death such as rigor mortis or dependent lividity.⁽⁴¹⁾ Given the timeframe for the development of these signs it is unlikely that they would artificially reduce the denominator in the control group (all OHCA events of cardiac origin where resuscitation was attempted). If it is assumed that the effect of these biases is negligible then it should not matter which denominator is used, since the relative risk ratio will remain constant when the denominators in each group are the same. Therefore it is still justifiable to use absolute numbers of survivors as long as both groups can be considered equal in every respect. Stratified randomisation according to both study centre and type of community unit was carried out to ensure that this was the case. However, observed presumed cardiac arrests in the control group occurred more often in residential settings (RR 1.37, 95% CI 1.16 to 1.60) and less often in public settings (RR 0.68, 95% CI 0.56 to 0.83), compared with the treatment group. Since publicly-located AEDs are designed primarily to treat OHCA events occurring in public this may have contributed to increased survival in the treatment group. The major factor contributing to the difference in definite OHCA events of cardiac origin was the number of presumed OHCA events of cardiac cause who

were dead on arrival and so received no EMS resuscitation attempt (86 in control group compared with 62 in the treatment group [RR 1.36, 95% CI 1.03 to 1.79]). Since this is likely related to the greater proportion of residential OHCA in the control group, failing to calculate a survival rate using a comparable denominator (in this case all definite OHCA where resuscitation was started) may overestimate the effect of the intervention. Therefore in this review the primary outcome (survival to hospital discharge) was calculated based on the total number of OHCA where resuscitation was attempted.

Calculated in this way, the results show that although there were twice as many survivors in the intervention group as in the control group, this was not statistically significant (RR 1.67, 95% CI 0.95 to 2.94). The mean estimate of survival was 23% in the intervention group and 14% in the control group, corresponding to a risk difference (RD) of 9% (95% CI 0% to 19%).

2.2.3.2 FIRE SERVICE FIRST RESPONDER PROGRAMMES

Four studies⁽²⁷⁻³⁰⁾ examining the effect of fire-fighter first responder AED programmes were identified. One⁽²⁷⁾ of these compared the intervention to standard EMS care and three studies⁽²⁸⁻³⁰⁾ compared it to a combination of EMS care plus fire-fighter CPR.

Smith et al.⁽²⁷⁾ reported the results of a controlled trial investigating the effect of equipping fire-fighters with AEDs and simultaneously dispatching fire services with ambulance paramedics to emergency calls in Melbourne, Australia. The control area, which was described as being peripheral to the intervention area, was covered by the normal ambulance service only. No difference in survival to discharge was observed between groups, despite a statistically significant reduction in mean time to arrival of an AED-equipped rescuer in the intervention group (mean difference -1.6 minutes, 95% CI -1.99 to -1.21).

Sweeney et al.⁽²⁸⁾ reported the results of a crossover trial conducted in North Carolina, USA, examining the effect of adding AEDs to an existing fire-fighter first-responder service that operated in parallel with an EMS ambulance service. Twenty-four fire companies were selected and trained in the use of AEDs. The group was divided in two and each was allocated AEDs on an alternating basis, rotating every one to two months over the course of the study. The companies without AEDs at a given period continued to be dispatched to

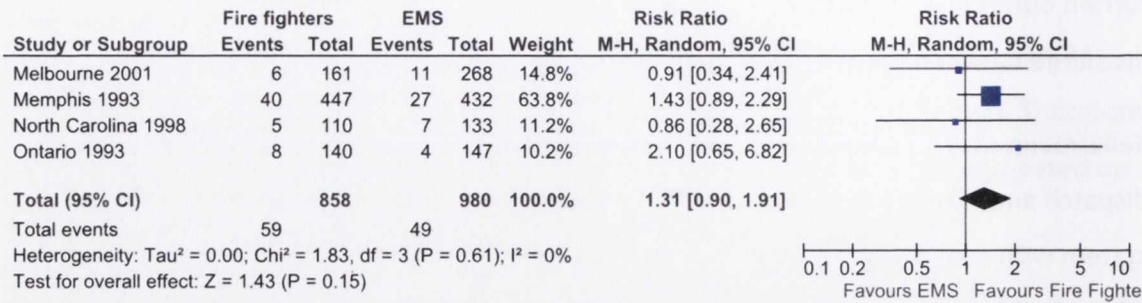
OHCA cases and acted as the control for the group with the AEDs. Exclusion criteria included traumatic arrest, age younger than 12 years, or weight less than 90 pounds. The study was carried out from 1992 to 1995. This study found no significant difference in survival to discharge between the intervention and control groups.

Kellermann et al.⁽²⁹⁾ conducted a crossover trial comparing an EMS system involving dual dispatch ambulance paramedics and AED-equipped firefighter first responders to an EMS system with dual dispatch ambulance paramedics and firefighter first-responders providing CPR only. The study was conducted in Memphis, USA, between March 1989 and June 1992. The study found no statistically significant increase in survival associated with the provision of AEDs to fire-fighter first responders.

Shuster et al.⁽³⁰⁾ conducted a before-and-after comparison to determine the effect of introducing AEDs to an existing fire-fighter first responder system in the region of Hamilton-Wentworth in Ontario, Canada. Control (pre-intervention) data were recorded for the six months prior to AED introduction and experimental data were recorded in the six months afterwards. There was no significant difference in survival from OHCA before and after the intervention despite a decrease in mean time to arrival of an AED-equipped rescuer (mean difference -2.54 minutes, 95% CI -3.45 to -1.63).

Study quality appraisal rated three studies as moderate quality⁽²⁷⁻²⁹⁾ and one as weak.⁽³⁰⁾ Combining the results of all four studies using random effect meta-analysis failed to show a statistically significant effect of the intervention on survival (RR 1.31, 95% CI 0.90 to 1.91, see Figure 2.2). Overall mean survival in the intervention group was 6.1% compared with 4.8% in the control group, corresponding to a risk difference (RD) of 0.01 (95%CI -0.01 to 0.03).

FIGURE 2.2 META-ANALYSIS OF SURVIVAL TO DISCHARGE FOR STUDIES INVOLVING FIRE-FIGHTER FIRST RESPONDERS



2.2.3.3 POLICE FIRST RESPONDER PROGRAMMES

Four studies⁽³¹⁻³⁴⁾ examining the effect of police first responder AED programmes were identified.

Sayre et al.⁽³¹⁾ reported the results of a controlled trial examining the effect of adding AED-equipped police first responders to an EMS system that already included dual dispatch of AED-equipped fire-fighters and ambulance paramedics to suspected OHCA. The study was set in Cincinnati, USA, a city with four separate police districts. One district was chosen for the intervention and the remaining three districts acted as controls. The study duration was two years. Over the course of the study, police were dispatched to more than 60% of treated OHCA in the intervention group. Among the 9.1% of cases where police arrived first at the scene no patient survived to discharge. Results of the study indicated that there was no survival benefit associated with the intervention.

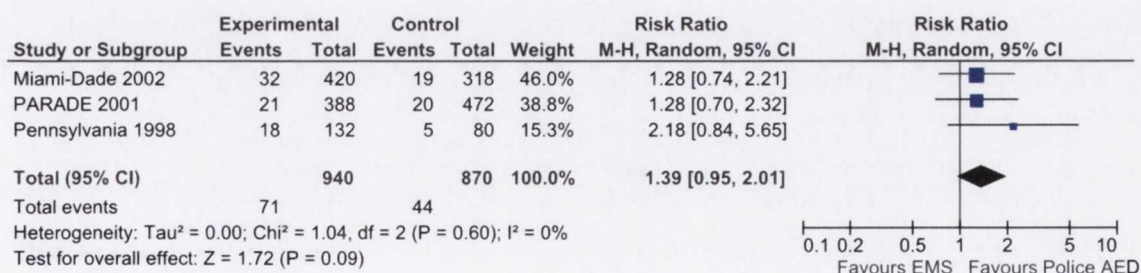
Myerburg et al.⁽³²⁾ described an observational study of a first responder intervention involving 1,900 police officers in Miami-Dade, USA, over the course of six month in 1999. Prior to the intervention the EMS system consisted of a single-tier system involving ambulance dispatch only. There was no significant difference in overall survival rates for OHCA between the periods before and after the intervention. The authors did report an increase in survival for those with a shockable rhythm on first contact (OR 2.1, 95% CI 1.0 to 4.2). There was also a statistically significant decrease in mean time to arrival of an AED-equipped rescuer (mean difference -2.70 minutes, 95% CI -3.19 to -2.21).

Groh and colleagues⁽³³⁾ conducted an observational study to assess the impact of providing AEDs to police first responders in rural and suburban Indiana, USA. Police first responders and usual EMS personnel were dispatched simultaneously to all suspected OHCA. To be included in the study, communities had to have a mean pre-intervention emergency response time of between 8 and 15 minutes. Over the course of the study, police arrived before traditional emergency services in only 7% of cases. There was no significant difference in survival to discharge between the intervention and control groups.

Mosesso et al.⁽³⁴⁾ compared OHCA outcomes in the two years before and three years after the addition of AEDs to an existing police first responder programme in seven suburban municipalities in Pennsylvania, USA, between 1990 and 1995. Despite reduction in mean response times, there was no statistically significant difference in survival to discharge between the two time periods.

One study was excluded from the meta-analysis of police first-responder programmes because the study area had pre-existing dual dispatch of AED-equipped fire-fighters and standard EMS.⁽³¹⁾ Quality appraisal of the remaining three studies⁽³²⁻³⁴⁾ rated them all as weak. Pooled analysis failed to identify a statistically significant impact of police first responder programmes on OHCA survival (RR 1.39, 95% CI 0.95 to 2.01, see Figure 2.3). Overall pooled mean survival in the intervention group was 7.0% compared with 5.1% in the control group, corresponding to a risk difference (RD) of 0.02 (95%CI 0.00 to 0.04).

FIGURE 2.3 META-ANALYSIS OF SURVIVAL TO DISCHARGE FOR STUDIES INVOLVING POLICE FIRST RESPONDERS



2.2.3.4 COMBINED PROGRAMMES

Six studies examined the effect of a combined intervention involving more than one method of providing rapid defibrillation. These included a combination of police and fire-fighter first responders (1 study), fire-fighter first responders in parallel with improvements in the EMS dispatch system (1 study), public provision of AEDs in conjunction with fire-fighter defibrillation (2 studies), simultaneous introduction of AEDs to ambulances and some public areas (1 study), and a programme involving mobile AED provision to trained lay volunteers and police officers (1 study).

Saner et al.⁽³⁵⁾ reported the results of a Swiss study that combined fire-fighters first responders and public AED placement. Over 500 fire-fighters from 36 voluntary fire brigades were trained in the use of AEDs and dispatched to suspected cardiac emergencies at the same time as EMS ambulances. The only public site selected for AED placement was the train station of the largest town in the study area. Data from an 18 month period ending in 1998 was compared to OHCA survival over an eight year period (2001 to 2008) following the introduction of the programme. No statistically significant effect on survival to discharge was found (RR 3.10, 95% CI 0.18 to 53.60).

The SAving Lives in the Stockholm Area (SALSA, Hollenberg 2009) project⁽³⁶⁾ compared OHCA outcomes before and after the introduction of an early defibrillation programme that involved placing AEDs in public venues as well as dispatching AED-equipped fire-fighters in parallel with traditional emergency medical responders to all suspected cases of OHCA. Sixty-five locations were chosen for AED placement, including larger shopping centres, public transport stations, sports stadiums and airports. Forty-three fire stations also received AEDs and first responder training. Where fire-fighters and emergency medical services were dispatched simultaneously, fire-fighters arrived first in 36% of cases. Only three of the 863 OHCA cases occurred in public areas that were equipped with AEDs and none of these patients survived to discharge. The overall results indicated that the intervention was associated with a statistically significant increase in survival at one month (RR 1.59, 95% CI 1.01 to 2.51).

The Northern Ireland Public Access Defibrillation (NIPAD, Moore 2008) study⁽³⁷⁾ used a before-and-after design to estimate the impact of a system that combined lay volunteer and AED-equipped police first responders. Lay volunteers operated a rota, with AEDs being kept in the possession of the person who was on-call at any particular time and brought to the cardiac arrests in the volunteer's own vehicle. Police AEDs were kept in police patrol vehicles. In cases of dual dispatch, first responders arrived before emergency medical services in 23% of cases, but no significant effect on survival to discharge was reported.

The Brescia Early Defibrillation Study⁽³⁸⁾ (BEDS, Cappato 2006) combined the public placement of seven AEDs with the addition of 42 AEDs to an ambulance service already equipped with manual defibrillators. No information was provided on how the specific sites for AED installation were chosen. A historical cohort of 692 patients treated between 1997 and 1999 were used as the control group. Over the course of the study (2000 to 2002) 702 arrests were recorded. This study reported a significant improvement in survival to discharge (RR 3.15, 95% CI 1.53 to 6.48).

Van Alem et al.⁽³⁹⁾ conducted a crossover trial examining the effect of the introduction of an AED programme involving both police and fire-fighter first responders in Amsterdam, the Netherlands, between 2000 and 2002. The study groups both consisted of one fire brigade region and three police districts. Allocation of AEDs was rotated between groups every four months, with the group without AEDs at any one time serving as controls. Police were dispatched during both the experimental and control periods while the fire brigade was dispatched during the experimental periods only. No significant difference in survival to discharge (RR 1.29, 95% CI 0.79 to 2.12) was observed.

The Ontario Prehospital Advanced Life Support (OPALS, Stiell 1999) study⁽⁴⁰⁾ was a three phase before-and-after trial that examined the effect of a number of interventions designed to improve survival following OHCA. The first phase involved the introduction of ambulance AEDs and established a baseline for subsequent comparison. The second phase assessed the impact of a rapid defibrillation programme that included: 1) reduction in dispatch times; 2) more efficient deployment of existing ambulances; and 3) fire-fighter first responders equipped with AEDs. Results showed improved survival to discharge (RR 1.35, 95% CI 1.03 to 1.75).

2.2.3.5 OUT-OF-HOSPITAL CARDIAC ARREST IN CHILDREN

Paediatric OHCA were explicitly excluded from the study population in 11 of the 15 studies identified. Eligibility criteria ranged from ≥ 8 years^(26;31) to ≥ 18 years.^(33;34;39) The mean age of the population in the four studies that included all OHCA was greater than 60 years. Therefore no evidence was identified on the effect of public access defibrillation in paediatric populations.

The optimal energy dose for paediatric defibrillation is unknown.⁽⁴²⁾ It is recommended that AEDs with dose attenuators are used to avoid high defibrillation doses in children between one and eight years of age and manual defibrillation is recommended in children less than one year old.⁽⁴³⁾ Descriptive studies of paediatric out-of-hospital cardiac arrests have found inconsistent results; some show a positive association between public access AED use and survival at one month⁽⁴⁴⁾ while others show no significant survival benefit associated with defibrillation prior to hospital arrival.⁽⁴⁵⁾

A 2004 consensus statement from the American Heart Association suggested that an AED be placed in all schools with a reasonable probability of cardiac arrest in the next five years, those with any student at high risk, or those schools with an emergency to shock time of greater than five minutes.⁽⁴⁶⁾ Review of school-based AED programmes^(47;48) reported some promising results, but no strong evidence of the effectiveness of this intervention was identified. Studies reporting data that do not support the suggestion that all schools should be equipped with defibrillators have also been published.⁽⁴⁹⁾

2.2.3.6 FACTORS AFFECTING SURVIVAL IN OUT-OF-HOSPITAL CARDIAC ARREST

The results of the systematic review search were combined with those of a separate search in Medline and Embase for data on factors predicting survival in OHCA to identify which characteristics are most strongly associated with improvements in this outcome.

A systematic review⁽¹⁶⁾ of predictors of survival in OHCA that pooled data from 79 studies involving 142,740 patients showed that among the strongest predictors of survival are return of spontaneous circulation (ROSC, chances of survival increase by 16% to 34%), initial shockable rhythm (15% to 23%), arrest witnessed by either a bystander (6% to 14%) or EMS

(5% to 18%) and receiving bystander CPR (6% to 14%). The combination of initial VF rhythm and ROSC is highlighted in a survival model⁽⁵⁰⁾ based on US registry data that found survival among this group was 54%. Regression analyses of data from studies^(33;40;51-53) involving public access defibrillation have generally identified the same predictors of increased survival. However, not all have found a significant association between survival and bystander CPR⁽⁵³⁾ or increasing age.⁽⁵¹⁾ The interdependency that exists between predictors of OHCA survival makes it difficult to identify specific targets for improvement. That a shockable rhythm is a stronger predictor than response time has been explained by the fact that an initial VF rhythm 'tends to occur where the underlying pathology is not inevitably fatal, and it also acts as a surrogate for response interval since asystole ensues in all cases within minutes'.⁽⁵⁴⁾ Other variables that are also unlikely to be independent include location of arrest, which affects response times, and age, which can be a surrogate for co-morbidity. Some clinical attributes associated with improved survival, such as ROSC, are only available after resuscitation has started and so cannot be directly targeted by an intervention like public access defibrillation. Given these interdependencies the available evidence on predictive factors is considered to 'fundamentally reflect the time to effective first aid (CPR) or definitive treatment, together with comorbidity and underlying pathophysiology for which first observed rhythm is a surrogate'.⁽⁵⁴⁾

The relationship between survival and EMS response time is, therefore, of central importance since it provides the rationale for rapid defibrillation. In an analysis of 3,263 witnessed VF OHCA's over a ten year period, Gold et al.⁽⁵⁵⁾ reported that survival does not decline at a constant rate over time. They noted no appreciable decline in survival for those treated between one and four minutes after collapse, a 5.2% absolute reduction in survival per minute for those treated within five to ten minutes, and a 1.2% reduction in survival per minute for those treated 11 to 15 minutes after collapse. However, not all studies support the notion that there is no significant decline in the odds of survival over the first four or five minutes,⁽⁵⁶⁾ and a study examining the relationship between out-of-hospital cardiac arrest survival and response times in England⁽⁵⁷⁾ that modelled survival as a linear function of time estimated that a one minute reduction in response time was associated with a 24% increase in the odds of survival. Despite the different findings regarding the first few minutes

immediately after an arrest, the significant benefit associated with achieving EMS response times within four or five minutes has been highlighted by a number of studies.^(58;59) This finding is consistent with the three-phase model of cardiac arrest⁽⁶⁰⁾ that describes an initial electrical phase lasting approximately four minutes, during which defibrillation is most effective.

A number of large-scale population-based case series involving public access defibrillation are available that report overall outcomes in the study area, without the benefit of a control group against which to estimate effect. These can provide useful data on the implications of introducing public access defibrillation programmes outside of an experimental study setting.

Kitamura et al.⁽²⁰⁾ reported a large case-series of all OHCA in Japan between 2005 and 2007 where resuscitation was attempted. Over the course of this period a number of public and private initiatives were put in place to increase the availability of AEDs, which saw the total number of public access defibrillators increase from 9,906 (7.8 per 100,000 population) to 88,265 (69 per 100,000 population). These AEDs were located in a range of locations including schools (25%); medical/nursing facilities (19%); workplaces (16%); sports (4%), cultural (3%) or public transport (3%) facilities. Resuscitation was attempted on a total of 168,827 OHCA of cardiac origin, of which 55,271 (33%) were witnessed by bystanders and 12,631 (7%) had a shockable rhythm. The first shock was delivered by public access AEDs in 462 cases (3.7%), by EMS in 11,697 cases (92.6%) and in 472 cases (3.7%) no shock was delivered. Survival at one month with minimal neurological impairment was 32% in the public access AED group compared with 14% in the EMS group. Over the three years, a statistically significant increasing trend was reported for bystander initiated CPR (43% to 54%), ROSC (21% to 28%), survival at 1 month (19% to 28%) and neurologically intact survival at 1 month (11% to 19%) in the subset of bystander-witnessed VF OHCA. Multivariate regression analysis found that earlier administration of shock and earlier initiation of CPR were associated with a good neurologic outcome, but whether the shock was provided by bystanders or EMS personnel was not. When the group who received a first shock from a public AED were examined in isolation, regression analysis found that

increasing availability of AEDs was associated with a reduced time from collapse to defibrillation and an increased probability of neurologically intact survival.

A population-based cohort study⁽⁶¹⁾ carried out in the US and Canada between 2005 and 2007 compared survival in cases where an AED was applied before the arrival of EMS to cases where bystander CPR was initiated without the use of an AED. Among a total of 13,769 OHCA included in the study, 32% (4,402) received bystander CPR and 2% (289) had an AED applied before the arrival of emergency medical services. Pre-EMS defibrillation was mainly performed by lay volunteers (35%), healthcare workers (32%) or police (26%). Overall survival to discharge was 7%. No details are provided on the diffusion of PAD programmes in the study area. The main objective of the study was to examine the association between pre-EMS AED delivery and survival by performing a multivariate regression analysis adjusting for factors such as age, gender, CPR initiation, location (public or private), EMS response times and initial rhythm. Results showed that early AED application was associated with increased survival (OR 1.75, 95% CI 1.23 to 2.50). The study does not reveal the extent to which public access defibrillation programmes actually increase AED use.

An analysis of registry data on almost 20,000 OHCA events in Denmark⁽⁶²⁾ between 2001 to 2010 found that a shockable rhythm, bystander witness and bystander CPR were all strongly associated with 30-day survival, which increased from 3.5% to 10.8% over the course of the study period. Public access defibrillation was only introduced in Denmark towards the end of the study period so rates of bystander defibrillation were low throughout (1.1% in 2001, 2.2% in 2010). However, when used, bystander defibrillation was positively associated with survival (OR 4.4, 95% CI 3.3 to 6.0). A subsequent case series study⁽¹⁹⁾ examining the results of the Danish PAD programme reported that 48 (6%) of the 807 AEDs included in the study were connected to an OHCA victim in the first 28 months of the intervention and that the 30-day out-of-hospital cardiac arrest survival rate was 52%.

In summary, time from collapse to either CPR or defibrillation is the most important predictor of OHCA survival that can be directly affected by PAD interventions. The greatest improvement in survival occurs when this time period is less than four minutes. Large case series have reported that increasing availability of public AEDs is associated with a reduction in the time from collapse to defibrillation and improved outcomes for patients. However,

data on the strength of this association are lacking and more work needs to be done to fully understand how diffusion of publicly available AEDs in urban and rural environments impacts on OHCA survival.

2.2.3.7 SAFETY

Potential safety implications associated with PAD interventions include failure to access or dispatch AEDs when required, device malfunction, injury to patients or first responders (e.g. from improper use or inappropriate shocks) and adverse psychological reactions in responders.

No major adverse events were reported in the included studies. Only four^(28;34;36;63) studies reported specific incidents that led to the failure of an AED to be dispatched or to function correctly. These included two studies^(28;34) published in 1998 that reported a total of nine cases of device failure due to 'electrode drying' (3 cases), no shock and subsequent inability to recover data (4 cases), recurrent 'connect electrode' prompt from the device which prevented analysis (1 case) and inability to read the LCD screen because of cold temperature (1 case). A more recent study (2009) in which AED-equipped first responders were dispatched to only 66% of treated cardiac arrests in the study area reported that the most common reason for dispatch failures and delays were difficulties identifying true cases of OHCA at the time of the emergency call.⁽³⁶⁾ A comprehensive analysis of adverse events occurring during the PAD trial⁽⁶³⁾ reported 36 incidents from 649 presumed OHCA events. There were two patient-related adverse events (rib fractures) not related to AED use. Seven first responder adverse events were reported, including one pulled muscle, four cases of increased emotional stress and two responders who felt pressured into participating by their employer. No first responder was harmed by an AED. There were 27 device-related adverse events; 20 devices were stolen, three were moved to locations that were inaccessible and there were four incidents of mechanical difficulty or battery failure (none of which affected patient safety as another AED was available). There were no inappropriate shocks administered and no device failed to shock when indicated.

A qualitative study⁽⁶⁴⁾ examining the psychological profile of PAD first responders was carried out in the UK in 2008 to gain insight into possible factors contributing to the

seemingly low incidence of adverse psychological reactions compared with professional ambulance crews who attend traumatic events. The results highlighted the importance of having confidence in being able to perform as trained, a realistic appreciation of one's own limitations as a lay responder and an ability to act with emotional detachment when required. An element of self selection appears to be at work, since these protective characteristics appeared to be present without formal training.

The issue of device accessibility in programmes that involve static AEDs located in public areas was examined in the context of the Danish PAD scheme,⁽⁶⁵⁾ which is based around a voluntary network of AEDs in sports and transport facilities, residential areas, private businesses and public buildings. A database of all registered devices is used by EMS dispatch centres to identify the nearest AED in the event of a cardiac arrest. All AEDs registered in Copenhagen were included in the study (n=552), approximately half of which were located in government or municipal buildings. The study found that only 9.1% of all AEDs were accessible 24 hours a day, seven days a week and that AED coverage decreased by 53% during the evening, night-time and weekends, which is when 62% of all cardiac arrests in public locations occurred. A similar analysis examined the extent of public defibrillator use in Hampshire, UK, where programmes to raise public awareness and make public defibrillators available have been running for the past 12 years.⁽⁶⁶⁾ The study area had a total of 673 public defibrillators in 278 locations, including shopping centres, commercial properties and GP surgeries. The local ambulance service maintained a database of known defibrillator locations, aimed at improving the use of these devices in OHCA. Results showed that 1,035 OHCA calls to the ambulance service were received during the one year study period, with the caller being aware of an AED being available in 44 cases (4.3%). Of these, the AED was retrieved and attached to the patient prior to the arrival of ambulance paramedics in 18 cases (41%). Overall, public access AEDs were successfully deployed prior to the arrival of EMS in only 1.7% of all OHCA events.

Two studies^(67;68) examining safety and reliability of AED devices were identified, both of which used FDA-compiled data. A review⁽⁶⁷⁾ of recalls and safety alerts in the US between 1996 and 2005 found that 21% of AEDs were affected and every major AED manufacturer recalled products over the ten year study period. The most common reasons for issuing an

FDA advisory were electrical (15%), cable (13%) or software (12%) issues, failure to shock (10%) and failure to detect (8%). A more recent study⁽⁶⁸⁾ analysed all adverse event reports where a patient died between the years 1993 and 2008. A total of 1,150 events were identified. The most common device failures occurred during the attempt to charge and deliver the intended shock (45%) or when the device powered on, but failed to complete rhythm analysis (22%). A cause of device failure could be identified in approximately 80% of cases, with pads/connectors (24%) and battery/power (23%) being the most frequently cited components. Backup devices were mentioned in 41% of reports and backup units delivered shocks to the patient in approximately one third of cases.

In summary, the risks posed to patients and the public from PAD interventions are small and the devices themselves are generally regarded as reliable and safe when used properly. However, maintaining the accessibility of these devices and ensuring that they are used when an OHCA occurs nearby has been reported as being problematic in some areas that have achieved large scale diffusion of public AEDs.

2.2.3.8 APPLICABILITY OF THE RESULTS IN AN IRISH CONTEXT

The major limitations to directly applying the results of the identified studies in an Irish context are differences in the setting (demographics and population density), the context (existing EMS infrastructure, prior diffusion of AEDs) and the intervention (configuration of PAD programme). Results obtained in individual studies were dependent on the interaction of all three of these factors, so even adjusting for differences between Ireland and a given study setting in any one domain does not allow for a reliable estimate of the expected clinical impact.

In terms of setting, the chief limitation was that no study described a national programme that included a broad range of areas with different population densities. In studies that did include both urban and rural areas the number of AEDs and OHCA events was small. Included studies also differed in the type of EMS service that existed at baseline and the extent to which publicly-accessible AEDs were already available. Median EMS response times in the control arms of included studies was 7.5 minutes, compared with 11 minutes in Ireland⁽⁶⁹⁾ and Ireland already has widespread ad-hoc deployment of AEDs on a voluntary

basis. The type of PAD intervention described in studies also differed considerably from that which is outlined in the proposed legislation, which provides for the deployment of AEDs in an extensive list of designated places throughout the country.

2.2.4 DISCUSSION

Automatic external defibrillators (AEDs) were introduced in all ambulance services in Ireland in the late 1990's,⁽⁷⁰⁾ almost 30 years after Pantridge and Geddes became the first to report the use of mobile defibrillation units to treat OHCA's in Belfast.⁽⁷¹⁾ Research interest in the provision of AEDs to lay first responders through the implementation of PAD programmes has grown substantially in recent years and a wealth of literature exists on this topic. However, the results of a systematic review of effectiveness found that relatively little of this published material consists of experimental studies comparing these types of intervention to routine EMS care. Fifteen primary studies were identified, which examined three main types of PAD programme: firefighter first responders, police first responders and public AED provision for use by bystanders who witness an OHCA. Assessment of study quality using a validated appraisal tool rated eight studies as weak, five as moderate and two as strong. The most common type of study design was a before-and-after comparison of cross sectional data within the study area, which was used in nine of the 15 included studies. The other six studies were controlled clinical trials, one of which was randomised. The scarcity of RCT data likely reflects the difficulty in conducting adequately powered trials given the logistical complexity of these interventions and the relatively low incidence of OHCA.

This review failed to identify any comparative studies showing a statistically significant improvement in survival when firefighter first responder AED programmes are added to standard EMS care. Pooled data from four studies comparing these two interventions also failed to show a significant effect. While not statistically significant, the overall mean estimate of survival in the intervention group was 1% higher than in the control group (95% CI -1% to 3%). Results of studies involving a combination of firefighter AED provision and EMS dispatch improvement⁽⁴⁰⁾ or public AED provision⁽³⁶⁾ showed an improvement in OHCA survival (RR 1.35 [95% CI 1.03 to 1.75] and RR 1.59 [95% CI 1.01 to 2.51], respectively), but a

combined firefighter and police AED programme⁽³⁹⁾ did not. A lack of overall consistency of findings was also apparent; the firefighter plus public AED trial⁽³⁶⁾ found that survival at one month was improved, but survival to hospital admission was not, while the firefighter plus police first responder study⁽³⁹⁾ found improved survival to hospital admission, but no difference in survival to discharge.

No study examining police first responder AED programmes reported a significant OHCA survival benefit and a meta-analysis of all three studies comparing police AED provision with routine EMS care also failed to identify a significant beneficial effect. Although not statistically significant, the mean estimate of effect in all three studies favoured police first responder AED provision and showed an overall mean increase in survival of 2% in the intervention group compared with controls (95% CI 0% to 4%). A combined intervention involving police and lay first responders in Northern Ireland⁽³⁷⁾ reported no benefit compared with routine EMS care.

The most positive result of all the identified studies (BEDS study, Italy)⁽³⁸⁾ involved a combined intervention that saw 42 AEDs being added to the existing EMS and seven AEDs installed in public locations in the study area (survival to discharge RR 3.15, 95% CI 1.53 to 6.48). The fact that the majority (85%) of study AEDs were added to the existing EMS system, coupled with the lack of information on how public areas were selected and the fact that only 16% of survivors were treated with a public AED, limits the applicability of these results.

The best evidence for the effect of the public provision of AEDs comes from the PAD trial,⁽²⁶⁾ which compared CPR plus AED training combined with public AED provision to CPR training alone. When survival to discharge in the PAD trial was calculated as a rate (as opposed to the absolute number of survivors in each group, see section 2.2.3.1), the difference between groups was not statistically significant (RR 1.67, 95% CI 0.95 to 2.94), despite there being twice as many survivors in the intervention group (30, compared with 15 in the control group). This corresponds to an overall mean increase in survival of 9% in the intervention group compared with the control group (95% CI 0% to 19%). A significant

beneficial effect was observed for survival to admission (RR 2.06, 95% CI 1.41 to 3.01) and neurologically intact survival (RR 2.63, 95% CI 1.30 to 5.31).

PAD interventions are generally considered safe for both patients and rescuers. No serious adverse events were reported in included studies. Among the less serious events associated with public access defibrillation include increased emotional stress in responders, AED battery failure and devices being placed in inaccessible locations. No studies reported the delivery of inappropriate shocks and no study published after 1998 reported device failure that prevented the use of an AED on a patient.

Defibrillation is the definitive treatment for ventricular fibrillation (VF).⁽⁷²⁾ The rationale for public access defibrillation is that it reduces the time from cardiac arrest to first shock, resulting in more people being treated before VF deteriorates to asystole. To examine this premise and provide additional context to the systematic review results, an analysis of population-based registry data was carried out to identify the degree to which changes in response times can independently predict improvements in survival. This concluded that the three most important factors associated with OHCA survival are time to CPR initiation, time to defibrillation and the initial rhythm detected, with initial rhythm acting as a surrogate for underlying pathology and being dependent to some extent on response time. There were conflicting reports of the effect of elapsed time on the odds of survival, but broad agreement that the strongest positive association was observed when response time was dichotomised at four minutes.

In many developed countries, public access defibrillation has been given a prominent role in efforts to increase survival rates from cardiac arrest. Various patient groups and professional bodies have published statements in support of PAD interventions including the American Heart Association (AHA),⁽¹⁷⁾ the American College of Emergency Physicians (ACEP),⁽⁷³⁾ the European Society of Cardiology (ESC) and European Resuscitation Council (ERC).⁽¹⁸⁾ The need for effective initiatives in this area is apparent from the fact that OHCA survival rates have not significantly improved over the last 30 years despite the development of new treatments and widespread introduction of evidence-based guidelines.⁽¹⁶⁾ The lack of progress in this area has been attributed to a combination of ageing populations,⁽⁷⁴⁾ longer EMS response times due to growing urban populations⁽⁷⁵⁾ and

a declining incidence of VF arrests.^(76;77) Improved secondary treatment of ischemic heart disease⁽⁷⁸⁾ and the use of implantable cardioverter-defibrillators⁽⁷⁹⁾ have been identified as contributing factors to the observed decline in VF arrests.

Despite the widespread support for PAD interventions, caution needs to be exercised in relation to their practical implementation and expected benefits. This review found that the majority of studies were of poor methodological quality and therefore at high risk of bias. Results from the single RCT on publicly-accessible AEDs may have limited transferability beyond the specific setting and EMS system in which it was conducted. Consideration must be given to how well EMS response times and AED placement in specific studies align with any prospective PAD programme in Ireland, and whether the temporal and spatial characteristics of OHCA arrest in this country are sufficiently similar to those of the study settings to justify an expectation of similar clinical outcomes. As pointed out elsewhere,⁽⁸⁰⁾ inappropriate placement and maintenance of AEDs can seriously undermine their effectiveness and lead to a decline in the organisational structure of the programme. Unrealistic expectations of the overall impact on OHCA must also be tempered by the fact that over 70%⁽⁸¹⁻⁸³⁾ of OHCA in Ireland occur in the home, so the impact of PAD on overall survival is likely to be low.

2.2.5 Conclusion

There is widespread international support for the introduction of PAD programmes and evidence from a range of sources indicates that decreasing the time from collapse to defibrillation is an essential part of improving survival in OHCA. However, there is less agreement on what type of programme should be implemented. Although the clinical justification for any system of rapid defibrillation appears strong, there is currently a lack of evidence demonstrating the effect of these interventions in practice. Many of the studies identified in this review were of poor methodological quality and in some the intervention included AEDs being added to EMS, which by now is standard practice. The highest quality evidence available is for the provision of static AEDs in public areas, with results indicating that when placement is carefully considered and appropriate training is provided this type of intervention is associated with a greater improvement in OHCA survival than firefighter or police first responder programmes.

2.3 COST-EFFECTIVENESS OF PUBLIC ACCESS DEFIBRILLATION

2.3.1 INTRODUCTION

This chapter reviews the existing evidence on the cost-effectiveness of international PAD programmes and describes a de novo decision analysis model comparing the cost-effectiveness of a number of potential configurations of an Irish PAD programme based on the mandatory provision of static AEDs in designated building types, compared with the current standard of care involving undirected AED provision on a voluntary basis.

2.3.2 REVIEW OF ECONOMIC ANALYSES OF PUBLIC ACCESS DEFIBRILLATION

A review of cost-effectiveness studies was carried out to assess the available cost-effectiveness evidence for PAD interventions and inform the economic analysis of a prospective Irish PAD programme. Studies were included if they compared the costs and consequences of PAD to routine EMS care for OHCA events that occurred in a public place or modelled the expected clinical and/or cost implications of different PAD programme configurations.

2.3.2.1 METHODS

A search was carried out in Medline, Embase, NHS Economic Evaluation Database (EED), Health Economics Evaluation Database (HEED) and the HTA database for economic analyses of PAD programmes. The search in Medline and Embase was carried out in tandem with the systematic review of clinical effectiveness (see Appendix 2.1). No methodology filters were used in that search so the returned results included economic analysis studies. These were identified and recorded during the screening and review process. Searches in NHS EED and the HTA database were performed in the Cochrane library and searches in HEED were performed in the HEED search portal (Wiley online library) up until May 2014.

2.3.2.2 RESULTS

A total of 16 relevant studies were identified (see Table 2.3).

TABLE 2.3 PAD COST-EFFECTIVENESS LITERATURE SEARCH RESULTS

Citation Database	Relevant Studies
Medline & Embase	8
HTA Database	2
NHS EED	8
HEED	11
Total	29
Duplicates	12
Reports of same study	1
Unique studies	16

The year of study publication spanned from 1990 to 2013. There was a high degree of heterogeneity in study design, setting, measured outcomes and included costs. The identified studies included 14 modelled cost-effectiveness studies and two costing studies (Table 2.4).

2.3.2.3 COST-EFFECTIVENESS STUDIES

Overview of studies

Fourteen studies reporting the results of economic analyses of rapid defibrillation programmes were identified. Eleven of these were set in North America, with one set in each of Scotland, Sweden and Denmark. There was significant heterogeneity in the type of PAD intervention assessed. Four studies evaluated static AED provision across a range of public locations, with six others examining AED provision in only one particular type of setting (casinos, long-term care facilities, homes of high risk patients, aircraft or schools). Four studies modelled rapid defibrillation programmes involving mobile AEDs carried by police, firefighters or voluntary first responders. All decision analysis models consisted of a decision tree structure to model patients until hospital discharge, with studies that examined longer term outcomes adding a Markov component to model successive years post-discharge. Further details on each included study are provided in Appendix 2.2.

TABLE 2.4 SUMMARY OF PAD COST EFFECTIVENESS STUDIES

Study	Intervention	Results
Nichol 2005 ⁽⁸⁴⁾ and 2009 ⁽⁸⁵⁾	CEA based on the PAD trial (CPR only versus CPR+AED)	Defibrillation by volunteers was associated with an incremental cost of \$46,700 (€44,900) per QALY
Folke 2009 ⁽⁸⁶⁾	Public access defibrillation scheme in Copenhagen, Denmark	Incremental cost per QALY calculated for different AED placement strategies; \$33,100 (€28,900) for ERC guidelines*; \$51,100 (€44,500) for AHA guidelines**; \$79,400 for existing placement and \$135,900 (€118,500) for unguided total coverage of city
Walker 2003 ⁽⁸⁷⁾	Deployment of AEDs in all major airports, railway and bus stations in Scotland	Total direct costs to the ambulance service of deploying 31 AEDs in 17 sites was £18,325 per year. QALY gain was 0.44, giving a cost per QALY gained of £41,146 (€62,300)
Cram 2003 B ⁽⁸⁸⁾	AEDs in selected public locations such as airports, sports venues, hotels and restaurants. Sites assumed to have a 20% annual probability of an OHCA	Outcomes were reported per site; mean annual cost was \$3,400 and QALY gain was 0.114, giving an annual cost of \$30,000 per QALY gained (€31,300)
Sund 2012 ⁽⁸⁹⁾	Dual dispatch of EMS and fire services in Stockholm	16 additional lives saved and cost per life saved of €60,000
Nichol 2003 ⁽⁹⁰⁾	Public access defibrillation by lay responders in casinos in the US	Public access defibrillation provided by non-traditional responders in a casino setting had an incremental cost of \$56,700 (€57,900) per additional QALY. If responder wages while being trained were included this rose to over \$100,000 per QALY
Groenveld 2005 ⁽⁹¹⁾	Training unselected laypersons in CPR/defibrillation and deploying AEDs in their own home	Cost per trainee was \$62 and each trainee yielded 2.7 quality-adjusted hours of survival, giving a cost per QALY of \$202,400. Home AED deployment increased the cost per QALY to \$2,489,700 (€2.5M).
Berger 2004 ⁽⁹²⁾	AED deployment in public high schools in the USA	If the intervention saves 5 people over 5 years it was calculated to have an ICER of \$108,344 (€122,100) per life year gained. If it saved 10 people over 5 years the resulting ICER would be \$55,897 (€63,000)
Cram 2003 A ⁽⁹³⁾	AED deployment on commercial aircraft	Aircraft AED deployment increased survival to discharge from 2.1% to 16.7%, cost of AED deployment \$5million, cost per QALY gained was \$34,000

Forrer 2002 ⁽⁹⁴⁾	Police AED programme in four suburban communities in the US	Time from call to first shock reduced by 1.8 minutes, with a resulting estimated survival benefit of 0.24 lives saved per year, giving a cost per year of life saved of \$16,060 (€19,200)
Groeneveld 2001 ⁽⁹⁵⁾	AED deployment on US commercial aircraft	Deploying AEDs on all commercial aircraft would save 33 additional lives annually, with an ICER of \$94,700 (€100,500). Only deploying AEDs on large commercial aircraft would save an additional 7 lives per annum with an ICER of \$35,300 (€37,400)
Foutz 2000 ⁽⁹⁶⁾	Placing AEDs in long-term care facilities (LTCF) in Cincinnati, Ohio, USA	5 additional lives saved (survival rate increased from 1.25% to 4.4%) at a cost of \$439,185, giving a cost per life saved of \$87,837 (€99,000)
Jermyn 2000 ⁽⁹⁷⁾	Firefighter first responder programme in urban and rural Australia.	Cost per life saved was AUS\$6,776 in urban areas and AUS\$49,274 in rural areas.
Nichol 1998 ⁽⁹⁸⁾	Public access defibrillation involving lay responders or police	Public access defibrillation was associated with a median incremental survival of 0.7% and a median cost per additional QALY of \$44,000 (€32,600). In an urban emergency medical services system with an overall survival rate of 8%, a police AED programme was associated with a median cost of \$27,200/QALY

CEA – Cost effectiveness analysis, PAD – Public access defibrillation, CPR – Cardiopulmonary resuscitation, AED – Automatic external defibrillator, QALY – Quality Adjusted Life Year, OHCA – Out of hospital cardiac arrest, * European Resuscitation Council (ERC) guidelines recommend placement of AED in locations with an incidence of one cardiac arrest every two years.⁽⁹⁹⁾ ** American Heart Association (AHA) guidelines recommend placement of AED in locations with an incidence of one cardiac arrest every five years.⁽¹⁰⁰⁾

Quality of included studies

Modelled cost-effectiveness studies were assessed using the ISPOR questionnaire to assess the relevance and credibility of modelling studies.⁽¹⁰¹⁾ Relevance was assessed on the grounds of the study population, characteristics of the intervention, outcomes measured and the overall study context. The credibility of the results was considered using criteria related to the design, validation and analysis methods, the quality of the data used, as well as how the results were reported and interpreted and whether the authors had any conflicts of interest. In all, studies were rated on a total of 11 criteria, with eight of the 14 studies fulfilling six or more. Results of the quality assessment are provided in Appendix 2.3.

Clinical outcome data

Nine studies used estimates of survival to hospital admission and discharge from parallel clinical studies or the available literature at the time the analysis was performed.^(85;86;88;89;91;93;95;97;98) Others used local registry OHCA data⁽⁹⁶⁾ or modelled the increase in survival as a function of reduced response times.⁽⁹⁰⁾ One study estimated outcomes by assuming that all OHCA in PAD areas would have the same outcomes as those with an EMS response time of less than three minutes.⁽⁸⁷⁾ The time horizon used in the majority of studies (10/14) was the lifetime of OHCA patients. The other four studies used a time horizon of between four and 10 years. Long-term quality of life data associated with different levels of neurological impairment post-discharge were taken from the literature. In addition to the utility gain for those who survive an OHCA, one study applied a small passive utility benefit for all people who could potentially benefit from the intervention, due to an increased sense of security believed to be provided by a PAD scheme.⁽⁹³⁾

Cost data

The majority of studies (9/14) adopted a societal perspective, with the remaining studies taking the perspective of either the health service only or the health and police/fire service, depending on the type of programme. Equipment costs were taken from clinical studies (where the cost-effectiveness analysis was being conducted alongside a study) or obtained from suppliers. Annual maintenance costs for AEDs were based on surveys of suppliers or as a percentage of the total device cost. An estimate of the lifespan of AED devices was obtained from device manufacturers. Training costs were handled differently in a number of studies: some obtained costs from training providers or based it on instructor wages,^(88;90;97) while others included the cost to employers for trainee time at the routine average hourly rate,⁽⁹⁵⁾ or at a reduced level of one third of the average hourly rate.⁽⁹¹⁾ One study combined annual training and maintenance costs as a percentage of the unit cost of the device;⁽⁹⁸⁾ two studies did not include training costs at all.^(92;93) Treatment costs were generally obtained from the literature or from parallel clinical studies. One study did not include treatment costs on the basis that they were equal for both comparators.⁽⁹⁸⁾ Only two studies^(86;94) did not discount future benefits or costs. With the exception of one study that used differential discounting of benefits and costs (1.5% and 6%, respectively),⁽⁸⁷⁾ the discount rate used was

3%, 4% or 5%. Costs reported in each of the studies were inflated to 2013 using the local consumer price index and expressed in Irish Euro using the purchasing power parity exchange rate.⁽¹⁰²⁾

Summary of results – static AEDs located in public areas

Five studies reported cost-effectiveness results for programmes involving static public AEDs, reporting ICERs ranging from €28,900/QALY to €62,300/QALY.^(85-88;90)

A 2003 US study, examining a strategy of placing AEDs in selected public locations assumed to have a 20% annual probability of an OHCA event, calculated a cost per additional quality-adjusted life year (QALY) gained of €31,300.⁽⁸⁸⁾ This contrasts with a 2009 study based on the Copenhagen PAD scheme that calculated a cost per QALY gained of €44,500 based on AED placement in areas with a 20% annual risk of an OHCA event.⁽⁸⁶⁾ This study also calculated results for different placement strategies, highlighting the importance of guided placement of AEDs in PAD programmes. The European Resuscitation Council (ERC) recommendation of placing AED in locations with at least a 50% annual probability of an OHCA resulted in a cost per QALY gained of €28,900, whereas unguided placement resulted in a cost of €118,500 per additional QALY.⁽⁸⁶⁾ The economic evaluation carried out as part of the PAD trial (US and Canada) reported the cost-effectiveness of volunteer CPR training plus AED provision compared with volunteer CPR training only and calculated an incremental cost per QALY of €44,900.⁽⁸⁵⁾ This study involved AED placement in residential and public community areas with at least a 50% annual probability of a cardiac arrest (as evidenced by OHCA records) or the equivalent of at least 250 adults aged more than 50 years present at that location for more than 16 hours per day.

Some of the best clinical results for PAD programmes have been observed in casinos, where there are large numbers of security personnel available to respond to an OHCA event and public areas are constantly monitored by CCTV to detect unusual activity. A 2003 US analysis of casino-based PAD programmes calculated a cost per QALY gained of €57,900.⁽⁹⁰⁾ This analysis included the wage costs of training instructors, but not the wage costs for employees receiving training, on the basis that it would occur during their regular duties.

When the opportunity cost of the time needed for training is taken into account the cost per additional QALY gained was over €100,000.

Finally, a 2003 study that modelled AED deployment in all major airports, railway and bus stations in Scotland, and which only included direct costs to the health service, estimated a cost per QALY gained of €62,300.⁽⁸⁷⁾ The modelled programme involved 31 AEDs being deployed across 17 locations compared with a situation where no public AEDs were available in any of these areas.

Summary of results – all other studies

Two studies estimated the cost-effectiveness of programmes involving police first responders. Both were based in the US and involved urban or suburban settings. Nichol (1998)⁽⁹⁸⁾ estimated the median cost per QALY gained at €32,600, while Forrer (2002)⁽⁹⁴⁾ only reported cost per life year gained, which was €19,200. The only economic evaluation of firefighter first responder programmes was a cost-benefit analysis set in Stockholm, using data from the SALSA trial.⁽⁸⁹⁾ This reported a total of 16 additional lives saved, with a cost per life saved of €60,000.

Two studies reported the cost-effectiveness of AED deployment on US commercial aircraft. Groeneveld (2001)⁽⁹⁵⁾ estimated that AED deployment on all commercial aircraft would result in a cost per QALY gained of €100,500. If AEDs were deployed only on large (>200 passengers) commercial aircraft, this reduced to €37,400 per QALY gained. Cram (2003)⁽⁹³⁾ modelled a cohort over one year based on aircraft with an average of 110 passengers per flight and reported a cost per QALY gained of €34,700.

The three remaining studies calculated the cost-effectiveness of PAD interventions in schools, long-term care facilities and in the home. The analysis of school-based AED deployment did not estimate the clinical benefit, but instead gave incremental cost-effectiveness ratios (ICERs) ranging from €122,100 to €63,000 depending on whether it would save 5 or 10 lives over five years.⁽⁹²⁾ Foutz (2000)⁽⁹⁶⁾ estimated a cost per life saved of €99,000 for AED deployment in long-term care facilities in the US. Another US study

examined the cost-effectiveness of AED deployment in the home and found that this was not likely to be cost-effective, with a cost per QALY gained of almost €2.5 million.⁽⁹¹⁾

2.3.2.4 COSTING STUDIES

Two costing studies were identified in the search. The most recent of these was from 2010⁽¹⁰³⁾ and reported cost data for patient transport, treatment and hospital stay that was collected as part of an observational study comparing OHCA cases involving an onsite AED, dispatched AED or no AED. The results found total costs for survivors after onsite AED use (€32,500) were lower than for dispatched AED cases (€37,900) or no AED use (€34,800). An earlier costing study⁽¹⁰⁴⁾ examined the relationship between costs and OHCA case characteristics such as time to defibrillation and EMS arrival, whether CPR was performed and neurological outcomes. Results indicated that the proportion of overall costs for patients with poor neurological outcomes (CPC>2) increase with longer time to arrival of EMS and time to defibrillation.

2.3.2.5 DISCUSSION

Decision analysis models have been used to estimate the cost-effectiveness of public access defibrillation in a range of settings, reporting ICERs ranging from under €30,000/QALY to over €100,000/QALY. All of the models identified in the literature review were structured as either a decision tree, or as a mixed decision tree/Markov model. A decision tree structure is well suited to modelling the initial phase of OHCA, since it is an event-driven process where the time between the event and the primary outcome (survival to discharge) is relatively short. A Markov element is more suitable for capturing the longer term outcomes for patients, who may have different neurological status or ongoing treatment needs in the years after hospital discharge.

Relevant measures of effectiveness include cost per life saved (increase in survival to hospital discharge), cost per life year gained and cost per QALY gained. One study factored in a utility benefit for all people who could potentially benefit from the intervention whether they had an OHCA or not, based on a belief that PAD programmes give people a greater sense of security.⁽⁹³⁾ However, the inclusion of a passive benefit of this type was not included in any other study. Increased CPR training and OHCA awareness as a result of

BLS/AED training is an additional benefit of a PAD programme that can potentially increase bystander intervention rates even in the absence of a defibrillator. From a societal perspective, relevant direct costs include the equipment and training costs needed to institute, operate, maintain and coordinate a PAD programme, as well as hospitalisation and long-term treatment costs. Indirect costs include the time required to train lay responders and productivity costs associated with mortality and morbidity as a result of OHCA.

2.3.2.6 APPLICABILITY OF THE EVIDENCE

Some of the PAD programmes included in the economic evaluation literature review were outside the scope of this analysis. These included assessment of AED deployment solely in aircraft, long-term care facilities and the homes of people at increased risk of an OHCA.

Although there is no stated threshold below which a technology is automatically considered cost-effective in Ireland (with the exception of a current agreement for pharmaceuticals at €45k/QALY⁽⁹⁾), three of the five studies examining public AED placement reported ICERs that would generally be considered acceptable. However, the transferability of these results is questionable. Many of these studies were carried out over a decade ago in the US, which has implications for their applicability to present day Ireland. The use of Irish data to inform assumptions about the treatment pathway, long-term outcomes and costs for out-of-hospital cardiac arrest survivors may result in significant changes to the incremental costs per QALY for the intervention.

Another major limitation is the differences that exist between the proposed Irish PAD scheme and the previously modelled programmes, many of which were confined to limited geographical areas or a small list of designated AED locations. Of the four studies that examined static AED provision in public areas, two were limited to densely-populated urban areas only,^(85;86) one assumed that each AED would be used once every five years (instead of estimating this parameter by comparing AED distribution and out-of-hospital cardiac arrest incidence) and the final study,⁽⁸⁷⁾ which modelled a Scottish national PAD scheme, identified a total of 17 eligible sites involving a total of 31 defibrillators. In contrast, the draft Irish legislation outlines a nationwide scheme that encompasses both urban and rural areas,

and identifies a comprehensive set of over 43,000 designated places that would need to provide AEDs and train staff.

Another important difference between Ireland and the various study settings is the degree of AED diffusion prior to the introduction of an organised PAD programme. It is estimated that there are approximately 9,000 functional AEDs in circulation throughout Ireland at present, a level comparable to some areas that have implemented a formal PAD scheme. Although placement of these AEDs has not been centrally directed, many high incidence locations (e.g. airports) already have AEDs available. This means that the incremental benefit achievable from a structured PAD programme is likely to be less than if it was being compared to a base case involving no pre-existing AED provision.

2.3.2.7 CONCLUSION

A number of previous economic analyses have estimated ICERs that would generally be considered to be within an acceptable range to support the introduction of public access defibrillation. However, the available literature does not provide enough information to reliably estimate the cost-effectiveness of an Irish programme, or to compare the likely consequences of different PAD programme configurations.

2.3.3 COST-EFFECTIVENESS ANALYSIS METHODS

2.3.3.1 DESCRIPTION OF THE ECONOMIC MODEL

A decision analysis model was built to compare the costs and benefits associated with different PAD programme configurations, compared with the current process of care for people who experience an OHCA in Ireland. The baseline comparator is a mixture of paramedic-delivered EMS, ad hoc distribution of public AEDs and a limited number of police, fire-service or community first responder groups in various locations.

2.3.3.2 STUDY QUESTION

The study objective was to determine the cost-effectiveness of a range of PAD configurations in Ireland.

2.3.3.3 TYPE OF ECONOMIC EVALUATION

This was a cost-utility analysis (CUA), which calculated the cost and the utility (in quality-adjusted life years gained [QALYs]) for each PAD programme and compared these across competing alternatives. PAD programmes were also compared in terms of effectiveness only, using life years gains (LYG), survival to hospital discharge and neurologically intact survival (discharged in CPC 1).

2.3.3.4 STUDY PERSPECTIVE

Costs and benefits were assessed from an Irish societal perspective. This included direct and indirect costs incurred by the publicly-funded health and social care system, other public sector departments, patients, and designated places with responsibility for providing AEDs and training staff in BLS/AED. Also included were the productivity losses associated with mortality and morbidity as a result of an OHCA.

National guidelines for the economic evaluation of health technologies in Ireland recommend that the payer perspective (health service) should be adopted when assessing costs.⁽¹⁰⁵⁾ Given the nature of PAD interventions and the degree to which costs fall outside of the health service, it is appropriate to take a wider societal perspective in this assessment. A secondary analysis examined cost-effectiveness from the perspective of the publicly-funded health service only.

2.3.3.5 TECHNOLOGY

The technology being assessed was programmes directing deployment of static AEDs in public locations, combined with provision of BLS/AED training to staff employed in these designated locations. The aim of the intervention was to reduce the time from onset of cardiac arrest to when defibrillation is performed, thus increasing the chances of survival in OHCA.

2.3.3.6 CHOICE OF COMPARATORS

The base case was routine care, which includes the current EMS ambulance service as well as ad-hoc public AED provision and a limited number of first responder groups covering

specific areas. A systematic review of clinical effectiveness indicated that improvements in OHCA survival are potentially greater for PAD programmes combining static AED deployment and training than for firefighter or police first responder programmes. Based on the results of this review, the comparators included in the analysis were limited to those involving the placement of static AEDs in a given set of designated places. These comparators range from programmes involving the comprehensive set of places included in the draft legislation, to more targeted programmes when the provision of AEDs is limited to building types with the highest OHCA incidence.

A total of six PAD programmes were modelled in this analysis, which differed in regard to the building types required to make AEDs publicly available. Table 2.5 shows the complete list of building types included in each comparator, along with the total number of AEDs in each (including existing AEDs). The naming scheme reflects the number of AEDs in each comparator as a percentage of the total number under full implementation of the proposed legislation (e.g. PAD15% includes approximately 15% of the total number of AEDs that would be in place in Ireland if the legislation was introduced in full).

OHCA incidence in different building type was calculated by cross referencing two years of national OHCAR data on the location of OHCA with Geodirectory data on the locations of buildings within each category, as described in section 2.3.4 (Estimates of Effect), below.

TABLE 2.5 MODELLED PAD COMPARATORS

Comparator Name	PAD 15%	PAD 20%	PAD 25%	PAD 45%	PAD 55%	Legislation
Total Number of AEDs (including existing units)	6,547	7,818	11,445	20,016	24,262	43,089
Building Types included (NACE classification)						
Hospital Activities	x	x	x	x	x	x
General Medical Practice Activities	x	x	x	x	x	x
Dental Practice Activities		x	x	x	x	x
Other Passenger Land Transport N.E.C.	x	x	x	x	x	x
Passenger Air Transport	x	x	x	x	x	x
Transportation stations and incidental services		x	x	x	x	x
Sea And Coastal Passenger Water Transport		x	x	x		x
Inland Passenger Water Transport		x	x	x		x
Secondary Education	x			x	x	x
Tertiary Education	x			x	x	x
Primary Education				x	x	x
Technical And Vocational Secondary Education				x	x	x
Other Education				x	x	x
Fitness Facilities	x			x	x	x
Operation Of Sports Facilities				x	x	x
Activities Of Sport Clubs				x	x	x
Other Amusement And Recreation Activities				x		x
Operation Of Arts Facilities	x			x	x	x
Creative, Arts And Entertainment Activities	x			x	x	x
Operation Of Historical Sites And Buildings				x	x	x
Botanical/Zoological Gardens, Nature Reserves				x		x
Museums Activities				x		x
Activities Of Religious Organisations						x
Public Order And Safety Activities	x	x	x	x	x	x
General Public Administration Activities		x	x	x	x	x
Justice And Judicial Activities		x	x	x		x
Retail Sale In Non-Specialised Stores			x	x	x	x
Other Accommodation					x	x
Hotels And Similar Accommodation						x
Beverage Serving Activities						x
Holiday And Other Short-Stay Accommodation						x
Restaurants And Mobile Food Service Activities						x

Abbreviations: PAD – Public access defibrillation; NACE – Statistical Classification of Economic Activities in the European Community (in French: Nomenclature statistique des activités économiques dans la Communauté européenne); N.E.C – Not elsewhere classified

2.3.3.7 TARGET POPULATION

The target population was all EMS-attended OHCA patients where resuscitation is attempted. It includes OHCA patients with any heart rhythm, witnessed and unwitnessed arrests, and those that occur in the home as well as in public. It excluded non-EMS attended OHCA patients and those where no attempt at resuscitation is made due to obvious signs of death.

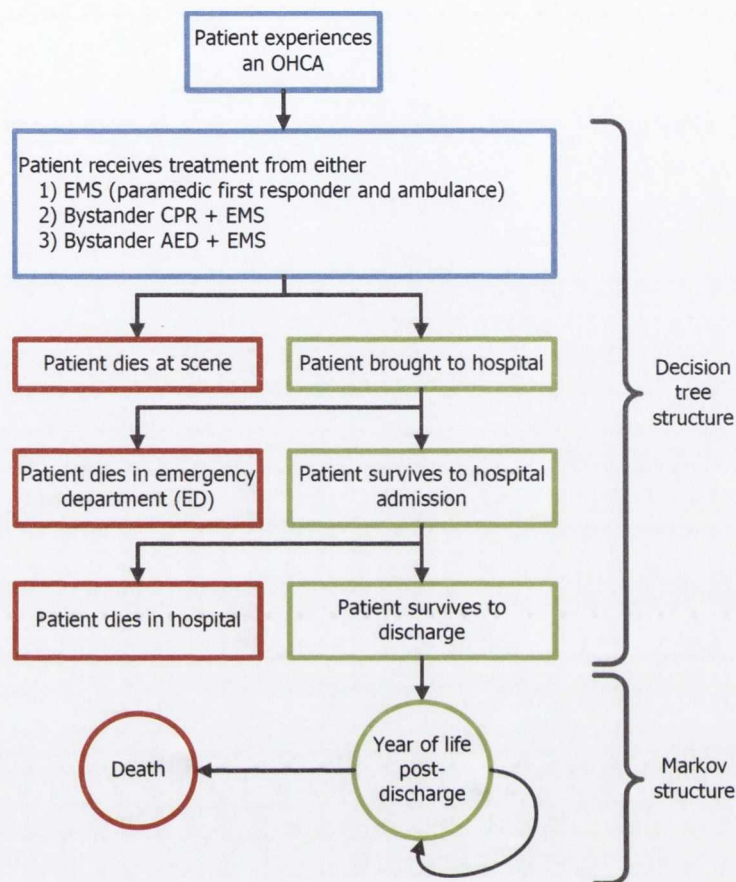
2.3.3.8 TIME HORIZON

The average cost and clinical benefit per patient for each of the PAD comparators was estimated by modelling one year's cohort of EMS-attended OHCA patients in whom resuscitation was attempted, from the time of the initial arrest to life expectancy.

2.3.3.9 MODEL STRUCTURE

The primary clinical endpoint in OHCA is survival to hospital discharge. The patient pathway from the initial arrest to death or hospital discharge was modelled as a decision tree. Longer term outcomes such as the number of additional life years, quality of life, and subsequent long-term costs associated with ongoing treatment of the underlying cause of the cardiac arrest were captured using a two state Markov model that followed each OHCA survivor to life expectancy. A generic diagram of each comparator arm for the model is shown in Figure 2.4. The model was fully probabilistic, with each parameter being defined as a distribution that most appropriately reflected the range of values that were possible. The overall benefits and costs of competing PAD programmes were calculated by randomly sampling individual parameter values over the course of 10,000 replications. The economic model was developed and analysed using TreeAge Pro 2014 software, and all graphs were produced in Excel.^(106;107)

FIGURE 2.4 PAD MODEL STRUCTURE



2.3.3.10 SENSITIVITY ANALYSIS

A probabilistic model was used that explicitly takes into account the uncertainty in the model parameters. As part of the model evaluation, all of the key parameters were varied within plausible ranges that were derived from published evidence. Where published evidence was limited or unavailable, plausible ranges were derived with the support of expert opinion.

Deterministic univariate sensitivity analysis was used to examine how sensitive the results were to fluctuations in each parameter. In this analysis each parameter in turn is fixed at its upper and lower bounds while all the other parameters are held at their average value.

2.2.3.11 DISCOUNT RATE

Discounting is a technique that allows comparison between costs and benefits that occur at different times. It reflects a societal preference for benefits to be realised in the present and costs to be experienced in the future. Costs and benefits were discounted at the rate of 5% as prescribed by the Department of Finance.⁽¹⁰⁵⁾ The discount rate was varied (from 3% to 7%) in a univariate sensitivity analysis only.

2.3.4 ESTIMATES OF EFFECT

2.3.4.1 CLINICAL OUTCOMES BY TYPE OF TREATMENT

The Out-of-Hospital Cardiac Arrest Register (OHCAR) provides data on the proportion of patients who are first treated by paramedics, bystanders who perform CPR and bystanders who perform defibrillation. It also records the proportion within each of these groups who are brought to the emergency department, admitted and discharged from hospital and the cerebral performance category (CPC) scores at discharge for each group. This information was used to model the base case and estimate average outcomes associated with each type of first response (EMS, bystander CPR and bystander defibrillation).

2.3.4.2 PROBABILITY OF RECEIVING EACH TYPE OF TREATMENT IN EACH COMPARATOR

The modelled PAD programmes differ in terms of the list of designated places where static AEDs could be deployed. Geodirectory, a national database maintained by the Irish postal service that contains the location and primary economic activity associated with all addresses in Ireland was used to estimate the number and location of designated places specified in each type of public access defibrillation programme.⁽¹⁰⁸⁾

The number and location of existing AEDs was estimated using data from AED suppliers on the volume of sales in Ireland, unpublished survey data from the National Ambulance Service on the availability of publicly accessible AEDs in a sample of urban and rural areas, and reports from AED initiatives, such as the MERIT project, designed to increase AED deployment.⁽¹⁰⁹⁾

It is noted that there is uncertainty about the effective range of an AED, with a previous study having modelled it between 100 metres and 300 metres.⁽¹¹⁰⁾ The American Heart Association recommends that AEDs be placed so that they can be reached within a 1 to 1.5 minute brisk walk.⁽¹⁷⁾ Given average maximum walking speeds of 2.17 m/s for people aged between 20 and 70,⁽¹¹¹⁾ 200 metres represents the upper limit for the distance within which AEDs can be expected to be used, and this is taken as the effective range of the device. The proportion of patients predicted to receive bystander defibrillation was calculated based on OHCAR data on arrests that occurred within 200 metres of existing AED locations. By comparing national OHCAR data on the location of OHCA with the locations of designated places from the Geodirectory, the number of arrests likely to occur within 200 metres of an AED was estimated for each of the proposed PAD configurations.

The geospatial analysis used to derive these estimates was carried out by researchers in OHCAR, the HSE Health Intelligence Unit and the Health Information and Quality Authority. Since the OHCA register achieved full coverage in 2012, overall national data on outcomes by type of first response was available for two years (2012 and 2013). Due to the relatively small numbers involved, some of the outcomes are subject to substantial uncertainty. Increases in the proportion of patients treated by bystander defibrillation will result in a decrease in the proportions of patients treated by either EMS or bystander CPR only. These decreases were estimated using data on the relative proportion of patients receiving each intervention at present, adjusted for the number of additional people that would be BLS/AED trained in each PAD programme. This was based on the assumption that the increase in the overall number of CPR-trained people will increase the proportion of OHCA patients who receive any type of bystander intervention, since trained volunteers can perform CPR even when no AED is available. By applying the OHCAR data on outcomes for patients in each of these groups it was possible to estimate the likely clinical outcomes from the initial cardiac arrest to hospital discharge associated with each type of PAD programme. Data on average life expectancy and health-related quality of life (HRQoL) post-discharge for cardiac arrest survivors was estimated from a 2014 review of the available literature carried out by the Health Information and Quality Authority.⁽¹¹²⁾ Table 2.6 shows the estimates for the main clinical outcome parameters. See Appendix 2.4 for the full list of parameters used.

TABLE 2.6 PAD OUTCOME PARAMETERS

Parameter	Mean value (95% CI)*			Source
	Proportion of patients who are first treated by			
	EMS	CPR-Only	PAD-CPR	
Base case	44.0%	48.6%	7.4%	Irish data from the OHCAR database on cardiac arrest incidence within 200 metres of AED locations. ^(108;113)
PAD15%	43.7%	47.6%	8.7%	
PAD20%	43.6%	47.7%	8.8%	
PAD25%	43.0%	46.5%	10.5%	
PAD45%	41.7%	45.5%	12.8%	
PAD55%	41.1%	45.5%	13.4%	
Legislation	38.3%	47.2%	14.5%	
Survival to emergency department (ED)				
EMS	62% (59-66)			Irish data from the OHCAR database on clinical outcomes by type of first response. ⁽¹¹³⁾
CPR only	53% (48-57)			
PAD-CPR	46% (39-54)			
Survival to hospital admission having survived to ED				
EMS	25% (20-31)			
CPR only	28% (23-33)			
PAD-CPR	51% (35-67)			
Survival to hospital discharge having survived to admission				
EMS	33% (20-47)			
CPR only	37% (28-46)			
PAD-CPR	53% (36-70)			
CPC scores at hospital discharge by type of initial response				
	CPC1	CPC2	CPC3	
EMS	85% (75-93)	13% (6-22)	2% (0-7)	
CPR only	80% (70-88)	12% (6-21)	8% (3-15)	
PAD-CPR	86% (72-95)	14% (4-27)	1% (0-5)	
Post-discharge annual survival				
CPC1	92% (90-94)			HIQA Systematic Review 2014 ⁽¹¹²⁾
CPC2	92% (90-94)			
CPC3	79% (77-82)			
QALY outcomes by CPC score				
Baseline QALY	0.78 (0.77-0.79)			
QALY in CPC1	0.93 (0.87-0.97)			
QALY in CPC2	0.75 (0.66-0.83)			
QALY in CPC3	0.40 (0.31-0.50)			

CI – confidence interval; EMS – emergency medical services; CPR – cardiopulmonary resuscitation (from bystanders); PAD – public access defibrillation (from a bystander); AED – automatic external defibrillator; ED – emergency department; CPC – cerebral performance category; QALY – quality-adjusted life year; OHCAR – Out of hospital cardiac arrest register; HIQA – Health Information and Quality Authority; * Where no 95% CI is shown that value is derived from other (sampled) parameters.

2.3.5 ESTIMATES OF COST

The largest incremental cost associated with PAD schemes is the setup cost. In addition to the cost of the AEDs, this also includes the cost of cabinets to store the devices, signage, staff training and setup of a national AED database. Staff training costs include the cost of an accredited instructor and the opportunity cost of staff time. There are also ongoing costs associated with the programme, including replacement AED pads and batteries and refresher training for staff. The majority of the costs are incurred immediately on the introduction of the scheme, with replacement pads and BLS/AED refresher training required approximately every two years and replacement batteries required roughly every five years.

Costs for AEDs, replacement pads, replacement batteries, signage and storage cabinets were obtained from supplier websites. The price of an AED ranged from under €900 to €7,000, depending on supplier, make and model, and technical specifications. The estimate used in the analysis is based on a model with a battery life of five years, and is consistent with the devices most commonly purchased by first responder groups and government departments that currently provide an onsite AED for public use. In the cost-effectiveness analysis the combined cost of owning and operating an AED was calculated as the equivalent annual cost (EAC), based on the upfront cost of acquisition annuitised over the lifespan of the device plus the average annual maintenance cost of replacement pads, batteries and staff retraining.⁽²⁾

The annual cost of running a national EMS-linked AED register is calculated as the staff cost of one full-time-equivalent (FTE) clerical officer grade plus the estimated annual cost of the required hardware and software. These IT costs were estimated based on the costs involved in running similar registries that are currently in operation elsewhere, and include the cost of hosting, licensing and support services.⁽¹¹⁴⁾

The total number of AEDs and training sessions required is based on the number of designated places specified in each comparator, using the assumption that each designated place will require one AED and, on average, training for two members of staff.

Short term treatment costs associated with out-of-hospital cardiac arrest include the cost of an ambulance callout, the cost of care in the emergency department and in-hospital care for patients who survive to hospital admission and discharge. Since the population is all EMS-attended OHCA where resuscitation was attempted, an ambulance callout is required for all patients across all comparators. It is assumed that the average cost of this callout is the same whether or not the patient survives to hospital, so there is no incremental cost associated with it and it can be excluded from the analysis.

Long-term care costs include medication and hospitalisation costs for the underlying aetiology as well as care costs associated with any lasting neurological impairment. In this analysis the annual cost of care for CPC 1 and CPC 2 survivors post-discharge is calculated based on HIPE⁽¹¹⁵⁾ data indicating that approximately 15% will receive an implantable cardioverter defibrillator (ICD) and an assumption that the remaining 85% will receive pharmacological treatment for the secondary prevention or management of coronary artery disease and other underlying cardiac pathologies.

Annual care costs for patients with CPC 3 include the annual cost of pharmacological treatment plus the cost of a full-time carer, estimated as the annual full time carers allowance from the Department of Social Protection. Productivity costs associated with premature mortality and morbidity as a result of OHCA are also included, which are calculated using the human capital approach based on Central Statistics Office (CSO) data on employment and earnings by age and gender, weighted according to the demographics of OHCA population in Ireland.

A full list of the cost parameters included in the model is provided in Appendix 2.4. Table 2.7 shows the estimates for some of the main cost parameters in the model.

TABLE 2.7 PAD COST PARAMETERS

Parameter	Mean value (95% CI)	Source
Number of additional AEDs required		
Base case	0	Geodirectory data on number of places adjusted for estimated current AED availability. ⁽¹⁰⁸⁾
PAD15%	1,879 (1,605-2,161)	
PAD20%	3,145 (2,709-3,574)	
PAD25%	6,779 (6,064-7,489)	
PAD45%	15,340 (13,879-16,805)	
PAD55%	19,596 (17,760-21,386)	
Legislation	38,395 (34,885-41,847)	
PAD implementation parameters (all costs exclude VAT, where applicable)		
Unit cost of AED	€1,189 (973-1,447)	Equipment and training suppliers in Ireland (see Appendix 2.5) and expert opinion. ^(116;117)
Unit cost of replacement pads	€46 (38-57)	
Unit cost of replacement battery	€165 (136-201)	
Lifespan of AED	8 years (6-10)	
Lifespan of AED pads	2 years (1.5-2.5)	
Lifespan of battery	5 years (4-6)	
Cost of AED signage	€12 (10-15)	
Cost of AED storage cabinet	€134 (111-164)	
Instructor cost for initial training per person	€80 (66-96)	
Time needed for initial training	5 hours (4.5-5.5)	
Interval for retraining	2 years (1.2-3.3)	Micro-costing of resource use and staff time carried out in conjunction with Irish expert in emergency medicine. ⁽¹¹⁸⁾
Instructor cost for refresher training per person	€50 (41-61)	
Time required for refresher training	3 hours (2.6-3.4)	
Cost of care for death in ED	€679 (451-988)	
Cost of hospital care for patient who dies in hospital	€17,911 (15,290-20,868)	HIPE DRG costs ⁽¹¹⁹⁾
Cost of hospital care for patient surviving to discharge	€22,835 (18,287-28,150)	Gillespie 2010 ⁽¹²⁰⁾ Sanders 2005 ⁽¹²¹⁾
Annual cost of medical care post-out-of-hospital cardiac arrest in CPC1	€3,964 (3,242-4,798)	
Annual cost of medical care post-out-of-hospital cardiac arrest in CPC2	€3,964 (3,242-4,798)	

Annual cost of care (medical plus carer) post-out-of-hospital cardiac arrest in CPC3	€14,421 (8,220-23,772)	Gillespie 2010 ⁽¹²⁰⁾ Dept Social Welfare Full time carers allowance ⁽¹²²⁾
Cost of one hour of trainee time	€25 (23-28)	CSO average hourly labour costs ⁽¹²³⁾
Average productivity loss	€12,006 (10,236-14,021)	Productivity losses as a result of out-of-hospital cardiac arrest mortality and morbidity were based on average workforce participation and earnings in the out-of-hospital cardiac arrest cohort, taking account of the age-sex distribution of this group. ⁽¹²⁴⁾
Annual cost of AED database	€69,259 (56,786-83,872)	Annual running costs, including equipment (hardware, software, licensing, hosting and support, based on the Danish AED register and similar Irish systems) and staff ⁽¹¹⁴⁾
Number of trainees per AED	2 (1-3)	Assumption
VAT	23%	Standard VAT rate ⁽¹²⁵⁾

Abbreviations: CI – confidence interval; AED – automatic external defibrillator; PAD – public access defibrillation; ED – emergency department; DRG – diagnosis related group; OHCA – Out-of-hospital cardiac arrest; HIPE – Hospital in-Patient Enquiry database; CSO – Central Statistics Office, VAT – Value added tax

2.3.6 RESULTS OF THE ECONOMIC ANALYSIS

The results of the comparison of each of the proposed PAD configurations compared with current practice (base case) are provided separately for effectiveness outcomes (survival to hospital discharge, neurologically intact survival [CPC1] and life years gained) and utility outcomes (quality-adjusted life years gained).

2.3.6.1 OUT-OF-HOSPITAL CARDIAC ARREST SURVIVAL

Predicted annual survival to hospital discharge and neurologically intact survival (CPC1) for the entire OHCA cohort for are shown in Tables 2.8 and 2.9, respectively for each of the modelled comparators

TABLE 2.8 PREDICTED ANNUAL SURVIVAL TO HOSPITAL DISCHARGE

Strategy	Absolute annual survival to hospital discharge n [95% CI] (%)	Relative annual increase in survival to hospital discharge compared to base case n (%)	Average cost per additional survivor to discharge (€)
Base case	107 [83-135] (5.81%)	N/A	N/A
PAD15%	109 [84-137] (5.91%)	2 (1.7%)	484,891
PAD20%	110 [84-137] (5.92%)	2 (1.9%)	713,007
PAD25%	112 [86-140] (6.04%)	4 (4%)	665,881
PAD45%	115 [89-144] (6.21%)	7 (6.9%)	862,206
PAD55%	116 [90-145] (6.26%)	8 (7.7%)	973,716
Legislation	117 [91-146] (6.35%)	10 (9.3%)	1,581,862

TABLE 2.9 PREDICTED ANNUAL NEUROLOGICALLY INTACT (CPC1) SURVIVAL

Strategy	Absolute annual neurologically intact discharges n [95% CI] (%)	Relative annual increase in neurologically intact discharges n (%)	Average cost per additional neurologically intact discharge (€)
Base case	89 [68-114] (4.83%)	N/A	N/A
PAD15%	91 [69-116] (4.91%)	1 (1.7%)	549,421
PAD20%	91 [69-116] (4.92%)	2 (1.9%)	802,042
PAD25%	93 [71-118] (5.03%)	4 (4.1%)	750,179
PAD45%	96 [73-122] (5.18%)	6 (7.2%)	969,930
PAD55%	97 [74-123] (5.22%)	7 (8.1%)	1,101,062
Legislation	98 [75-124] (5.29%)	9 (9.5%)	1,813,017

2.3.6.2 LIFE YEARS GAINED (LYG)

Figure 2.5 shows where each comparator lies on the cost-effectiveness plane when outcomes are measured in life years gained (LYG). No strategy is strictly dominated (less effective and more costly than another strategy), but the PAD20% option is weakly dominated by some combination of PAD15% and PAD25%.

FIGURE 2.5 COST-EFFECTIVENESS PLANE (LYG)

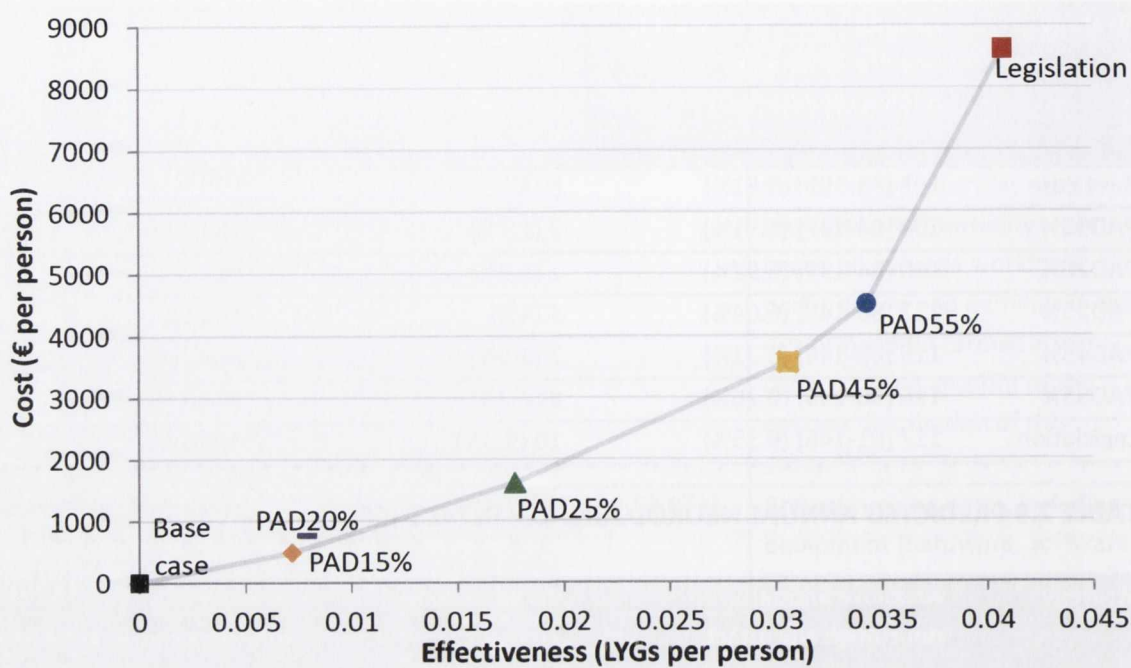


Table 2.10 shows the incremental cost-effectiveness ratios (ICERs) per LYG for each comparator relative to the next best option, excluding dominated strategies (PAD20%).

TABLE 2.10 ESTIMATED INCREMENTAL COST-EFFECTIVENESS RATIOS (LYG)

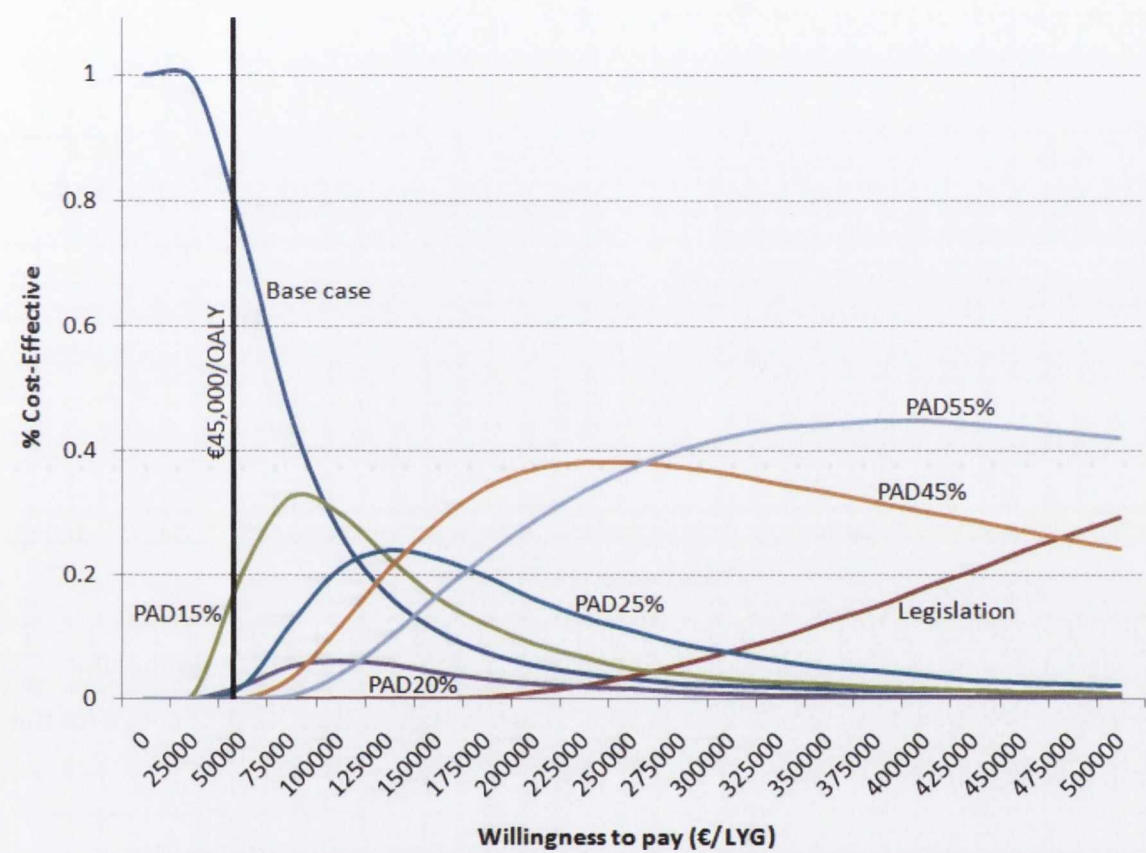
Strategy	Cost (€)	Incremental Cost (€)	Effectiveness (LYG)	Incremental Effectiveness (LYG)	ICER* (€/LYG)
Base case	16,952	-	0.433	-	-
PAD15%	17,443	491	0.4402	7.1737×10^{-3}	68,444
PAD25%	18,574	1,131	0.4507	1.0532×10^{-2}	107,385
PAD45%	20,510	1,935	0.4636	1.2861×10^{-2}	150,457
PAD55%	21,457	948	0.4673	3.6879×10^{-3}	257,052
Legislation	25,571	4,113	0.4738	6.4816×10^{-3}	634,566

* Due to rounding error the ICER value calculated using the incremental cost and incremental effect values reported in this table may differ from the ICER value reported in the table. Where any such differences do occur please note that the ICER value reported in the table provides the most accurate estimate.

The degree of uncertainty about the ICER for each intervention is examined using cost-effectiveness acceptability curves (CEAC). This shows the probability that any of the non-dominated PAD strategies is cost-effective for a given willingness to pay threshold (Figure 2.6). At a threshold of €45,000/LYG, PAD15% is the most cost-effective option in 16% of

simulations. The ICER for the proposed legislation compared to the base-case, as opposed to the next best option, is €211,529/LYG.

FIGURE 2.6 COST-EFFECTIVENESS ACCEPTABILITY CURVE (LYG)



2.3.6.3 QUALITY-ADJUSTED LIFE YEARS GAINED (QALYs)

Figure 2.7 shows where each comparator lies on the cost-effectiveness plane when outcomes are measured in quality-adjusted life years gained (QALYs). As with the LYG analysis, no strategy is strictly dominated (less effective and more costly than another strategy), but the PAD20% option is weakly dominated by some combination of PAD15% and PAD25%.

FIGURE 2.7 COST-EFFECTIVENESS PLANE (QALY)

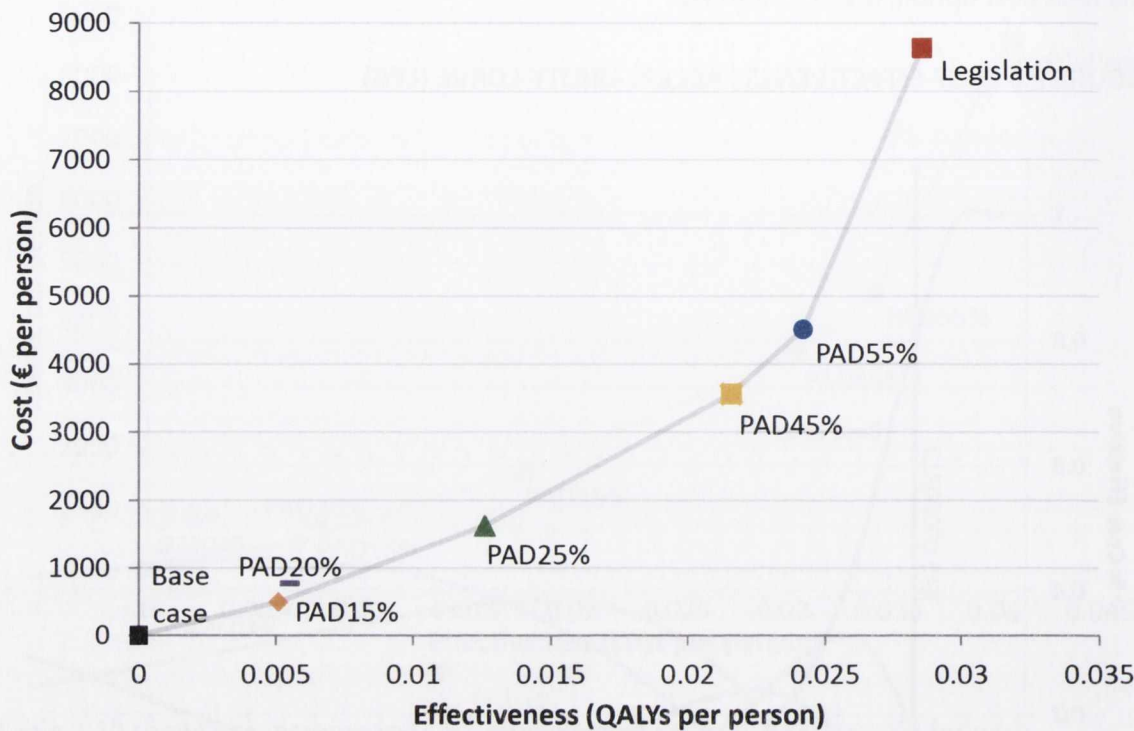


Table 2.11 shows the incremental cost-effectiveness ratios (ICERs) for each comparator relative to the next best option, excluding dominated strategies (PAD20%). The ICER for the proposed legislation compared to the base-case is €301,204/QALY.

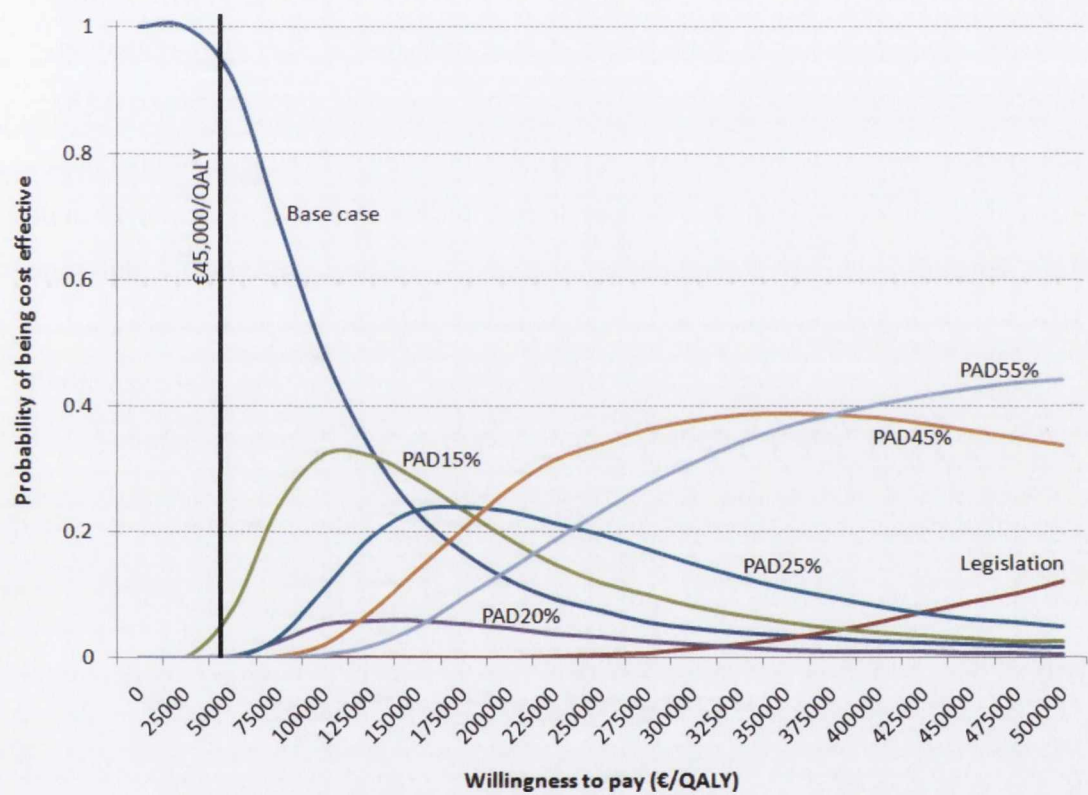
TABLE 2.11 ESTIMATED INCREMENTAL COST-EFFECTIVENESS RATIOS (QALY)

Strategy	Cost (€)	Incremental Cost (€)	Effectiveness (QALY)	Incremental Effectiveness (QALY)	ICER* (€/QALY)
Base case	16,954	-	0.3004	-	-
PAD15%	17,446	492	0.3055	5.1443x10 ⁻³	95,640
PAD25%	18,577	1,131	0.313	7.4780x10 ⁻³	151,243
PAD45%	20,518	1,941	0.322	9.0655x10 ⁻³	214,108
PAD55%	21,467	949	0.3246	2.5405x10 ⁻³	373,545
Legislation	25,589	4,122	0.329	4.4397x10 ⁻³	928,450

* Due to rounding error the ICER value calculated using the incremental cost and incremental effect values reported in this table may differ from the ICER value reported in the table. Where any such differences do occur please note that the ICER value reported in the table provides the most accurate estimate.

The cost-effectiveness acceptability curves (CEAC) showing the probability that any of the non-dominated PAD strategies is cost-effective for a given willingness to pay threshold is shown in Figure 2.8. At a threshold of €45,000/QALY, PAD15% is the most cost-effective option in 5% of simulations.

FIGURE 2.8 COST-EFFECTIVENESS ACCEPTABILITY CURVE (QALY)



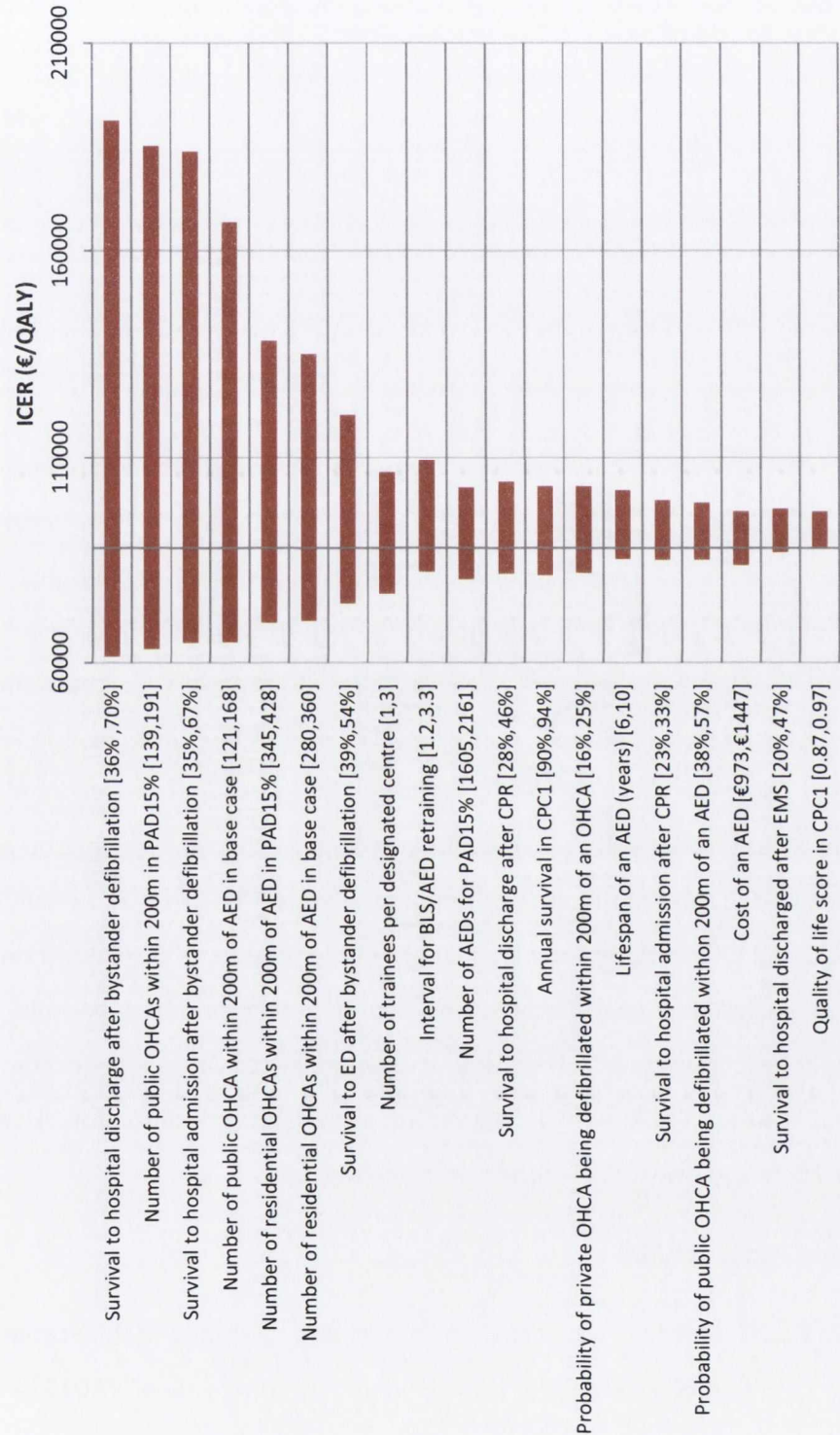
With the exception of a current agreement for pharmaceuticals,⁽⁹⁾ there is no stated threshold in Ireland below which a technology is automatically considered cost-effective and reimbursed. Historically, for technologies evaluated from the perspective of the health services in Ireland, the probability of cost-effectiveness at thresholds of €20,000 and €45,000 per QALY have been reported, per national HTA guidelines.⁽¹⁰⁵⁾ In a cost-effectiveness analysis from a societal perspective, the threshold used should reflect how much society is prepared to pay for an additional QALY. Results of a secondary cost-utility analysis from the perspective of the publicly-funded health and social care system shows

that when the set-up costs associated with device acquisition and staff training for all designated places not owned by the HSE are excluded, the proposed legislation dominates all other public access defibrillation configurations, with a 89% chance of being cost-effective at a willingness to pay threshold of €20,000/QALY (see Appendix 2.6).

2.3.6.4 SENSITIVITY AND SCENARIO ANALYSES

A number of sensitivity and scenario analyses were undertaken to determine how sensitive the results were to changes in parameter values and to estimate the cost-effectiveness given a range of different assumptions. A tornado diagram showing the most influential parameters in the deterministic sensitivity analysis of the strategy with the lowest ICER estimate in the cost-effectiveness analysis using QALY outcomes (PAD15%) is shown in Figure 2.9. In the sensitivity analysis all costs and benefits were varied between their upper and lower plausible ranges (95% confidence intervals). These diagrams show the difference in the mean ICER estimate when each input parameters is varied. The parameters are shown in descending order of influence, providing a visual representation of those with the greatest impact on the ICER for a given strategy.

FIGURE 2.9 SENSITIVITY ANALYSIS OF ICER ESTIMATE FOR PAD15% (QALY OUTCOMES)



Scenario analysis was carried out to examine the likely impact of potential future changes in a number of key parameters on the cost-effectiveness of PAD programmes. Two possible scenarios are examined:

Scenario 1: International experience in implementing PAD programmes has shown that high-volume purchasing of AEDs has the potential to significantly decrease the unit price.⁽¹¹⁴⁾ This is most likely to occur when there is a centralised purchaser who can negotiate with suppliers. Although this is not necessarily a feature of the proposed Irish PAD programme, it may be worth consideration if it has the potential to increase the overall cost-effectiveness of the intervention. For the purpose of this scenario analysis the unit price of an AED is reduced from approximately €1,190 to €490, exclusive of VAT.

Scenario 2: In the cost-effectiveness analysis the probability of someone receiving bystander defibrillation if they experience an OHCA within 200 metres of an AED is modelled using historical Irish data. The prospective national PAD programmes being evaluated include the setting up of an AED register that is linked to the emergency services. This has the potential to increase the number of people who are defibrillated by bystanders since anyone who reports a possible OHCA can be alerted to the presence of a nearby AED that they might otherwise have been unaware of. Bystander intervention may also be increased as a result of greater awareness of OHCA as a result of a national PAD initiative and an increase in the number of BLS/AED trained people. In this scenario analysis it is conservatively assumed that this beneficial impact on AED utilisation only applied to OHCA that occur in public areas, and has no impact on the rate of AED utilisation for OHCA occurring in private locations or in the home.

Scenario 1: Reduced cost of AEDs

The ICERs for QALY outcomes for each of the non-dominated strategies in this scenario are shown in Table 2.12. The ICER estimate for the most cost-effective option (PAD15%) is

reduced from around €96,000 to €70,000 per additional QALY, which would still not be considered cost effective using conventional willingness to pay thresholds.

TABLE 2.12 ESTIMATED COST-EFFECTIVENESS ANALYSIS RESULTS GIVEN A SUBSTANTIAL REDUCTION IN AED COST

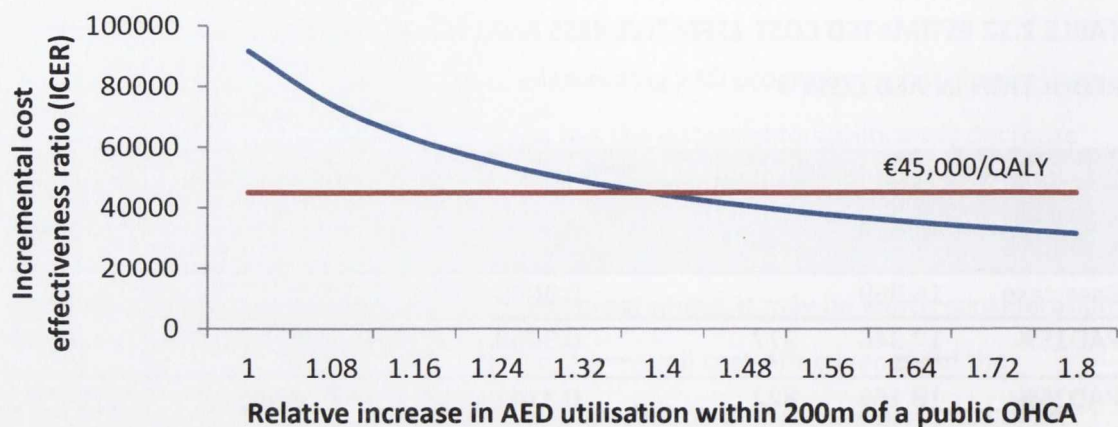
Strategy	Cost (€)	Incremental Cost (€)	Effectiveness (QALY)	Incremental Effectiveness (QALY)	ICER* (€/QALY)
Base case	16,969	-	0.3015	-	-
PAD15%	17,346	377	0.3069	5.3821x10 ⁻³	70,047
PAD25%	18,168	822	0.3142	7.2796x10 ⁻³	112,918
PAD45%	19,573	1,404	0.3233	9.0658x10 ⁻³	154,867
PAD55%	20,253	680	0.3259	2.6207x10 ⁻³	259,468
Legislation	23,195	2,943	0.3303	4.4752x10 ⁻³	657,626

* Due to rounding error the ICER value calculated using the incremental cost and incremental effect values reported in this table may differ from the ICER value reported in the table. Where any such differences do occur please note that the ICER value reported in the table provides the most accurate estimate.

Scenario 2: Increased utilisation of AEDs in out-of-hospital cardiac arrests that occur within 200 metres of an AED

A threshold analysis showing the impact of increasing AED utilisation for OHCA that occur in a public area, assuming that the rate of AED use for out-of-hospital cardiac arrests in residential areas remains unchanged, on the ICER for PAD15% is shown in Figure 2.10. This shows that an increase of approximately 40% in the rate of AED use would be required for public out-of-hospital cardiac arrests that occur within 200 metres of an AED for the ICER to approach a threshold of €45,000/QALY.

FIGURE 2.10 SCENARIO ANALYSIS FOR INCREASED UTILISATION OF AEDS FOR PUBLIC OHCAS ONLY



Interpretation of these results is constrained by the absence of evidence showing the impact a PAD programme involving CPR/AED training, an EMS-linked AED register and increased public awareness of OHCA is likely to have on AED utilisation rates. A 2011 US study found that an EMS-linked AED register has the potential to improve public AED usage prior to EMS arrival.⁽¹²⁶⁾ This study examined the possibility of increased AED use when an EMS dispatcher could alert callers to the presence of an AED within a 0.1 mile radius (160 metres). Over the course of the study, 22 of 763 OHCA cases had a public access AED applied prior to EMS arrival, while a further 59 occurred in the vicinity of an AED that could have been identified by a dispatcher with access to AED registry information when the call was received. Therefore over the course of the three year study, a linked system could have alerted an additional 7.7% (59/763) of all cases to the presence of a nearby device. However, it is unlikely that AED utilisation would ever reach 100%, since this would require the availability of a bystander who was able to retrieve and use the AED in all cases, combined with complete accessibility of all registered AEDs at all times. There are also major challenges in setting up the AED register itself, which is evident from the experience of those involved in developing the Irish AED register recommended in the 2006 report of the Sudden Cardiac Death Task Force.⁽¹²⁷⁾

It is also important to note that this scenario analysis assumes full registration of all AEDs. While any prospective database should aim to identify as many existing AEDs as possible,

the proposed legislation only stipulates that owners of designated places are required to register their device. Failure to register a large proportion of existing AEDs in any future EMS-linked AED database may affect the applicability of the results of this scenario analysis, particularly for the more scaled down PAD configurations (PAD15% and PAD20%), where the proportion of existing AEDs in non-designated places is highest.

2.3.6.6 EXPECTED VALUE OF PERFECT INFORMATION (EVPI)

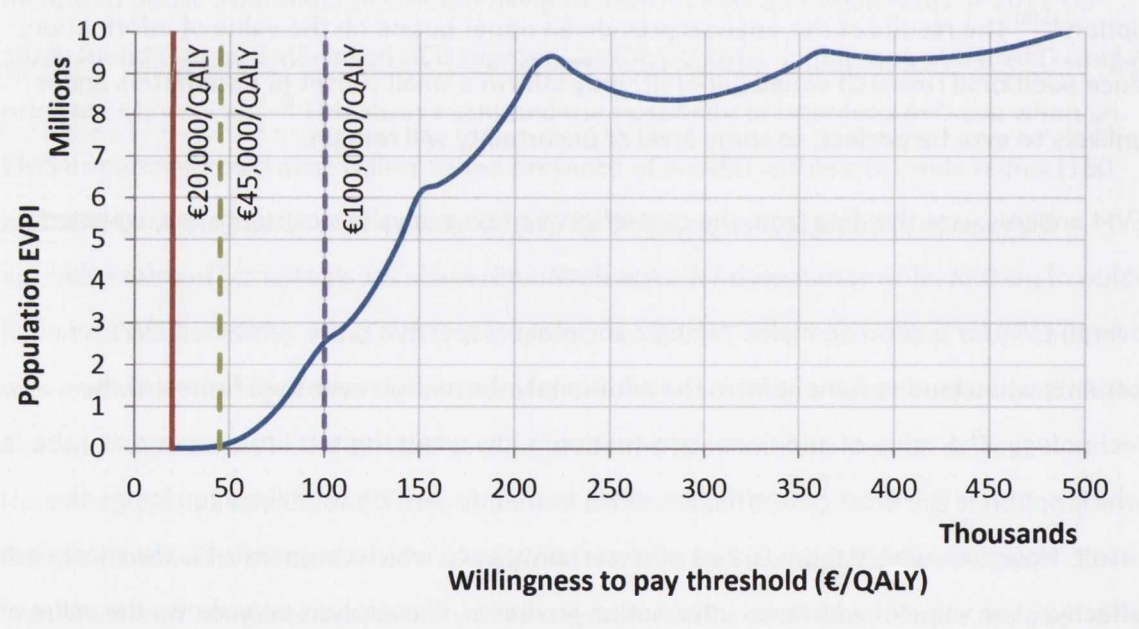
The results of the cost-effectiveness and sensitivity analyses show how the different PAD programmes compare to each other given the currently available evidence. Expected value of perfect information (EVPI) analysis provides a way to investigate the value of acquiring more evidence before deciding which PAD programme is the most cost-effective. It examines both the probability that a decision based on existing evidence will be wrong and the consequences of a wrong decision, and uses this to calculate the monetary value of acquiring perfect information, thus eliminating the possibility of taking the wrong option.⁽¹²⁸⁾ The results of this analysis provide an upper bound on the value of information, since additional research would generally only inform a small subset of parameters and is unlikely to ever be perfect, so some level of uncertainty will remain.

EVPI analysis uses the data from the cost-effectiveness analysis to calculate the expected value of perfect information each time the decision is made for a patient. Therefore the overall EVPI for a decision maker taking a societal perspective is the combined EVPI for all patients who stand to benefit from the additional information over the lifetime of the technology. The value of additional information is low when there is little uncertainty about which option is the most cost-effective, since more information is unlikely to change the result. However, where there is a lot of uncertainty as to which comparator is the most cost-effective, the value of additional information increases. The analysis only shows the value of additional information for the comparators modelled in the analysis and does not provide any indication of the value of including alternative programmes, such as those based on location-specific OHCA incidence rather than OHCA incidence by building type.

In this analysis the EVPI was calculated over the course of 10 years of a PAD programme, assuming an average annual incidence of 1,850 out-of-hospital cardiac arrests in Ireland.

Figure 2.11 shows the EVPI curve for all PAD options modelled. From the CEAC for this analysis (Figure 2.8) it can be seen that there is little uncertainty that, at a willingness-to-pay threshold of less than €45,000 per QALY, the base case is the most cost-effective option. This is mirrored in the EVPI curve, which shows that the value of additional information below this threshold is negligible. As the threshold approaches €100,000/QALY, PAD15% begins to emerge as the most cost-effective option and the value of perfect information to inform decision making is approximately €2.5 million. The EVPI curve continues to rise sharply after that, reflecting the high degree of uncertainty about the optimal strategy at high WTP thresholds. Peaks are evident at €160,000/QALY, where PAD25% emerges as the optimal strategy, and again at €220,000/QALY, where PAD45% emerges as the optimal strategy. However, these threshold values are far in excess of those that have been used previously in Ireland and elsewhere.

FIGURE 2.11 POPULATION EVPI CURVE FOR ALL PUBLIC ACCESS DEFIBRILLATION OPTIONS



2.3.6.7 LIMITATIONS OF THE ECONOMIC MODEL

There are important limitations associated with the economic analysis that need to be considered when interpreting the results. These can broadly be assigned to two categories: parameter uncertainty and model uncertainty. Parameter uncertainty arises where there is a lack of reliable data to inform model inputs, such as the clinical outcomes associated with

bystander defibrillation or the costs of equipment. There can also be uncertainty related to parameter variability, since some parameters naturally vary over time even when measured accurately. Model uncertainty (also called structural uncertainty) stems from the choices made regarding the functional form of the model used to represent the real world. If the model fails to adequately capture the most important aspects of how PAD programmes would operate in reality, then there can be little expectation of an accurate result even if the true value of all input parameters were known.

Parameter uncertainty - availability, robustness and quality of available data

There is always a degree of uncertainty surrounding model parameters and standard methods to handle this have been used in the analysis. These include Monte Carlo simulation to quantify the level of confidence around the cost-effectiveness results, univariate deterministic sensitivity analysis to examine the effect of uncertainty associated with individual parameters and identify the principal drivers of cost-effectiveness, and scenario analysis to investigate the impact of potential major changes to key parameters. In this section, the strengths and weaknesses of the available Irish data on a number of key parameters are discussed further, along with the implications these may have for the model results.

In an ideal situation, data from high quality Irish studies showing the effect of different PAD programme configurations would be used to model cost-effectiveness. In the absence of these data, the model combined the likely number of OHCA that would occur within 200 metres of an AED with the probability of receiving bystander defibrillation to estimate the effect on survival and neurological status of survivors for a number of different PAD programmes. While this is the best available option for comparing the relative benefits of each of the comparators given the available data, it does have some important limitations. These are discussed below.

Uncertainty about the number and location of existing AEDs

There has been a high level of ad-hoc deployment of AEDs in public locations in Ireland. Based on sales figures over the last number of years obtained from suppliers, it is estimated

that there are approximately 9,000 operational AEDs currently in circulation. About half of these are thought to be in locations that would be classified as designated places under the proposed legislation. In the analysis the assumed locations of existing AEDs and OHCA events were varied to arrive at parameter distributions that reflect the high uncertainty associated with the data. Ultimately the best way to decrease this uncertainty is to establish a register of AEDs that provides high quality data on the location, accessibility, functional status and utilisation rates of publicly available AEDs and to combine this information with multiple years of national OHCA data on OHCA incidence.

Uncertainty about the type of first response

The Irish OHCA Register is an invaluable resource that provides national data on the number and location of OHCA events, the type of response first received by patients and their subsequent clinical outcomes. Basing survival outcomes on the type of first response involves an assumption that outcomes in these groups can be extrapolated in the comparators that involve many more AEDs. There is a risk that different PAD programmes will result in AED coverage of areas that differ from the current areas in ways that could alter the outcomes associated with the type of first response.

Lack of Irish data on health-related quality of life and long-term out-of-hospital cardiac arrest outcomes

No Irish data on average life-expectancy or quality of life for OHCA survivors by CPC category were available, so this was taken from international literature. In an analysis using QALY outcomes, these two parameters (survival and quality of life) determine the entirety of the clinical benefit in the model. Therefore any differences between Irish and international OHCA outcomes may have important implications for the analysis. While there are no data to suggest that outcomes in Ireland vary so considerably from those published elsewhere that the overall results of the analysis would be affected, the use of data generated in the context of Irish OHCA studies would decrease the level of uncertainty in relation to the anticipated benefits of different national PAD programme configurations.

Model uncertainty

Uncertainty in relation to the structure of the model was dealt with by eliciting expert opinion to describe the patient pathway at each stage of the process and comparing the approach used in this thesis with that of previous economic models of OHCA reported in the literature. The outputs for the base case were also validated against the OCHAR data to ensure that the model accurately represents the existing standard of care.

2.4 DISCUSSION

Modelled PAD programmes range from those representing a relatively modest rise in the number of public AEDs (1,900 more for PAD15%) to those that would involve a very substantial increase compared with the existing situation (38,400 more for the full legislation). This is reflected in the projected absolute increase in survival for each programme, which ranges from an average of two extra lives saved per year for PAD15% and PAD20%, to ten extra lives saved per year for the full legislation. The proportion of people with some degree of lasting neurological damage (CPC 2 or 3) is anticipated to remain the same across all strategies, although the absolute number will increase as a result of increased overall survival.

The choice of comparators was selected based on predicted OHCA incidence in different building types, with AED placement in the more scaled-down options being confined to those places with the highest likelihood of an OHCA event. Not surprisingly, the cost-effectiveness of successive options decreases (larger ICERs) as programmes are expanded to places with a lower incidence of OHCA, since a larger number of AEDs are required to gain one additional QALY. The most cost-effective comparator, which involved AED placement in public transport stations, medical practices, entertainment venues, schools [excluding primary] and fitness facilities, was associated with an ICER over twice that of willingness to pay thresholds routinely-used for pharmaceuticals in Ireland. Taking into account the uncertainty associated with individual model parameters, the willingness-to-pay threshold for an additional QALY would have to be in the region of €100,000 for PAD15% to be more cost-effective than the base case. The results of a value of information analysis for the modelled programmes found that, for the comparison between the base case and PAD15%, there was very little value in generating additional evidence to support decision-making at a willingness-to-pay threshold of €45,000/QALY, and at a threshold of €100,000/QALY the upper bound on the societal value of generating additional evidence to inform the decision was approximately one million euro.

These results of this study are relatively insensitive to large changes in the unit cost of AEDs, with decreases in the order of 60% failing to produce ICERs that would be considered cost effective using a willing to pay threshold of €45,000/QALY. Of greater significance was a

scenario analysis of potential changes in the probability of an AED being used when an OHCA occurs within 200m, which found that an increase of approximately 40% in AED utilisation rates for public OHCA (from 47% to 66%) would produce an ICER in the region of €45,000/QALY for the most targeted programme (PAD15%). A search of the literature failed to identify any studies reporting this outcome for countries that have implemented PAD programmes, so there is no evidence to show that an increase of any magnitude is achievable.

A secondary analysis from the perspective of the health service showed that when only costs that fall on the publicly-funded health system are included, all of the comparators are cost-effective compared with the present situation, with the most cost-effective being the programme outlined in the draft legislation. This is potentially misleading as increasing PAD coverage shifts more of the setup and maintenance costs to the wider public and private sectors. Limiting the analysis to the perspective of the health service does not, therefore, provide a true reflection of the overall costs and benefits associated with a national PAD programme.

Five other studies reporting cost-effectiveness results for programmes involving static public AEDs were identified.^(85-88;90) There was significant heterogeneity in the analysis methods used in these studies, and a high degree of variability in the results (which are reported after adjustment for purchasing power parity and inflated to 2014 Euro). Three studies used deployment rules based on the annual probability of an OHCA occurring; a 20% annual probability rule (where AEDs were placed in all locations with a likelihood of one OHCA every 5 years) was associated with ICERs of €31,300⁽⁸⁸⁾ and €44,500,⁽⁸⁶⁾ and a 50% annual probability rule (one OHCA every two years) produced ICERs ranging from €28,900⁽⁸⁶⁾ and €44,900.⁽⁸⁵⁾ One of these studies also examined undirected placement in an urban environment (one AED for every 100m² area) and reported an ICER of €118,500.⁽⁸⁶⁾ The two remaining studies identified specific building types in which AEDs were deployed. A US analysis of PAD programmes in casinos calculated a cost per QALY gained of €57,900.⁽⁹⁰⁾ This included the wage costs of training instructors, but not the wage costs for employees receiving training. When the opportunity cost of the time needed for training is taken into account the cost per additional QALY gained was over €100,000. The other study, which

modelled AED deployment in airports, railway and bus stations in Scotland and only included direct costs to the health service, estimated an ICER €62,300.⁽⁸⁷⁾

All of the PAD programmes included in the analysis were based on AED deployment by building type. In Ireland the programme is intended to be defined in law, in the same manner as the national workplace smoking ban⁽¹²⁹⁾ and other health and safety regulations that impose compliance and financial obligations on occupiers of public premises. From the point of view of health policymakers this type of approach has advantages; it is relatively straightforward to transpose into legislation since it allows designated places to be explicitly defined, responsibility for implementation is divested from the publicly funded health service, and it provides a mechanism to ensure compliance through the imposition of legal penalties. The disadvantage is that in terms of identifying high incidence locations it is a relatively blunt instrument, since it cannot easily discriminate between subsets of each building type, such as a particular set of sporting venues associated with higher OHCA incidence as a result of the number or demographic characteristics of attendees. Developing clear implementation rules for a more nuanced programme would require additional data that may not be readily available, such as average daily footfall at various locations, and national data on the precise location of OHCA events. Such programmes would also require constant re-evaluation to keep pace with changing demographics and location specific OHCA incidence, increasing the administrative burden of the programme. However, because they could potentially be more targeted, requiring less AEDs to save one additional life, these types of programmes are likely to be more cost effective as long as an effective deployment rule can be identified (with sufficient data to implement it) and the additional cost associated with regular reappraisal of AED deployment does not outweigh the additional benefits.

This study has several limitations. The clinical impact of PAD is based on combining the additional number of OHCA cases that will receive bystander defibrillation in each comparator with Irish data on clinical outcomes for those having an AED applied before the arrival of emergency services. This has lower external validity than the direct application of results from appropriate primary studies. Although one RCT involving static AED placement was identified, differences in the study setting limited the transferability of the results.

These differences included the fact that the study only included densely populated urban areas, whereas the PAD legislation would apply to the whole of Ireland, which is a predominantly rural country. Secondly, the deployment rule used in the study (based on OHCA incidence) differed from that used in the prospective Irish programme (based on building type). In order to overcome these difficulties it was necessary to find an alternative method of estimating the impact of a national PAD programme in Ireland. In the analysis outcomes observed from two years of national data on OHCA patients who received bystander defibrillation were applied to all additional cases that would receive this intervention in an expanded PAD programme. The external validity of this approach is lower than if it was based on study data and there is a risk that extrapolating these outcomes may introduce bias if there are inherent differences between these two groups, such as different risk profile or a longer time to defibrillation. However in the absence of data to indicate any such differences, this approach offers the best estimate of the likely benefit. Another limitation is the absence of an AED register recording the number and locations of existing AEDs, which instead had to be estimated using data from suppliers and regional survey data. Uncertainty about this parameter could affect the incremental costs associated with introducing a structured PAD programme. The effective range estimate for AEDs (200m) was a straight line distance, which may overestimate the proximity of AEDs to events that happen in densely populated urban areas where the distance on foot to the AED could be greater than 200m.

2.5 CONCLUSION

Ireland already has a high level of diffusion of AEDs on a voluntary basis, but this system is not standardised, coordinated or linked to emergency medical services. Based on current data, none of the PAD programmes evaluated would be considered cost-effective using conventional willingness to pay thresholds. However targeted AED deployment in higher incidence locations in combination with significantly increased utilisation of AEDs as a result of a national EMS-linked AED register and increased public awareness could render PAD programmes more cost-effective.

Therefore if a PAD programme is introduced in Ireland, it should target the mandatory deployment of AEDs to locations with the highest incidence of OHCA and be considered in conjunction with measures to increase the usage of publicly accessible AEDs. A process of performance evaluation and research should be incorporated from the outset to guide ongoing tailoring of the programme to maximise efficiency.

3. SCREENING FOR ATRIAL FIBRILLATION

3.1 BACKGROUND

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in general practice. It is characterised by a rapid and irregular contraction of the upper chambers of the heart, which diminishes its ability to pump blood efficiently. In some cases AF can be asymptomatic, while in others the person may experience palpitations, chest pain and shortness of breath. Different types of AF can be classified by the frequency of occurrence of the arrhythmia or by the underlying cause. In the 3-P system AF is classified as paroxysmal, persistent or permanent, depending on the temporal pattern of the arrhythmia and how it responds to treatment. Paroxysmal AF is defined as two or more episodes that terminate within seven days, persistent AF as one episode that lasts more than seven days, and permanent AF as having an episode that lasts more than a year and cannot be terminated by cardioversion.⁽¹³⁰⁾ Aetiological classification distinguishes between AF cases where there is no clinical or echocardiographic (ECG) evidence of structural heart disease (lone AF), or by the presence or absence of heart valve problems such as rheumatic mitral valve disease (valvular or non-valvular AF). The overall population prevalence of AF is around 2%, rising sharply with age. The median age of AF patients is 75 years and 70% are between 65 and 85 years old.⁽¹³¹⁻¹³³⁾ Estimates of AF prevalence in those aged over 80 vary from around 8% to greater than 15%.⁽¹³⁴⁾ Men are 1.5 times more likely than women to develop the condition, but because women have a longer life expectancy, the overall number of men and women with AF in older populations is approximately equal.^(135;136)

As well as reducing quality of life, non-valvular AF is associated with a fivefold increase in the risk of stroke.⁽¹³¹⁾ This is due to uncoordinated atrial activity disrupting blood flow through the heart, which increases the propensity for thrombus formation, particularly in the left atrial appendage. These clots may be pumped out of the heart and cause an ischaemic stroke by blocking an artery supplying blood to the brain. Compared with non-AF strokes, AF strokes are more likely to be fatal, and result in longer hospital stays, poorer functional outcomes and a lower chance of being discharged home afterwards for those

who survive.⁽¹³⁷⁾ It is estimated that there are approximately 8000 strokes annually in Ireland, with about a third of these being associated with underlying atrial fibrillation.^(138;139)

Recommended management of AF is outlined in the (draft) AF care pathway developed by the HSE National Clinical Programme for Stroke.⁽¹⁴⁰⁾ Diagnosis of the arrhythmia is made by ECG in patients with suspected AF or those with an irregular pulse. However, pulse palpation of patients who present without symptoms indicative of AF is not routinely carried out in primary care. Once diagnosed, patients may undergo further testing to rule out structural heart disease or other problems. Most patients receive pharmacological treatment to decrease the risk of stroke in AF, with treatment decisions being guided by the CHA₂DS₂-VASc score for AF stroke risk. The two main types of anti-thrombotic treatment are antiplatelet therapy and oral anticoagulation, which have been shown to reduce the risk of stroke by approximately 20% to 60%.⁽¹⁴¹⁾ Risks associated with these medications include an increase in the likelihood of haemorrhagic stroke or major extracranial bleeding. A minority of patients undergo invasive procedures to treat AF, including ablative surgery to modify electrical conductivity in the atrium itself, and left atrial appendage occlusion to seal off the area principally associated with thrombus formation.

It is estimated that over 30% of people with AF have no obvious symptoms, but are nonetheless at increased risk of stroke and systemic embolism.^(142;143) In the absence of screening, asymptomatic AF is diagnosed incidentally through routine physical examinations or after complications such as stroke or heart failure have occurred. The North Dublin Stroke Study found that 45% of strokes had underlying AF which was undiagnosed prior to the stroke.⁽¹⁴⁴⁾ AF would therefore appear to meet many of the Wilson-Junger criteria for a successful screening programme.⁽¹⁴⁵⁾ The natural history of the disease is well documented and includes a significant proportion of latent cases, a suitable test is available and effective treatments can be administered to those diagnosed, which substantially reduce the risk of serious injury or death from stroke. The idea of screening for this condition is not new,⁽¹⁴⁶⁻¹⁴⁸⁾ however there is renewed interest in the topic given the continued high incidence of stroke in many countries along with data showing that significant room for improvement remains in the identification and management of AF.⁽¹⁴⁹⁾ The overall evaluation of the benefits of a systematic screening programme for atrial fibrillation requires consideration of

the probability of adverse health outcomes in the absence of screening, the degree to which screening identifies all people who would suffer these adverse health outcomes and the magnitude of incremental health benefits of earlier versus later treatment resulting from screening.⁽¹⁵⁰⁾

The aim of this research was to review the available evidence on the impact of screening on AF detection and subsequent stroke outcomes. The best available evidence was then used to examine whether the costs of case finding (including diagnosis and treatment of patients diagnosed) are economically balanced in relation to possible expenditures on medical care as a whole. The objective was to address this issue in an Irish context, by estimating the cost-effectiveness of an opportunistic AF screening programme in primary care, which was recommended in the 2010 National Cardiovascular Health Policy and is currently being considered by the HSE National Clinical Programme for Stroke.⁽¹²⁾

3.2 CLINICAL EFFECTIVENESS OF AF SCREENING

3.2.1 INTRODUCTION

Atrial fibrillation is under-diagnosed and under-treated, especially in the elderly.^(141;151;152) Systematic screening for AF in general adult populations could potentially increase diagnosis rates by identifying people with asymptomatic AF as well as those who are symptomatic but remain undiagnosed because of failure to attribute symptoms to the arrhythmia and to seek medical attention. The effectiveness of the intervention depends on a number of factors, including the prevalence of undiagnosed AF, choice of screening strategy and its acceptability to the patient population, as well as the cardiovascular risk profile of screen detected people compared with those who present clinically.

3.2.2 METHODS

A search was performed in Medline, Embase and clinical trial registries (ClinicalTrials.gov, ISRCTN Registry, Stroke Trials Directory, the International Clinical Trials Registry Platform and the EU Clinical Trials Register) for studies examining the effectiveness of public access defibrillation interventions. Detailed search strings and the number of returned results for the search in Medline are provided in Appendix 3.1. The Cochrane RCT filter (sensitivity maximising) was applied to Medline and terms used by The Cochrane Collaboration to limit a search to RCTs in Embase were applied to Embase. Reference lists of all included papers were searched to identify potentially relevant articles. No date or language restrictions were applied to any of the searches.

Preliminary screening of all returned results was undertaken by a single person to eliminate duplicates and studies that were clearly not relevant. Assessment of the eligibility of studies and data extraction was performed independently by two people according to the inclusion criteria shown in Table 3.1. Disagreements were resolved by discussion.

TABLE 3.1 AF SCREENING REVIEW INCLUSION CRITERIA (PICOS)

Population	Men and women over the age of 40 years. Younger participants were excluded due to the extremely low incidence of AF in this population, which would render systematic screening unfeasible, and to avoid inclusion of studies involving specific patient groups (for example paediatric or elite athletes) where the aetiology, diagnosis and subsequent clinical management of AF may differ from age-related onset of AF.
Intervention	Studies comparing population-based, targeted or opportunistic screening programmes to no screening, where the control group relied on routine practice for the diagnosis of AF over the relevant time period. The method of detecting AF in the intervention group could consist of single or multi-step processes but the diagnosis needed to be ultimately confirmed using 12-lead or continuous ambulatory ECG interpreted by a GP, specialist or suitably trained ECG technician or nurse in both the intervention and control groups. Interventions that used pulse palpation alone or other types of ECG reading to confirm a diagnosis of AF were excluded.
Comparator	Diagnoses made during routine care, either incidentally or following presentation with indications for AF testing, that were subsequently confirmed using 12-lead or continuous ambulatory ECG interpreted by a GP, specialist or suitably trained ECG technician or nurse. Studies that only used an alternative systematic screening strategy, instead of routine practice, as the control were not eligible for inclusion.

Outcomes	The primary outcome being investigated was the difference in the detection of new cases of AF associated with systematic screening compared to routine practice. Secondary outcomes included the acceptability of systematic screening programmes within the target population measured by the level of uptake achieved or feedback elicited from the participants and health professionals involved and adverse events associated with screening, measured by the rate and severity of complications or adverse events associated with ECG or other forms of AF testing or psychological distress, change in quality of life and impact on well-being were included if these outcomes were measured using a validated scale.
Study type	All randomised controlled trials (RCT) and cluster randomised controlled trials (cluster-RCT) comparing systematic screening to routine practice were eligible for inclusion, irrespective of language or publication status.

Two people independently assessed the risk of bias in included studies in accordance with the guidelines stated in the Cochrane Handbook for Systematic Reviews of Interventions.⁽²⁵⁾ This was determined using the Collaboration's risk of bias tool included in section 8.5 of the handbook, which categorises studies as either high risk of bias, low risk of bias or unclear risk of bias.

Evidence synthesis was carried out using Review Manager (RevMan) software,⁽²⁴⁾ subject to an assessment of the clinical and statistical heterogeneity between studies.⁽²⁵⁾

Subgroup analysis was to be performed on the following groups subject to the availability of sufficient data.

- Over 65 years of age.
- Aged 65 to 75 years versus > 75 years.
- Men versus women.

The primary subgroup examined was the effectiveness of the intervention in the over 65 years age group. The comparator for this subgroup was people over 65 years for whom no screening programme was introduced. This group is of relevance for two reasons. Firstly, one of the features of an ideal screening programme in primary care is that there is a sufficiently high prevalence of the disease in the screened population to justify screening.⁽¹⁵³⁾ The prevalence of AF increases substantially with age.⁽¹³¹⁻¹³³⁾ The median age of AF patients is 75 years and 70% are between 65 and 85 years old. Therefore a screening programme in this group is likely to be more effective given the higher baseline prevalence of the condition compared to the overall population included in the review. The second reason why the over 65 age group is important is because they are a recognised group within most public health systems, thus providing an opportunity to capitalise on existing structures to effectively target a public health initiative such as a screening programme.

Given the increasing prevalence of AF with age, it may be logical to assume that the older the age group targeted by the screening programme the more effective it will be. To investigate this issue, a separate subgroup analysis of people aged 65 to 75 years versus those > 75 years was conducted in order to compare the effectiveness of systematic screening in an older population within the group for which screening is most likely to be implemented in practice (that is all over 65 years).

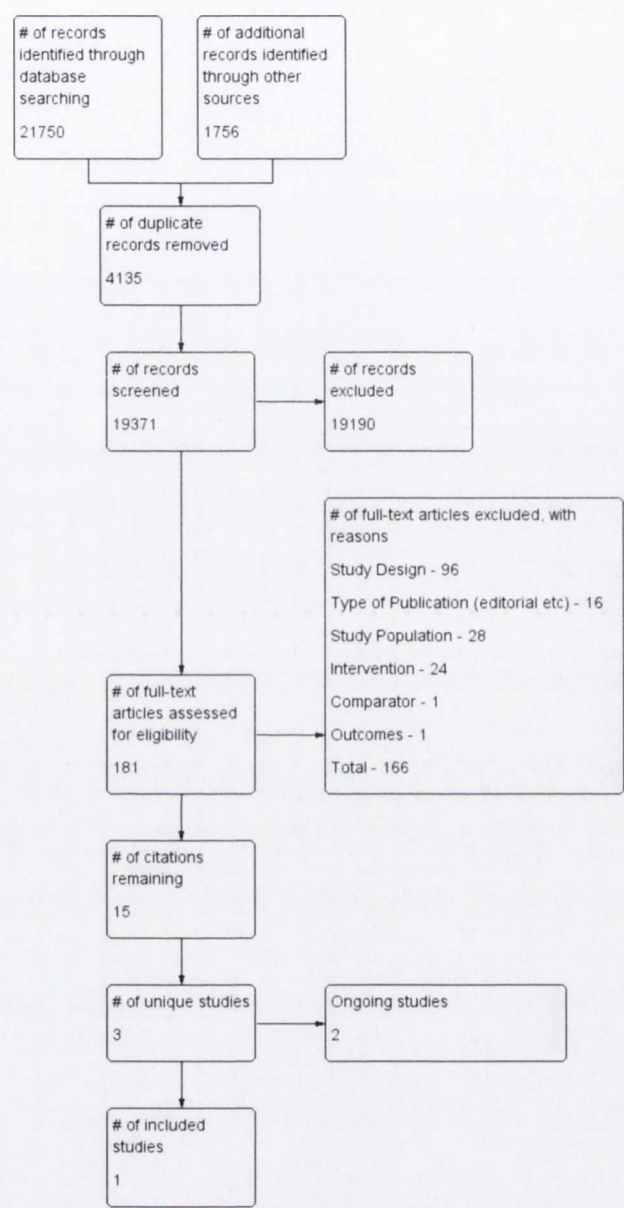
The effectiveness of systematic screening in men versus women was also examined in the subgroup analysis since there are a number of reasons to presume that gender could influence the effectiveness of a screening programme for AF. Men are more likely than women to develop the disease, which may make screening in men more effective given the higher underlying prevalence.^(135;141) However, women with AF are at greater risk of stroke (adjusted RR of 1.6 [95% CI 1.3–1.9]) and therefore may stand to benefit more from early detection.⁽¹⁴¹⁾ In addition to this, there are factors relating to the potential differences in the uptake of any screening programme in men and women that could impact on outcomes. The direction of this effect is uncertain, however. It has been reported that men are more reluctant than women to contact their GPs and other healthcare services.⁽¹⁵⁴⁾ In another study in the US it was found that despite excluding pregnancy-related visits, women were 33% more likely than men to visit a doctor, although this difference decreased with age.⁽¹⁵⁵⁾

However, others have reported that men are more likely to attend colorectal cancer screening than women.^(156;157) Since the rate of uptake of screening is such an important factor in determining the success of a screening programme it is worthwhile to separately investigate the differences in reported outcomes for men and women.^(158;159)

3.2.3 RESULTS

The search identified 23,506 citations. After removal of duplicates and screening out irrelevant studies, 181 citations were reviewed independently by two people. This produced one unique study that met the inclusion criteria.⁽¹⁵¹⁾ See Figure 3.1 for more details. No studies that evaluated the impact of screening on long term stroke outcomes were identified. Two potentially relevant ongoing studies were also identified.

FIGURE 3.1 FLOWCHART OF AF SCREENING SEARCH RESULTS



Included studies

The single study that met the inclusion criteria for this review was the SAFE (Screening for Atrial Fibrillation in the Elderly) study, a cluster-randomised trial comparing screening of those aged 65 years or over to routine practice in the primary care setting in the UK.⁽¹⁵¹⁾ A total of 25 general practices with computerised record keeping systems were randomised to either the control or intervention groups. Randomisation was stratified according to practice

size and level of deprivation (Townsend score). All practices within the intervention group received educational materials highlighting the importance of AF detection and the range of treatment options available. Healthcare professionals within these practices were encouraged to consider opportunistic pulse-taking during routine consultation. In total, 10,000 patients aged 65 years or older were randomly selected from the intervention practices and allocated equally between two different screening interventions embedded within the intervention arm. These were systematic screening, where patients were invited by letter to attend an ECG screening clinic, or opportunistic screening, where patients' GP records were flagged to prompt the GP to check the pulse whenever that patient next attended the practice for any reason, followed by ECG confirmation of an irregular pulse. Health professionals in control practices received no training; 5000 patients aged 65 years or older were randomly selected from this group for follow up as a comparator group receiving routine care.

Ongoing studies

The STROKESTOP study randomly assigned people aged 75 and 76 years from two separate regions within Sweden to treatment and control groups.⁽¹⁶⁰⁾ People without a history of AF in the treatment group were sent a letter inviting them to participate in an AF screening programme. Those who accepted the invitation were given handheld one-lead ECG recorders to use over the course of a two-week-period. Patients were instructed to take ECG recordings twice daily or when they experienced palpitations by placing their thumbs on the device, which then automatically transmitted a 30-second ECG tracing to a centralised database. In the case of inconclusive tracings, participants were offered additional ECG recordings at the discretion of the investigating cardiologist.

The study ran from March 2012 to June 2014 and invited a total of 14,387 people. The overall response rate was 54% (n=7,173). New diagnoses of AF were made in 218 patients (3.0%, 95% CI 2.7 to 3.5) in the screened group. Of the 666 patients with a prior diagnosis of AF, 517 (77.6%) were using oral anticoagulation (OAC), meaning 149 patients (2.1%) of the total screened population (7,173) had diagnosed AF but were not anticoagulated. Therefore 5.1% of patients screened benefitted from the intervention by being offered OAC. Among

newly identified cases, 93% accepted starting OAC, while the corresponding figure for those with previously diagnosed AF was 47%. However, the authors have not yet reported the rate of AF diagnosis in the control arm, so it is not possible to estimate the effect of screening on AF detection in this study. No major safety concerns associated with screening were reported.

The uptake rate of screening was relatively low (54%) so there is a risk of self-selection bias if there were inherent differences between the group that accepted screening and those that did not. The results are calculated using the denominator of those who accepted the invitation and were screened, and included those with a prior diagnosis of AF, (7,173) rather than doing an intention-to-treat analysis using the overall invited population (14,387). In contrast, the SAFE study calculated the detection rate as a percentage of the total invited population without a history of AF.

STROKESTOP investigators intend to follow study participants for five years to examine the impact of screening on the incidence of ischaemic stroke. They will also use registry data at five years to measure the detection rate of AF in the control group. Therefore currently there are no data on the relative effectiveness of this type of screening on AF detection or long term stroke outcomes.

A protocol for a randomised controlled trial (RCT) currently in progress in Spain was published in 2012.⁽¹⁶¹⁾ The authors planned to conduct a cluster randomised trial comparing opportunistic screening of over 65s in primary care with routine care, using the same screening test as the SAFE trial (pulse palpation followed by ECG confirmation), and recruit almost 13,000 participants over the course of 12 months. The estimated completion date for this study was March 2015. Contact with the principal investigator for this study revealed that a manuscript reporting the results of the trial is currently in preparation. Initial indications are that the authors will report that screening was not effective, with a greater number of irregular pulses having been detected in the control arm than the treatment arm.⁽¹⁶²⁾ The finding that opportunistic screening would decrease the number of irregular pulses detected is counterintuitive. Of particular interest will be further details on what

exactly constituted routine care in the Spanish primary care centres involved in the trial. The results of this study are not expected to be available until early 2016.

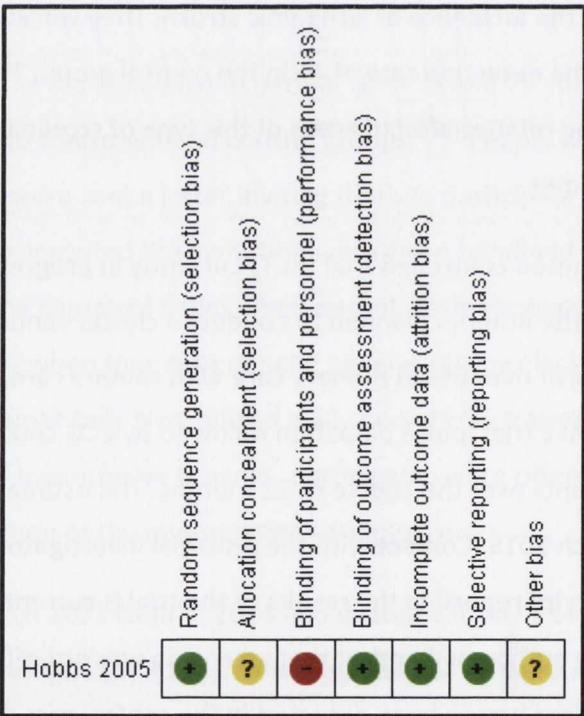
Excluded studies

Fifteen studies examining screening for AF did not meet the inclusion criteria for this review.^(146-148;163-174) The reasons for their exclusion are described in Appendix 3.2.

Risk of bias

Since only one study met the inclusion criteria, this review is limited to summarising risk of bias for that study across outcomes, with particular reference to the primary outcome of differences in the rate of detection of AF. A summary of the risk of bias assessment is shown in Figure 3.2.

FIGURE 3.2 RISK OF BIAS SUMMARY



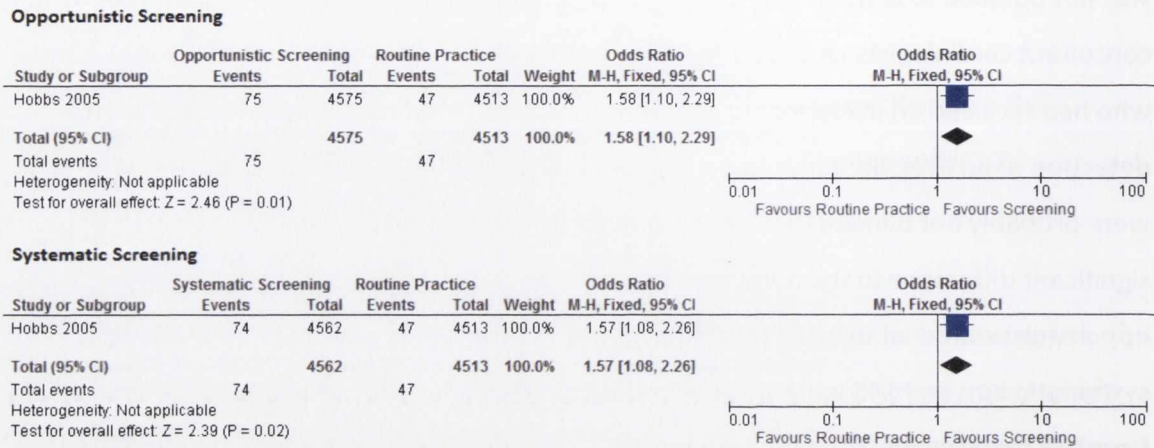
The randomisation methods used to allocate patients in the included study resulted in a low risk of bias since all centres were randomised at the same time, and the intervention and control groups were not known at the point of randomisation. There was no deliberate

concealment of allocation to the trial arms but the clusters (GP practices) were identified and recruited before randomisation was conducted. Given the nature of the intervention it was not possible to blind the participants. Detection bias was minimised by blinding the two consultant cardiologists who read the 12-lead ECG about whether ECGs were from patients who had received an invitation for screening (n = 2357) or were referred following the detection of an irregular pulse (n = 238). All ECG tracings were taken by practice nurses who were probably not blinded to which treatment arm individual patients were in. There was a significant difference in the numbers of patients excluded by GPs from the systematic and opportunistic arms of the trial following randomisation. Five hundred patients (10.1%) in the systematic arm and 195 patients (4%) in the opportunistic arm had either died, moved away from the practice area, or were terminally ill or otherwise unsuitable for screening. The risk of bias associated with this was low, however, since the same criteria were used to exclude patients in both arms of the intervention and 98% of the withdrawals from the systematic group were due to patients having died (246 patients) or moved away (245 patients). There was no suggestion of selective reporting in the included study. All outcomes specified in the trial protocol were reported.⁽¹⁷⁵⁾

Effects of interventions

For the primary outcome of detection of new cases of AF, results from the single included study showed that both systematic and opportunistic screening of people over the age of 65 years for AF in primary care was more effective than routine practice (OR 1.57, 95% CI 1.08 to 2.26 and OR 1.58, 95% CI 1.10 to 2.29, see Figure 3.3).

FIGURE 3.3 FOREST PLOTS OF OPPORTUNISTIC AND SYSTEMATIC SCREENING VERSUS ROUTINE CARE



There was no significant difference between systematic and opportunistic screening in terms of the number of new cases detected (OR 0.99, 95% CI 0.72 to 1.37). The number needed to screen in order to detect one additional case compared to routine practice was 172 (95% CI 94 to 927) for systematic screening and 167 (95% CI 92 to 806) for opportunistic screening.

When gender subgroups were analysed the results indicated that both systematic and opportunistic screening were more effective in men (OR 2.68, 95% CI 1.51 to 4.76 and OR 2.33, 95% CI 1.29 to 4.19, respectively) than in women (OR 0.98, 95% CI 0.59 to 1.62 and OR 1.2, 95% CI 0.74 to 1.93, respectively). The difference between the gender subgroups was statistically significant for systematic screening ($\text{Chi}^2 = 6.64$, $P = 0.01$; $I^2 = 84.9\%$) but not for opportunistic screening ($\text{Chi}^2 = 2.95$, $P = 0.09$; $I^2 = 66.1\%$). Subgroup analysis by age (65 to 74 years, 75 +) failed to show significant differences in the detection of new cases of AF between participants in these two age ranges.

The acceptability of the screening intervention was measured by the rate of uptake of screening and feedback from participants and health professionals. For systematic screening an invitation was considered accepted if the patient attended an ECG screening clinic following the receipt of the letter. For opportunistic screening a patient was considered to have participated in the programme if they agreed to have their pulse taken

opportunistically during a routine consultation and subsequently accepted an offer of an ECG if an irregular pulse was found. This differed from the analysis carried out within the included study, which considered uptake on the basis of those who agreed to have their pulse taken, even if they declined to have an ECG if an irregular pulse was found. The rationale for taking a different approach in this review was that since ECG confirmation was required to make a diagnosis, patients for whom this was indicated who did not proceed to have an ECG could not be said to have taken up the offer of screening since they had not completed the full two stage process. Uptake results are shown in Table 3.2.

TABLE 3.2 UPTAKE RATES OF SCREENING

Group	Systematic Screening	Opportunistic Screening
All	53%	46%
Men	57%	49%
Women	50%	41%
Aged 65 - 74	61%	49%
Aged 75+ age	43%	42%

Systematic screening was associated with a greater overall rate of uptake than opportunistic screening, with a higher rate of uptake of systematic screening being seen in both men and women. This trend was also observed in the 65 to 74 years age group, but for those aged over 75 years the uptake rates for both interventions were similar. Overall men were more likely to participate in screening than women, and people from the younger age group (65 to 74 years) were more likely to participate than those aged 75 years and over. A questionnaire concerning the acceptability of screening was administered to all patients undergoing an ECG within the intervention arm: 95% of those who completed this felt that screening was important (1810/1897); 17% (324/1897) felt that they didn't know what was involved; and 4% (70/1897) felt it wasn't convenient.

No specific adverse events associated with screening were reported. Anxiety levels and quality of life were measured at baseline and at the end of the study using the six-item Spielberger state anxiety inventory and the five-item EQ-5D. A total of 750 questionnaires were distributed to patients in the intervention arm prior to screening. Six hundred and twenty were returned: 311 from opportunistic patients (55 not completed) and 309 from

systematic patients (72 not completed). No significant difference was found between the two intervention arms at baseline for anxiety ($z = -0.392$, $P = 0.695$) or quality of life ($z = -0.334$, $P = 0.739$). A total of 777 post-screening questionnaires were distributed and 630 were returned, 535 of which were completed: 479 of these completed the six-item Spielberger state anxiety questions, and 520 completed the five-item EQ-5D questions. No significant difference was found between the two intervention arms at the end of the study for anxiety or quality of life. Patients diagnosed with AF had a higher anxiety score (38.12, 95% CI 35.89 to 40.35 versus 34.61, 95% CI 32.41 to 36.81) and a lower quality of life score (0.66, 95% CI 0.59 to 0.70 versus 0.73, 95% CI 0.68 to 0.77).

3.2.4 DISCUSSION

Only one study met the eligibility criteria for this review.⁽¹⁵¹⁾ No studies examining screening in populations under 65 years were identified and no studies reported the impact of screening on stroke outcomes. Two ongoing studies were identified that are likely to be of relevance to this review in the future.^(176;177)

Based on the results of one included study, this review found that both systematic and opportunistic screening increase the rate of detection of AF in those people aged 65 years and over compared with routine practice. There was no significant difference in the relative effectiveness of the two interventions.

The uptake rate in the overall study population for opportunistic screening was 46%, which was calculated based on the numbers of patients who agreed to have their pulse taken and to have an ECG if an irregular pulse was found. Thirty-four percent of those that were found to have an irregular pulse declined an ECG and were therefore not considered to have been opportunistically screened. Of those who did not consent to an ECG, 46% (56/122) already had a diagnosis of AF. When only those without a baseline diagnosis of AF are used to calculate uptake the percentage of patients who are discovered to have an irregular pulse but decline an ECG is 27%. The reasons for such a high dropout rate between irregular pulse finding and ECG are unknown. If the uptake rate is calculated solely on the basis of a patient consenting to having their pulse taken opportunistically during a routine consultation, then the uptake rate increases to 69%. The uptake rate of the included study is higher than that

observed in an earlier study within the same health system comparing systematic screening (via invitation to attend nurse led pulse palpation) to opportunistic screening that recorded an uptake rate of 29% in the opportunistic arm based on those who presented for any reason and consented to have their pulse taken regardless of whether or not an ECG was subsequently used to confirm the diagnosis.⁽¹⁶⁶⁾ Hobbs et al. concluded that these differences in uptake were due to improved coverage attained over the 12 months period of their study, compared to the other study which ran over six months.⁽¹⁶⁶⁾ An excluded study that was also conducted in the primary care setting in England invited all patients aged 65 years and over for a 12-lead ECG to screen for AF and reported an uptake rate of 85%.⁽¹⁴⁸⁾ The uptake rate of ECG screening reported in this study differs considerably from that of the systematic screening arm in the SAFE trial, which achieved an uptake rate of 53%.

Of the 74 new cases of AF identified in the systematic group, 22 (30%) were diagnosed outside of the screening programme. For opportunistic screening, a greater proportion of the 75 newly identified cases were diagnosed outside of the screening programme (44/75, 59%) than within it (31/75, 41%). When calculations are based only on patients who received the screening intervention, systematic screening has a detection rate of 2.2% compared with 0.9% for opportunistic screening. This implies a detection rate for those who did not participate in screening of 1% and 3% for the systematic and opportunistic groups, respectively. The detection rate in non-participants in the systematic arm is similar to that observed in the control arm (both approximately 1%), a figure which contrasts with the significantly higher detection rate seen in non-participants in the opportunistic arm (approximately 3%). The reasons for these differences are unclear, although it could potentially be associated with increased AF awareness as a result of the educational element of the intervention that occurred prior to screening.

Subgroup analysis of data from the single included study indicates that the effectiveness of both screening interventions is different in men and women. When male and female subgroups are analysed separately, both systematic and opportunistic screening continue to show a significant effect on new case detection compared with routine practice in men. No difference between either systematic or opportunistic screening and routine practice is seen in the subgroup of women. Possible reasons for this include differences in the prevalence of

AF in men and women, differences in the rate of uptake, or differences in the overall numbers in each group, which would result in subgroups being underpowered to detect significant effects. However this study included more women than men in both intervention groups (1958 men compared with 2604 women in systematic group; 1941 men compared with 2634 women in opportunistic group; 1880 men compared with 2633 women in control group) although it was still underpowered to detect effect sizes of the magnitude seen in the overall study within the subgroup of women. The rate of uptake of screening was higher among men than women (57% versus 50% for systematic; 49% versus 41% for opportunistic), but more women agreed to have their pulses taken in the opportunistic arm (71% versus 67%). It has consistently been shown that there is a higher prevalence of AF in men than in women and this is borne out in the baseline prevalences reported in this study (7.8% in males, 6.8% in females).⁽¹⁷⁸⁾ Therefore the differences in effect observed between the subgroups of men and women could be due to a combination of higher prevalence and greater rates of participation among men.

The study that met the inclusion criteria for this review compared systematic screening via an invitation to attend an ECG clinic and opportunistic screening via pulse palpation during routine consultations. However, there are a range of other strategies that could be used to screen for the arrhythmia in a variety of settings. As no studies comparing these to routine practice were identified, this review is limited in terms of the screening interventions that could be compared. Alternative screening strategies that have been described in studies that were excluded include the use of self screening methods,^(146;163) population based screening programmes using a national media campaign to invite participants,⁽¹⁷³⁾ systematic screening where patients are invited for pulse palpation rather than an ECG,⁽¹⁶⁶⁾ and opportunistic ECG recording.⁽¹⁷⁹⁾ A 2012 review of strategies for the detection of AF identified two studies examining the effectiveness of screening.^(151;166;180) The conclusions are in line with those of the SAFE trial, recommending opportunistic screening in the general population and highlighting that while a 12-lead ECG remains the standard investigation, the cost-effectiveness of newer technologies requires further research.

3.2.5 CONCLUSION

There is good evidence to show that screening improves detection rates of AF compared with routine care. No major safety concerns were identified and both opportunistic and systematic screening were reported to be acceptable to patients. A major limitation of the available evidence is the lack of data on the stroke risk profile of asymptomatic AF and the impact of screening on long term stroke outcomes and mortality.

3.3 COST-EFFECTIVENESS OF AF SCREENING

3.3.1 INTRODUCTION

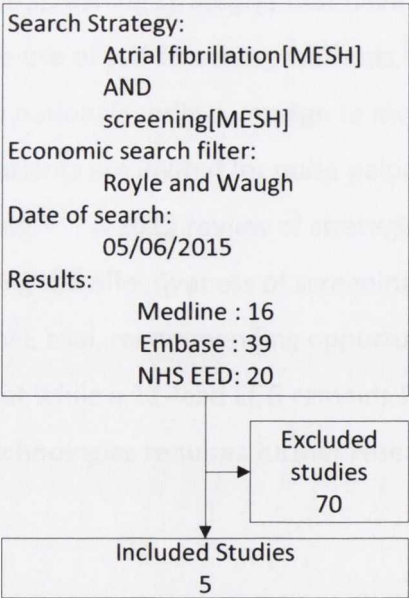
As the systematic review of the evidence shows, the only available evidence on AF screening relates to once off screening. Evaluating the cost-effectiveness of a prospective national screening programme for atrial fibrillation requires an estimate of the long term impact of successive screening rounds on AF detection. It also requires an estimate of the effect of earlier detection and treatment on the incidence and severity of AF related strokes. This section reports the results of a review of cost effectiveness studies of AF screening and describes the economic analysis carried out to estimate the cost effectiveness of AF screening in Ireland.

3.3.2 REVIEW OF ECONOMIC ANALYSES OF AF SCREENING

3.3.2.1 METHODS

A search for economic evaluations of screening for atrial fibrillation (AF) conducted in Medline, Embase and NHS EED identified five studies that compared any type of screening programme in the general population to usual care. Figure 3.4 shows the search strategy used and a flowchart of the results.

FIGURE 3.4 SEARCH STRATEGY AND RESULTS



3.3.2.2 RESULTS

Five studies were identified, two from the UK, and one each from Japan, Australia and Sweden. The included studies were all published between 2004 and 2015, and examined the cost-effectiveness of both systematic and opportunistic screening. Table 3.3 provides a summary of identified studies, each of which are described in more detail below. Among the excluded studies was a 2015 cost-effectiveness analysis of AF diagnosis using 30 day intermittent ECG and 24 hour continuous Holter monitoring in people who had a recent ischaemic stroke, which was excluded on the basis that the study did not examine the implications of screening in a general population.⁽¹⁸¹⁾

TABLE 3.3 SUMMARY OF AF SCREENING COST-EFFECTIVENESS STUDIES

Study	Setting	Perspective	Study (Costs)	Screening	Findings*
Maeda 2004 ⁽¹⁶⁷⁾	Primary care Japan	Societal	Cost-utility analysis (2001 USD)	Pulse palpation and ECG	Screening by pulse palpation and screening by ECG are both cost-effective (ICERs <€17,000/QALY)
Hobbs 2005 ⁽¹⁵¹⁾	Primary care UK	Health service	Cost-utility analysis (2003 GBP)	Pulse palpation and ECG	Screening by opportunistic pulse palpation has a 60% chance of being cost-effective). Systematic ECG screening is not cost-effective.
Lowres 2014 ⁽¹⁸²⁾	Community pharmacies Australia	Health service	Cost-utility analysis (2012 AUD)	ECG	ECG screening using a mobile phone attachment is cost effective (€3,311/QALY)
Rhys 2013 ⁽¹⁸³⁾	Flu vaccination clinics UK	Health service	Cost-effectiveness analysis (2011 GBP)	Pulse palpation	Cost per new case of AF diagnosed was €292
Aronsson 2015 ⁽¹⁸⁴⁾	Primary care Sweden	Societal	Cost-utility analysis (2014 EUR)	ECG	Prolonged, intermittent ECG recording was cost-effective (ICER €5,097/QALY)

* All results have been converted to 2014 Irish € using the relevant consumer price index and purchasing power parity

Annual pulse palpation and ECG in primary care

Maeda et al. examined the cost-effectiveness of community-based annual ECG or pulse palpation AF screening programmes compared with no screening for over 65s in Japan.⁽¹⁶⁷⁾ This was a cost-utility analysis with costs in (2001) US dollars and benefits in QALYs. They used a Markov model that differentiated between non-disabling, disabling and repeated disabling ischaemic and haemorrhagic strokes over a 25 year time horizon with costs and benefits discounted at 3%. In this analysis it was assumed that ECG and pulse palpation have sensitivities of 100% and 97%, respectively, that the screening programme would achieve uptake rates of 100% and that all detected AF cases would be anticoagulated. The study included direct costs associated with screening and treatment (apart from the capital costs of ECG equipment), as well as the cost of the patient's time, calculated using Japanese average salary data. Results for screening in men and women were reported separately. The incremental cost-effectiveness ratio (ICER) for annual pulse palpation in males was \$7,637 and \$9,968 in females. The ICER for annual ECG in males was \$7,830 and \$10,220 in females. The authors concluded that screening was cost-effective and that both screening tests were comparable in terms of the benefits and costs.

An economic analysis was carried out as part of the Screening for Atrial Fibrillation in the Elderly (SAFE) trial of opportunistic and systematic AF screening of over 65s in a UK primary care setting.⁽¹⁵¹⁾ This was conducted from the perspective of the National Health Service in the UK, but also included the opportunity cost of patient's time. Data on the sensitivity of pulse palpation (87%) and ECG (12-lead GP read ECG 80%) were taken directly from the trial. Long term outcomes were estimated from the literature, using an assumption that screen detected cases carry the same risk of stroke and systemic embolism as those detected through routine practice. Discrete event simulation was used to model a cohort of people from age 65 to death, differentiating between non-disabling and disabling ischaemic stroke. Costs and benefits were discounted at 3.5% annually. Results showed that the incremental benefit of opportunistic screening (in QALYs) was not significantly different from that of no screening, but was either cost neutral or marginally less costly. This resulted in a very flat cost-effectiveness acceptability curve (CEAC) indicating that opportunistic screening had approximately a 60% chance of being cost-effective at any given willingness to pay (WTP)

threshold. Opportunistic screening was more cost-effective than systematic screening, which was associated with a fivefold increase in the cost of AF case detection (GBP£1,787 versus GBP£363, 2003).

AF screening using iPhone ECG in pharmacies

Lowres et al. reported the results of a cost-utility analysis of screening for AF in community pharmacies using an ECG taken by a specially adapted iPhone and interpreted using a software algorithm reported to have a sensitivity of 98%.⁽¹⁸²⁾ The analysis was conducted from the perspective of the Australian health service, based on a cohort of men and women aged 65 to 84 years. Cost data were taken from a feasibility study using the iPhone ECG device carried out by the authors previously, and data on the long term effectiveness of AF detection were taken from UK registry data. Utility data were taken from previous studies estimating that each stroke prevented by screening resulted in a gain of 5.09 QALYs. Only costs were discounted, at a rate of 5% annually. It was assumed that the uptake rate of screening would be 50% and that adherence to treatment would be 55%. Results of this study found that screening was highly cost-effective, with an incremental cost of €3,142 per additional QALY gained through screening.

AF screening in flu vaccination clinics

Rhys et al. reported the results of a study examining the clinical effectiveness and costs associated with screening over 65s attending annual flu vaccination clinics in the UK using pulse palpation and ECG confirmation of an irregular pulse.⁽¹⁸³⁾ A total of 573 patients were screened and two new cases of AF were identified. The study was not a cost-effectiveness analysis, but did report the cost of identifying a new case (GBP£234). The cost was based on estimated ECG costs in primary care of £34 that included the cost of the time required for a nurse to perform an ECG (£12). Long term costs and benefits were not reported. The authors concluded that although acceptable to patients, screening at annual flu vaccination was ineffective.

AF screening using intermittent ECG recording

Aronsson et al. reported a cost-effectiveness analysis based on the STROKESTOP trial of screening of 75 and 76 year olds in Sweden using intermittent ECG recordings (see Section 3.2).⁽¹⁸⁴⁾ In this study, participants underwent an initial ECG screen and if AF was not detected they were requested to provide two 30-second ECG traces per day for two weeks from home, using a portable device that automatically transmitted the recordings to a central database. Although no information on the AF detection rate in the control group is currently available, data from the screened group indicated that this type of screening increased the known AF prevalence by 3%. The study also detected a further 2% who had a prior AF diagnosis but were not taking anticoagulant medication. Estimates of the effect of treatment were taken from the literature and cost data from 2014 were obtained from the Swedish healthcare system. It was assumed that 93% of AF patients would be anticoagulated with apixaban. QALY losses as a result of ischaemic and haemorrhagic stroke were included as QALY decrements (0.15 and 0.30, respectively) rather than as a QALY weighting based on baseline quality of life by age. A Markov model was used to estimate the costs and benefits of screening in a cohort of 1,000 patients over their entire lifetime. Results indicated that intermittent ECG screening of 75 year olds was cost-effective, with a cost per additional QALY gained of €4,313, compared with no screening.

3.3.2.3 DISCUSSION

All cost-utility analyses identified in this review concluded that AF screening is cost-effective compared with no screening. However there is a high degree of heterogeneity in the type of screening programme, study population and methods used to estimate the short and long term consequences of the intervention.

An appraisal of the available evidence was carried out per the International Society For Pharmacoeconomics and Outcomes Research (ISPOR) guidelines for assessing applicability, validity and transferability of findings.⁽¹⁰¹⁾ The most applicable studies in terms of screening programme and population were the Japanese and UK (SAFE) studies, which were the only ones to examine pulse palpation in primary care for over 65s.^(151;167) These produced conflicting results, with the Japanese evaluation finding that both annual pulse palpation

and annual ECG cost approximately the same, whereas the UK study found that the costs of systematic screening by invitation to ECG were five times that of opportunistic pulse palpation. Both studies found that screening was associated with marginal increases in the number of QALYs gained. The Japanese study assumed that the sensitivity of pulse palpation and ECG were higher than the estimates used in the UK trial. As the UK estimates were based on RCT data they have greater validity. Both studies used fixed estimates of the risk of stroke over the course of the study time horizon, rather than adjusting the risk based on the age of the cohort. Neither of the studies examined the impact of changes in the proportion of patients on antiplatelet versus anticoagulant therapy, and both studies were carried out prior to the widespread use of direct oral anticoagulants (DOACs, also referred to as new oral anticoagulants [NOACs]). They also failed to examine the impact of screen-detected AF patients potentially having a lower baseline risk of ischaemic stroke.

3.3.2.4 CONCLUSION

Two of the five cost-effectiveness studies identified examined annual opportunistic pulse palpation in those aged 65 years and over. While both ultimately found that screening was cost-effective, there are limitations in regard to the validity of some of the clinical and cost estimates used in the analyses. The applicability of the results to the present situation in Ireland is low, given the differences in healthcare costs and advances in the available treatments to reduce the risk of stroke in AF since these studies were carried out. Therefore to estimate the cost-effectiveness of a prospective national AF screening programme in Ireland it was necessary to develop an original economic model to simulate the anticipated costs and benefits associated with screening, using the best available Irish and international data on the epidemiology of AF and AF-related stroke, the effectiveness of treatment, the impact of AF and stroke on health related quality of life and the costs associated with diagnosis, treatment and long term care.

3.3.3 COST-EFFECTIVENESS ANALYSIS METHODS

3.3.3.1 TYPE OF ECONOMIC EVALUATION

A cost-utility analysis was carried out where costs are measured in Euro and utility is measured in quality-adjusted life years (QALYs).

3.3.3.2 TARGET POPULATION AND SETTING

The target population in the primary analysis was men and women aged 65 or over in Ireland. The setting was the Irish health system, where screening was carried out within GP-led primary care services. Stroke treatment was set in the acute public hospital sector and long term care was set in both public and private residential nursing homes and in the community, depending on where patients are discharged following a stroke.

3.3.3.3 TECHNOLOGY AND COMPARATORS

The technology being assessed was annual opportunistic AF screening of all men and women aged 65 or over by pulse palpation followed by ECG if an irregular pulse is detected. ECGs were performed in primary care and read by a GP with the aid of computerised interpretation algorithms. Screening takes place in GP practices when a patient attends for an appointment for any reason. The primary comparator is routine care, where testing for AF is generally only done when patients present with signs or symptoms indicative of the arrhythmia. The choice of comparator was informed by the recommendations contained in the National Cardiovascular Policy 2010-2019 and the pilot AF screening project conducted by the HSE National Clinical Programme for Stroke and was consistent with the best available evidence on the effectiveness of screening.

3.3.3.4 PERSPECTIVE, TIME HORIZON AND DISCOUNTING

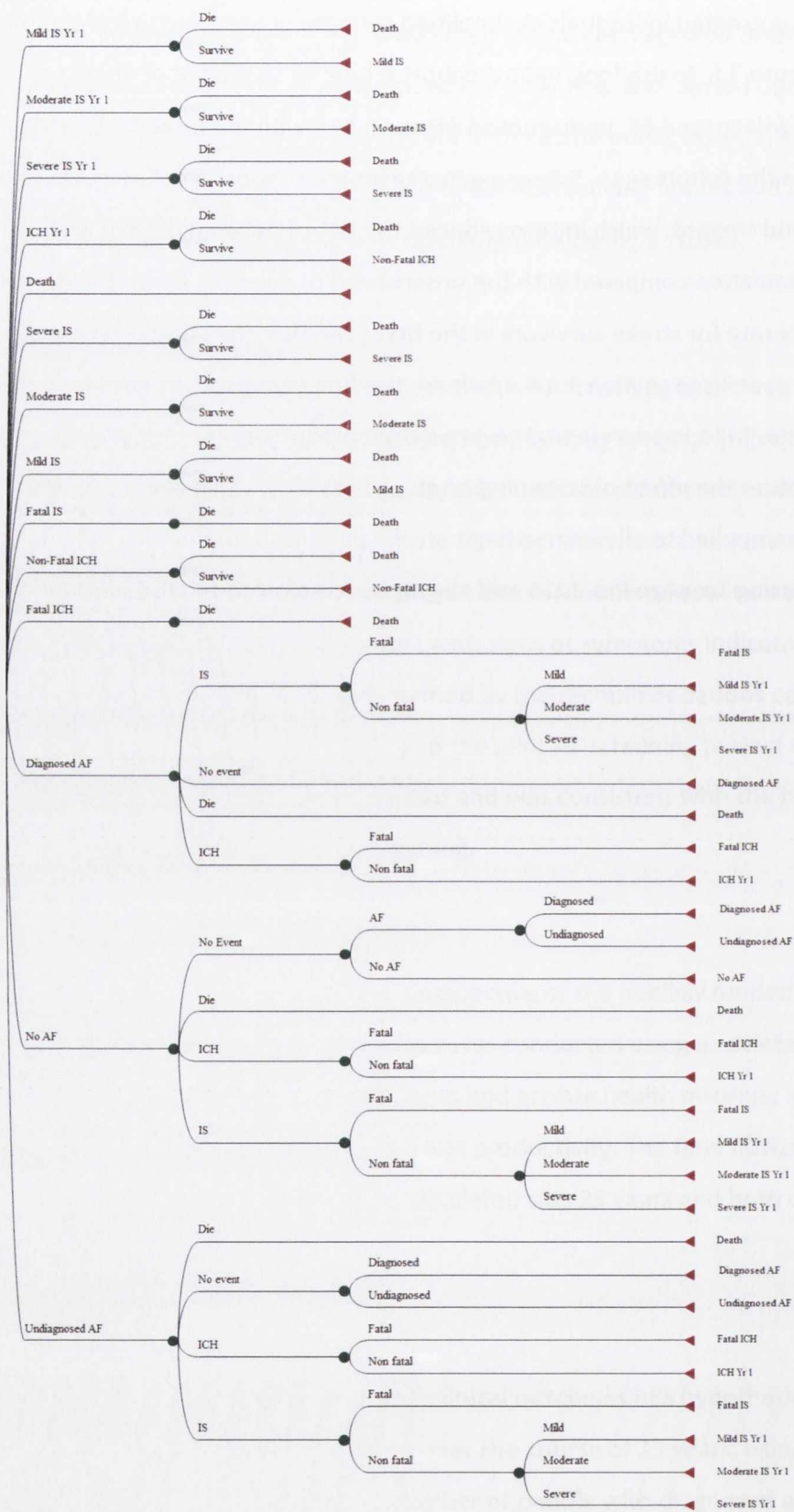
The primary analysis was carried out from the perspective of the publicly funded health and social care system in Ireland. A secondary analysis was conducted using a societal perspective that included costs that fall on patients and private health insurers, as well as indirect costs associated with informal care and lost productivity. The time horizon over which the costs and benefits of screening was calculated was 25 years and both costs and benefits were discounted at 5%.

3.3.3.5 MODEL STRUCTURE

A Markov model was used to simulate costs and clinical outcomes in a hypothetical cohort of men and women with and without screening over the course of 25 years, using a cycle length of one year. The model estimated the number of people with diagnosed and

undiagnosed AF in each group, as well as the incidence and severity of AF-related stroke in treated and untreated individuals. A simplified diagram of the structure of the model is shown in Figure 3.5. In this longitudinal cohort model all simulated patients begin in one of three states (diagnosed AF, undiagnosed AF or no AF), with the probability of developing AF increasing as the cohort ages. Screening increases the proportion of AF cases that are diagnosed and treated, which in turn reduced the risk of ischaemic stroke within the screened population compared with the unscreened population. Given the differences in the mortality rate for stroke survivors in the first year after the stroke compared with subsequent years (see section 3.3.4.7 below), the first year post stroke is modelled as a separate state. Mild, moderate and severe ischaemic strokes are modelled separately in order to capture the effect of screening on stroke severity, while average costs and outcomes are applied to all haemorrhagic stroke patients in the model. All analyses were carried out using TreeAge Pro 2014 and all graphs were produced in Excel.^(106;107)

FIGURE 3.5 MODEL STRUCTURE



3.3.3.6 SENSITIVITY AND SCENARIO ANALYSIS

Stochastic analysis methods were used to capture the uncertainty and variability associated with the input parameters, which were varied within plausible ranges derived from published evidence and expert opinion. All estimates of the incremental costs and benefits of screening were calculated using Monte Carlo simulation, using 10,000 iterations. Each iteration sampled parameter values from their defined distribution, providing the mean estimate of the incremental costs and benefits, along with the level of uncertainty associated with this estimate.

Deterministic univariate sensitivity analysis was performed to estimate the effect of uncertainty regarding individual parameter estimates. In this analysis, the model is run with each parameter in turn fixed at its upper and lower bounds while all other parameters are held at their average value. Scenario analysis was carried out to examine the potential impact of changes to some of the key parameters associated with screening. These are described in the section outlining how each parameter was estimated.

3.3.4 ESTIMATES OF EFFECT

Evaluation of the cost-effectiveness of screening requires estimation of the average probability of an event occurring in members of the simulated cohort, such as developing atrial fibrillation, having a stroke, dying, or being diagnosed with AF through screening, as well as the impact of treatment on the risks of experiencing these clinical outcomes. This section outlines how each of these parameter estimates was derived.

3.3.4.1 INCIDENCE OF ATRIAL FIBRILLATION

Accurately measuring the incidence of atrial fibrillation by age is challenging due to the characteristics of the disease, which can be minimally symptomatic or intermittent. There is currently no AF register in Ireland that records the number of people diagnosed by age group. The Irish Longitudinal Study on Ageing (TILDA) study recorded prevalence data by asking all 8,175 participants whether or not they had ever been diagnosed with AF and also by screening 4,890 participants using 3-lead ECG. The results of this showed an overall prevalence estimate of 3% in over 50s (approx 150 individual cases in total).⁽¹⁸⁵⁾ This was of

limited use in the analysis, which requires data on the risk of developing AF by year of age (incidence data).

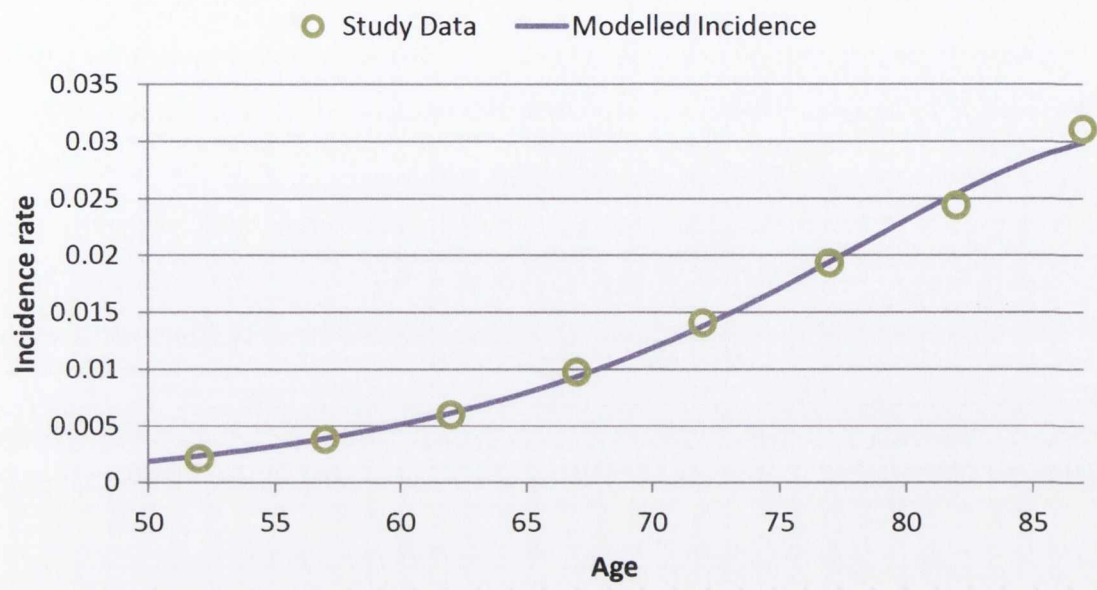
A number of international studies have estimated the incidence and prevalence of AF in the general population. One of the most recent and highly populated studies was carried out in Germany between 2006 and 2008, involving 8.3 million patients.⁽¹³⁴⁾ This produced relatively high estimates of AF prevalence compared with previous studies. Some of this difference is explained by the fact that the German study included any type of AF diagnosis whereas other studies only included permanent AF. It has also been suggested that AF prevalence has risen in many societies in the recent past due to an increased focus on detection, which could contribute to some of the difference between older and more recent studies.^(186;187) The risk that AF prevalence is overestimated in this study by including suspected (as opposed to definite) AF cases is low, since inclusion required two outpatient AF diagnoses in two different quarters or at least one inpatient AF diagnosis. Generally in these types of studies the risk of underestimating AF prevalence is greater than the risk of overestimation, since not every case of AF is diagnosed and some patients with AF may not visit a doctor regularly.⁽¹⁸⁸⁾ Given the large numbers of participants, thorough case ascertainment and the applicability of the setting (Western Europe), the German study⁽¹³⁴⁾ on AF incidence by age is the best available data to use in this analysis. When prevalence in the TILDA study is calculated for those aged 50 to 84 within the group of people that were screened (N=4,849) by adding those that were screen-detected to those that reported a previous diagnosis of AF, the prevalence of AF in Ireland is consistent with the German study. The real prevalence of AF is likely to exceed both these estimates, given the difficulty in detecting all prevalent cases.

Incidence by year from this study is modelled using a rational function of the form:

$$Incidence_{AF} = \frac{\beta_0 + \beta_1 Age}{1 + \beta_2 Age + \beta_3 Age^2}$$

The study data and fitted model are shown in Figure 3.6.

FIGURE 3.6 AF INCIDENCE



3.3.4.2 INCIDENCE OF STROKE

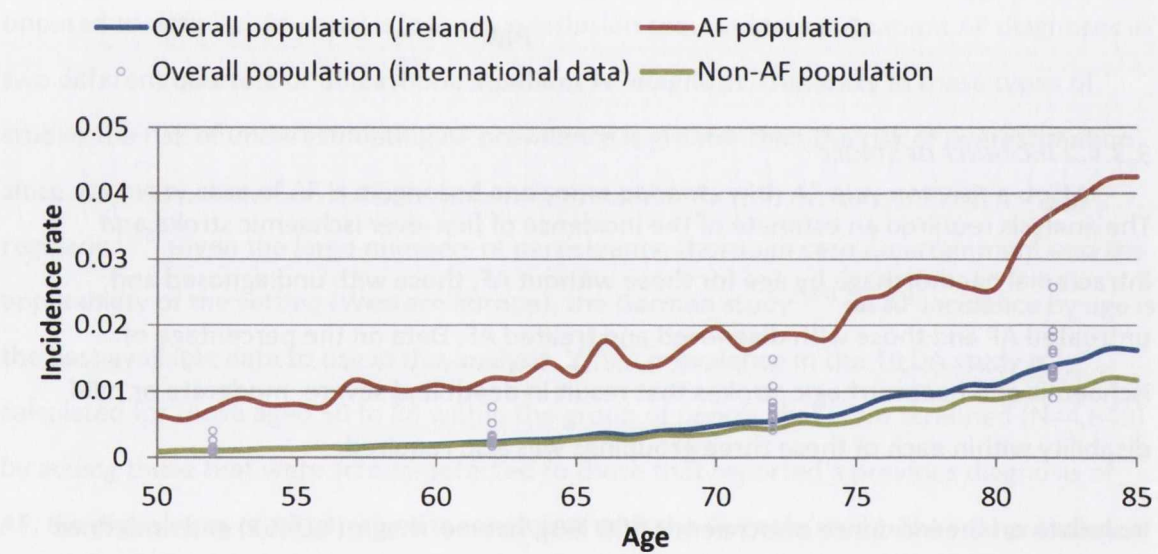
The analysis required an estimate of the incidence of first-ever ischaemic stroke and intracranial haemorrhage by age for those without AF, those with undiagnosed and untreated AF and those with diagnosed and treated AF. Data on the percentage of ischaemic and haemorrhagic strokes that result in death and severe, moderate or mild disability within each of these three groupings was also required.

Irish data on the incidence of ischaemic (ICD I63), haemorrhagic (I60-I62) and undefined (I64) stroke by year of age for those without a diagnosis of AF (ICD I48) were obtained from the hospital in-patient enquiry (HIPE) system for the period 2010 to 2014. Population data required to calculate overall incidence rates were obtained from the Central Statistics Office (CSO). To exclude, insofar as possible, cases of recurrent stroke, only one episode was included per patient, and that episode had to be an emergency, non-readmitted case. Undefined stroke cases (I64) were divided between ischaemic and haemorrhagic strokes in the same ratio as the incidence of definite ischaemic to haemorrhagic strokes, to avoid underestimating overall incidence. HIPE data on overall stroke incidence for those with and

without a diagnosis of AF are shown in Figure 3.7, which shows incidence rates consistent with those reported internationally.⁽¹⁸⁹⁾

The evaluation also required an estimate of the rate of ischaemic and haemorrhagic stroke in those without a diagnosis of AF. In the analysis this baseline risk is then adjusted if the person develops AF and is diagnosed, or if they develop AF and remain undiagnosed. The evidence used to inform these parameters is discussed below. Briefly, an AF diagnosis increases the risk of ischaemic stroke, but does not alter the risk of haemorrhagic stroke, whereas antithrombotic treatment decreases the risk of ischaemic stroke, but increases the risk of haemorrhagic stroke.

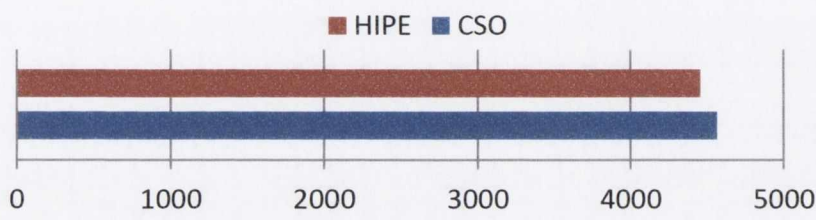
FIGURE 3.7 OVERALL INCIDENCE OF STROKE IN AF AND NON-AF POPULATIONS



Since HIPE only includes data on hospital admissions there is a risk that it will underestimate the total number of strokes due to the exclusion of people who are pronounced dead before being brought to hospital. Specific data on the number of such cases is unavailable. The recently established National Stroke Register relies solely on HIPE data and does not collect this information. To examine the potential impact of this issue the latest five years of data from the CSO on total death certificate mortality from ischaemic and haemorrhagic stroke (I60-I64, 2008 to 2012) were compared with HIPE data on the total number of stroke deaths in hospital during the same period (discharge code of 06 [Died with post mortem] or 07 [Died no post mortem]). There was only a 2% difference between the two (Figure 3.8),

which indicates that using the HIPE data will not result in a major underestimate of stroke incidence. This is consistent with the results of previous work carried out by The Economic and Social Research Institute (ESRI) comparing HIPE data from Dublin hospitals with that of the North Dublin Stroke Study, which found a difference of 3% in first-ever or recurrent stroke incidence.⁽¹⁹⁰⁾

FIGURE 3.8 TOTAL DEATHS FROM STROKE 2008-2012, CSO VERSUS HIPE

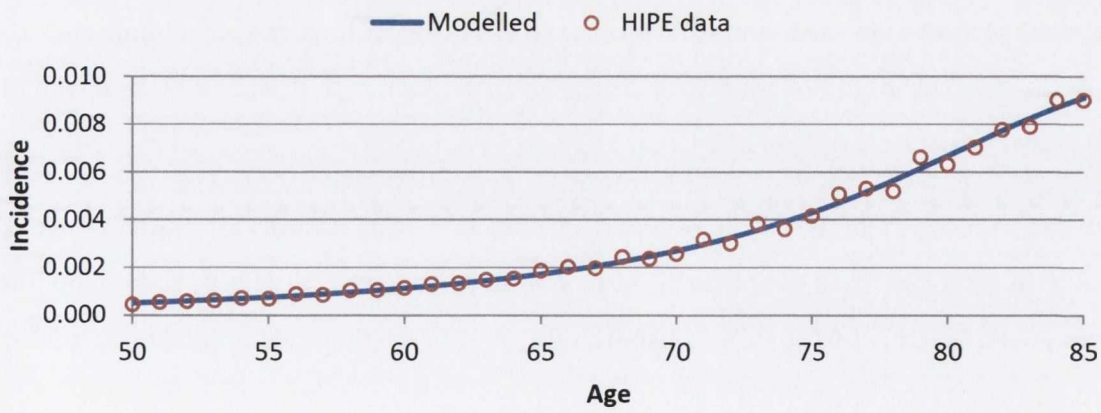


Incidence of ischaemic stroke in patients without AF

The estimated incidence of first ever ischaemic stroke by age for those without AF in Ireland is shown in Figure 3.9. This was modelled using a rational function of the form:

$$Incidence_{IS} = \frac{\beta_0 + \beta_1 Age}{1 + \beta_2 Age + \beta_3 Age^2}$$

FIGURE 3.9 BASELINE INCIDENCE OF ISCHAEMIC STROKE BY AGE

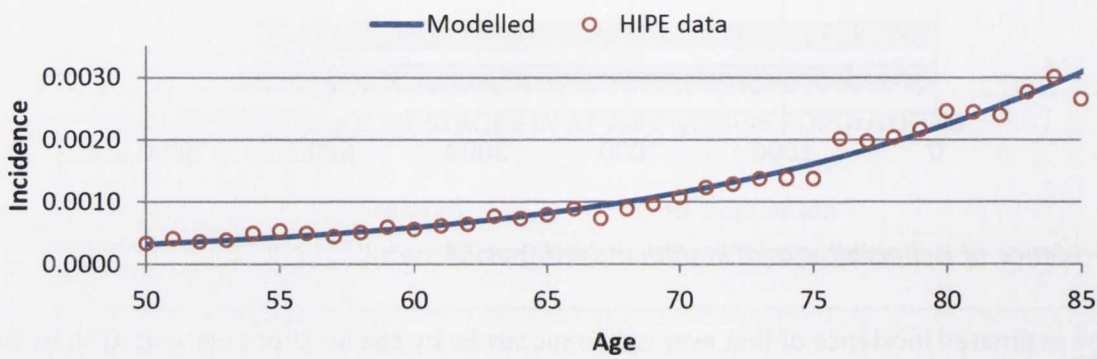


Incidence of haemorrhagic stroke in patients without AF

As with ischaemic stroke, the incidence of first-ever haemorrhagic stroke by age in people without AF was estimated using HIPE data and modelled as a 4th order polynomial (Figure 3.10):

$$Incidence_{HS} = \beta_0 + \beta_1 Age + \beta_2 Age^2 + \beta_3 Age^3 + \beta_4 Age^4$$

FIGURE 3.10 BASELINE INCIDENCE OF HAEMORRHAGIC STROKE BY AGE

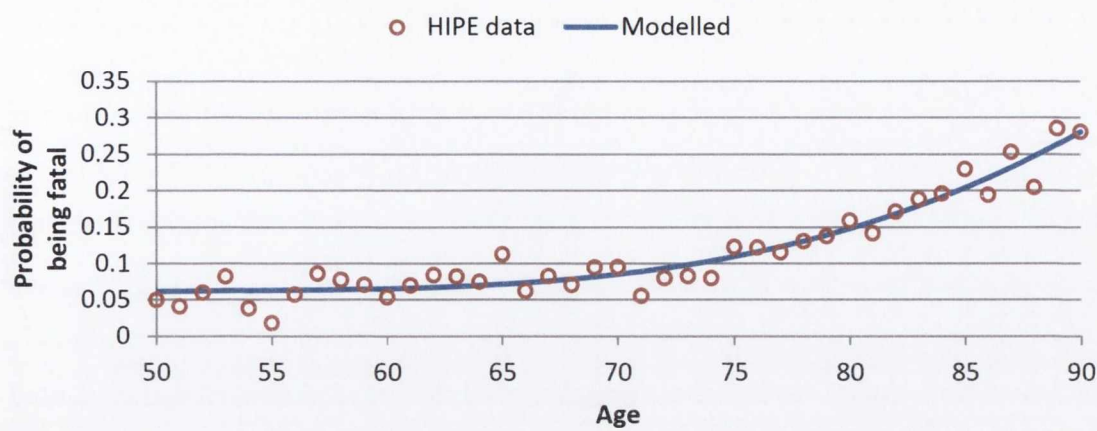


Probability of an ischaemic stroke being fatal in the absence of AF

Not only does AF increase the chances that a stroke will occur, but these strokes are more likely to be fatal and those who do survive are left with a greater degree of functional impairment than non-AF strokes.⁽¹⁹¹⁾ In order to capture this, the model applied the baseline probability that a first-ever non-AF stroke is fatal to those without the arrhythmia and applied the appropriate relative risk to those with AF (the risk of stroke associated with AF is dealt with separately further on).

The probability of a first ever non-AF ischaemic stroke being fatal was estimated by age, using HIPE data on the percentage of cases that died in hospital (discharge code of 06 [Died with post mortem] or 07 [Died no post mortem]). This parameter was modelled as a 3rd order polynomial (Figure 3.11).

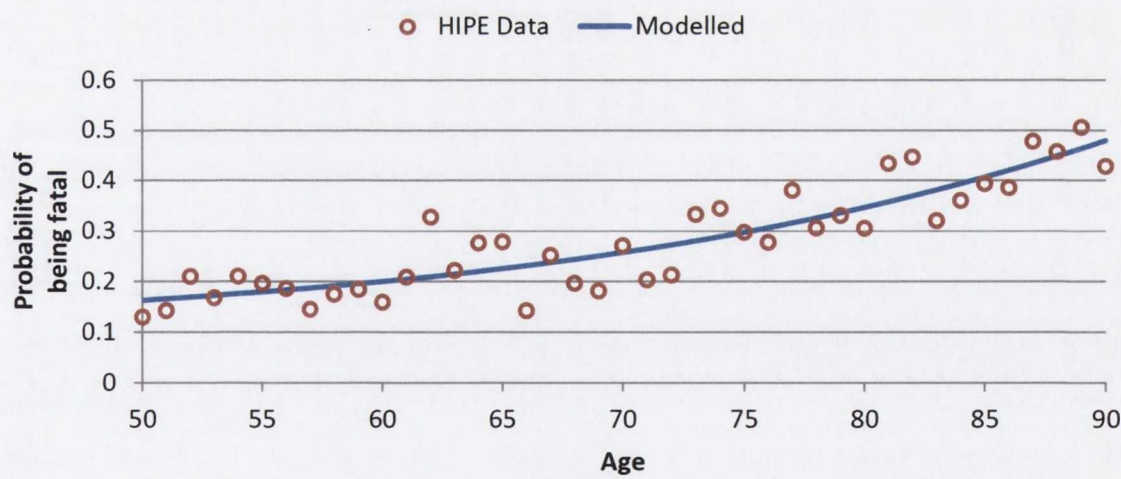
FIGURE 3.11 PROBABILITY OF A NON-AF ISCHAEMIC STROKE BEING FATAL



Probability of a haemorrhagic stroke being fatal in the absence of AF

The probability of a first ever non-AF haemorrhagic stroke being fatal, was estimated by age, using HIPE data on the percentage of non-AF haemorrhagic stroke cases that died in hospital (discharge code of 06 [Died with post mortem] or 07 [Died no post mortem]). This parameter was modelled as a 3rd order polynomial (Figure 3.12).

FIGURE 3.12 PROBABILITY OF A NON-AF HAEMORRHAGIC STROKE BEING FATAL

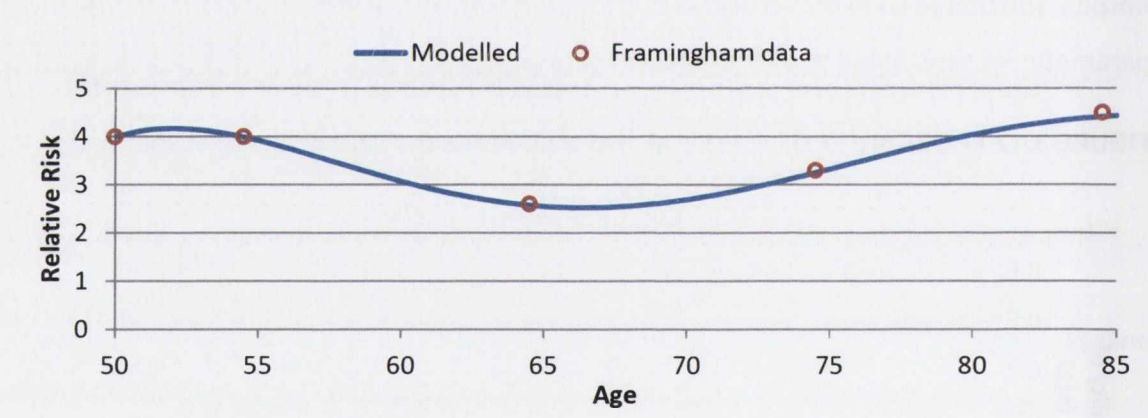


Relative risk of a ischaemic stroke in patients with AF

AF increases the risk of stroke. Therefore, it was necessary to estimate the relative risk of stroke by age, in those without AF (already covered above) and those with AF who are not receiving treatment. The best evidence on the relative risk of stroke associated with AF

comes from the Framingham Heart Study, which examined a cohort of 5,070 men and women free of cardiovascular disease (including atrial fibrillation) at baseline every two years during a 34-year follow up period prior to the widespread use of oral anticoagulation.⁽¹³¹⁾ Results of this study found that the risk of stroke is not uniform across all age groups. Relative risk of stroke associated with AF by age group (adjusted for other stroke risk factors [hypertension, coronary heart disease and cardiac failure]) is shown in Figure 3.13. This was modelled as a 5th order polynomial. The study included both ischaemic and haemorrhagic strokes, whereas ischaemic strokes are primarily of interest for this analysis. However they report that “stroke events resulting from haemorrhage accounted for only 11.6% of the total, and their exclusion would not appreciably influence the results of the analyses”.⁽¹³¹⁾

FIGURE 3.13 RELATIVE RISK OF STROKE IN AF VERSUS NON-AF PATIENTS, ADJUSTED FOR OTHER RISK FACTORS



Although there is some evidence to suggest that the risk of stroke varies by how long someone has had AF, insufficient data are available to reliably model stroke risk by time since onset of the arrhythmia. The relative risk used in the model was calculated based on AF patients that were diagnosed at a range of different time intervals. The limited available data suggest that the risk of stroke is as high, if not higher, than average immediately after the onset of the arrhythmia, so it is reasonable to apply the overall average risk within the population to all those with a diagnosis of AF.⁽¹⁹²⁾

As outlined in the clinical effectiveness section a major limitation of the available evidence is the lack of data on whether those identified through screening have the same stroke risk

profile as those diagnosed in routine care. The analysis examined the implications of screen-detected AF patients having a lower baseline risk of stroke and systemic embolism in a scenario analysis where the relative risk of stroke in undiagnosed versus diagnosed AF was varied between 0.50 and 1.⁽¹⁹³⁾

Relative risk of a fatal ischaemic stroke in patients with AF

As well as stroke incidence, the Framingham study also examined differences in the severity of AF versus non-AF stroke using the same cohort of 5,070 people in which the link between AF and stroke was first established.⁽¹⁹⁴⁾ During the 40 years of follow-up there were 501 first-ever ischemic strokes, 103 of which were in people with a diagnosis of AF. Multivariate regression analysis of 30-day post-stroke mortality controlling for age, smoking status and coronary heart disease gave an odds ratio (OR) of 1.84 (95% CI 1.04 to 3.27). When this odds ratio is converted to a relative risk using the formula,⁽¹⁹⁵⁾

$$Relative\ Risk\ (RR) = \frac{OR}{(1 - \rho_0 + (\rho_0 \times OR))}, \text{ where } \rho_0 = \text{baseline risk}$$

the relative risk of a fatal stroke with AF is 1.70 (95% CI 1.04 to 2.67).

3.3.4.3 Functional outcomes in survivors of AF and non-AF ischaemic strokes

The Framingham study also reported the proportion of the 150 survivors of first-ever AF and non-AF ischaemic stroke who had mild, moderate and severe symptoms at three, six and 12 months post-stroke.⁽¹⁹⁴⁾ Severity of symptoms was classified using a modified Barthel Index (BI).⁽¹⁹⁶⁾ A score of 40 or less indicated severe dependence in activities of daily living (ADL), a score of 85 or above indicated mild to no dependence in ADL, and an intermediate score implied moderate dependence in ADL. The economic model uses a Markov cycle length of one year, so functional outcomes at 12 months are used, with an assumption that no further improvement occurs after that time. Due to the high mortality associated with stroke the number of survivors at 12 months in the study was small (10 out of 30 in the AF group and 55 out of 120 in the non-AF group), which introduces significant uncertainty in the estimates. Point estimates for the long term functional outcome for AF and non-AF stroke patients are provided in Table 3.4.

TABLE 3.4 LONG TERM FUNCTIONAL OUTCOMES FOR AF AND NON-AF ISCHAEMIC STROKE

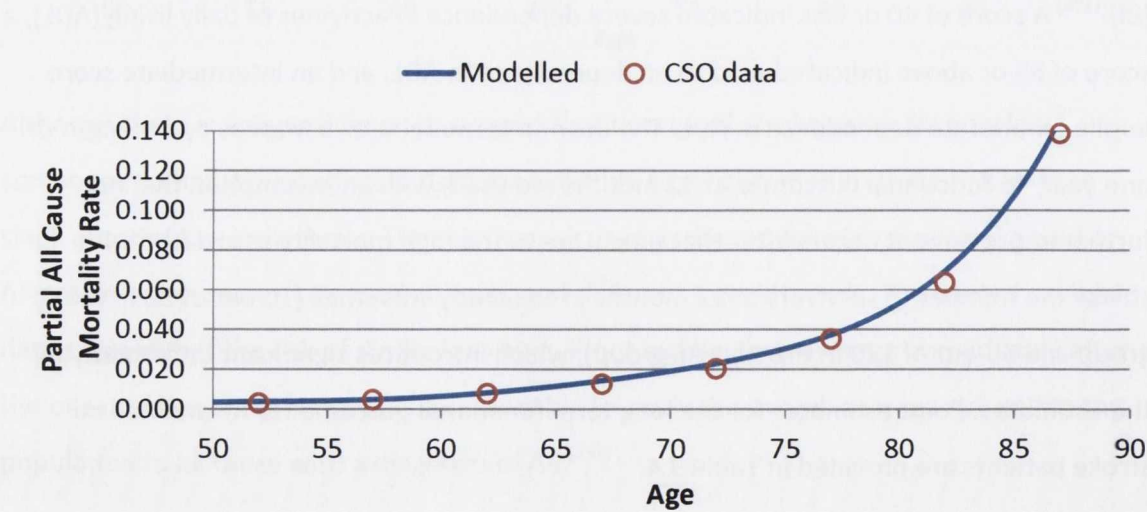
	Non-AF	AF
Mild or no dependency	0.64	0.40
Moderate dependency	0.25	0.30
Severe dependency	0.11	0.30

3.3.4.4 DEATHS FROM OTHER CAUSES

The economic model simulates a cohort of individuals with and without screening in order to estimate the incremental costs and benefits associated with the intervention. The model is, by necessity, a vastly simplified representation of real life that only includes the clinical outcomes that are directly affected by the intervention. It was also necessary to take account of the fact that people within the cohort can die as a result of causes other than stroke. To do this, partial all-cause mortality was calculated, which is the overall pooled mortality rate from all causes other than stroke and associated sequelae.

Data from the most recent available five-year period (2008-2012) on the number of deaths from all causes other than stroke (I60-I69) by five-year age group was obtained from the CSO, along with the corresponding population estimates over that time period, to calculate the age-specific partial all-cause mortality rate. In the analysis this outcome was modelled as a 6th order polynomial (see Figure 3.14).

FIGURE 3.14 MORTALITY RATE FROM ALL CAUSES OTHER THAN STROKE



3.3.4.5 EFFECTIVENESS OF TREATMENT

Having modelled the risk of stroke for those with and without AF, it was necessary to estimate the decrease in the risk and severity of stroke associated with treatment, as this is ultimately what determines the benefit associated with any change in case detection as a result of screening.

Effect of treatment on stroke risk

There are multiple treatment options for decreasing the risk of stroke in people with AF. Therefore the effect of treatment in the modelled cohort needs to be a composite parameter reflecting the proportion of people receiving each type of treatment and the relative effectiveness of each of these treatments in reducing the risk of stroke. Data on the current standard of care were obtained from TILDA, which recorded all medications prescribed for the 161 respondents who reported having a diagnosis of AF. The percentage of AF patients receiving each type of treatment based on this data is shown in Table 3.5, which also shows previous estimates of the standard of care derived from the North Dublin Stroke Study (NDSS, 2006 data) and the Irish National Audit of Stroke Care (INASC, 2007 data).^(197;198) The more recent TILDA data (collected between 2009 and 2011) show a higher proportion of AF patients receiving oral anticoagulation (OAC). However, the TILDA data are based on a cohort of people with AF regardless of stroke status, whereas the other two datasets are derived from cohorts of stroke patients who had a previous diagnosis of AF, which one would expect to be less well managed given the fact that a stroke had occurred. A letter circulated by the HSE Medicines Management Programme reported a threefold increase in direct oral anticoagulant (DOAC) prescribing rates between 2012 and 2014, with AF accounting for 80% of all DOAC prescriptions.⁽¹⁹⁹⁾ Given the significant rise in the use of DOACs in Ireland since the first TILDA survey was completed, the applicability of these data to the present day is questionable. The TILDA dataset has recently been linked to the Primary Care Reimbursement Service (PCRS) database, which provides more recent treatment information for those who were identified as having a history of AF. Data from a total of 68 patients indicate that there has been an increase in both the use of DOACs and the total proportion of AF patients receiving OAC (Table 3.5). However given the low

number of patients and the fact that the standard of care for people diagnosed before the widespread use of DOACs may differ from that of newly diagnosed AF cases, this is probably an underestimate of the total proportion of AF patients taking DOACs. Unpublished data from the AF screening pilot carried out by the HSE Stroke Programme in the first half of 2014 shows that a significantly higher proportion of new AF cases were prescribed DOACs compared with the other data sources (Table 3.5).⁽²⁰⁰⁾ The most recent PCRS data for overall DOAC use across all indications (October 2014) indicates that DOACs accounted for 35% of all patients taking oral anticoagulants (either DOACs or warfarin). UK data indicate that primary care centres with a sustained focus on optimal treatment for AF achieve OAC rates of around 60%.⁽²⁰¹⁾ This is consistent with the 2014 Irish data for warfarin and DOACs combined (59% to 66%). The UK data also show that increases in OAC rates correspond with decreases in the use of antiplatelet therapy, while the proportion of patients receiving neither treatment remains relatively constant at around 10%.⁽²⁰¹⁾

TABLE 3.5 ESTIMATED CURRENT STANDARD OF CARE FOR AF PATIENTS IN IRELAND

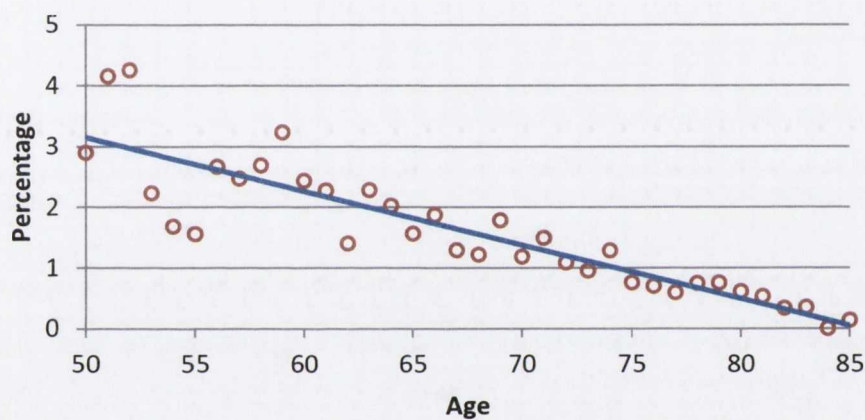
Population	Data Source	Warfarin	DOACs	Antiplatelet	None
AF population	TILDA (2009-2011, n=161)	38%	5%	47%	10%
	TILDA/PCRS (2014, n=68)	50%	9%	28%	13%
	AF Screening Pilot (2014, n=51)	26%	40%	18%	16%
Stroke population	NDSS (2006)	28%	-	55%	17%
	INASC (2007)	26%	-	52%	22%
Model estimate*	Combination of Irish and UK data	39%	21%	30%	10%

* UK primary care data from 2014 showing overall OAC rates of 60% and 2014 Irish PCRS data indicating that 35% of OAC patients are prescribed DOACs

In the primary analysis the current standard of care was estimated using an assumption that a total of 60% of newly diagnosed AF patients will receive OAC, with 35% of these being prescribed DOACs. These were modelled using a Dirichlet distribution to capture the uncertainty around these parameters. A sensitivity analysis was performed to examine the effect of varying these assumptions and to assess the potential impact of increasing rates of OAC and DOAC use.

Figure 3.15 shows HIPE data on the number of atrial ablation procedures as a percentage of incident AF cases in Ireland over five years from 2010 to 2014. This shows a marked decline by age, dropping to under 2% at age 65 to almost 0% at age 85. Due to the low numbers of cases and the fact that European guidelines state that discontinuation of warfarin therapy post-ablation is generally not recommended in patients at risk for stroke, coupled with uncertainty regarding its clinical effectiveness, surgical ablation is excluded from the analysis.^(141;202)

FIGURE 3.15 SURGICAL ABLATION PROCEDURES AS A PERCENTAGE OF INCIDENT AF CASES BY AGE, 2010 TO 2014 (HIPE)



The relative effectiveness of warfarin, direct oral anticoagulants (DOACs) and antiplatelet therapy compared with no treatment in reducing the risk of ischaemic stroke was obtained from Cochrane reviews of warfarin and antiplatelet therapy for preventing stroke in AF patients and a meta-analysis of all pivotal phase 3 trials of the four direct oral anticoagulants (dabigatran, rivaroxaban, apixaban and edoxaban) versus warfarin in non-valvular AF.⁽²⁰³⁻²⁰⁷⁾ Estimates of the relative effectiveness of warfarin and antiplatelet therapy compared with no treatment were derived from placebo controlled trials and the relative effectiveness of DOACs compared with no treatment are estimated through indirect comparison based on data comparing DOACs and warfarin. Where only odds ratios were reported these were taken to be equivalent to relative risks, given the rarity of the outcomes being measured (baseline risk ~0.05).⁽¹⁹⁵⁾ Table 3.6 shows the relative risk of ischaemic and haemorrhagic stroke for each of the three categories of treatment compared with placebo.

TABLE 3.6 CLINICAL OUTCOMES OF WARFARIN, DIRECT ORAL ANTICOAGULANTS AND ANTIPLATELET THERAPY VERSUS PLACEBO

	Ischaemic Stroke (RR [95% CI])	Intracranial Haemorrhage (RR [95% CI])
Warfarin ⁽²⁰⁴⁾	0.34 [0.23, 0.52]	2.38 [0.54, 10.50]
Antiplatelet Therapy ⁽²⁰³⁾	0.70 [0.46, 1.07]	1.32 [0.22, 7.80]
Direct Oral Anticoagulants ^(206;207)	0.31 [0.19, 0.53]	1.17 [0.21, 6.72]

Suboptimal warfarin anticoagulation

Anticoagulation with warfarin requires regular testing to ensure that effective therapeutic levels are maintained in the bloodstream. This measurement is called the International Normalised Ratio (INR). An INR of between 2.0 and 3.0 is considered optimal for stroke prevention in atrial fibrillation, with a recommendation that the time in this therapeutic range (TTR) should exceed 70%.⁽¹³⁷⁾ Achieving this target can be difficult due to natural variability between individuals’ INR levels, compliance rates, and drug, food and alcohol interactions. Well controlled clinical trials only achieved average TTR rates of 60%,⁽²⁰⁸⁻²¹¹⁾ and real-life studies have estimated that some patients may achieve optimal TTR for less than 50% of the time.^(141;212) There is a lack of national Irish data on average TTR rates for those receiving prophylactic anticoagulation for atrial fibrillation in the community. An RCT involving the anticoagulation management service in Cork University Hospital in 2007 found that TTR was 58.6% in the control group receiving usual care.⁽²¹³⁾ This is consistent with audit data from a general practice in Mallow, Co. Cork reporting a TTR point prevalence of 60.5% in 2009.⁽²¹⁴⁾ Since these are comparable to TTR rates achieved in the original RCTs of warfarin for non-valvular atrial fibrillation, this analysis applied the same relative risk of stroke to all patients treated with warfarin.

Suboptimal DOAC dosing

An analysis of DOAC prescribing in Ireland from January to October 2013 found that 16% of patients on rivaroxaban are on less than the recommended 20mg/day dosage for stroke prevention and approximately 66% of patients on dabigatran receive the lower dose of 110mg/bid, which was found to be non-inferior to warfarin in preventing ischaemic

stroke.⁽¹⁹⁹⁾ The impact of suboptimal dosing of DOACs will be examined in a scenario analysis that will apply the same therapeutic effect as warfarin in reducing the risk of ischaemic stroke, while retaining the same risk of bleeding and systemic embolism.

Effect of treatment on stroke severity

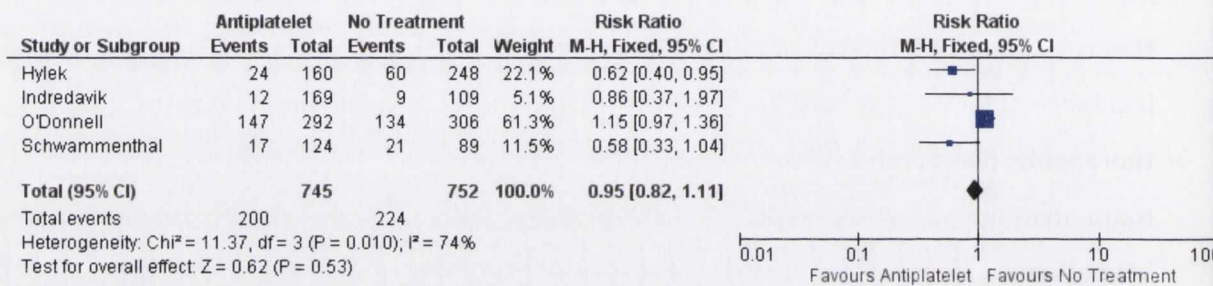
There is evidence to show that treatment of patients with atrial fibrillation is associated with a reduction in the proportion of fatal strokes and decreased stroke severity.^(215;216) The model requires data on mortality at one year, as well as the proportion of survivors who are left with mild, moderate or severe functional deficits. Two recent systematic reviews of stroke severity in patients with atrial fibrillation who were receiving prior antithrombotic therapy identified a total of 11 relevant studies.^(217;218) Of these, five reported data on the incidence of fatal stroke for those receiving no treatment, antiplatelet therapy, or therapeutic ($INR \geq 2$) and subtherapeutic ($INR < 2$) warfarin.^(215;216;218-220) Figure 3.16 shows a meta-analysis of all studies reporting short term mortality (at 30 days or prior to discharge) for patients with atrial fibrillation by type of prior treatment. Both therapeutic and subtherapeutic levels of warfarin are associated with a statistically significant decrease in the risk of fatal stroke, unlike antiplatelet therapy, which showed no difference. In the model, the estimated TTR point prevalence in Ireland of 60% was used to calculate a weighted relative risk of 0.67 (95% CI 0.54 to 0.86) of a stroke causing death for those receiving warfarin treatment. The relative risk for those receiving DOACs was assumed to be equivalent to therapeutic warfarin (RR 0.59 [95% CI 0.46 to 0.76])

As described earlier, long term functional outcomes from AF versus non-AF stroke were taken from the Framingham Study, which used the modified Barthel Index to measure the percentage of survivors with mild, moderate and severe impairment at one year post-stroke. None of the studies examining the impact of prior treatment on stroke severity report this outcome. The best available evidence comes from a 2003 US study that reported functional outcomes at discharge as measured using the modified Rankin Scale (mRS), which classified strokes as severe (mRS=5), major (mRS = 3,4) and minor (mRS=0,1,2).⁽²¹⁵⁾ Although this categorisation is slightly different to the Framingham study, if it is assumed that the relative differences between each category as a result of prior treatment are broadly consistent, and

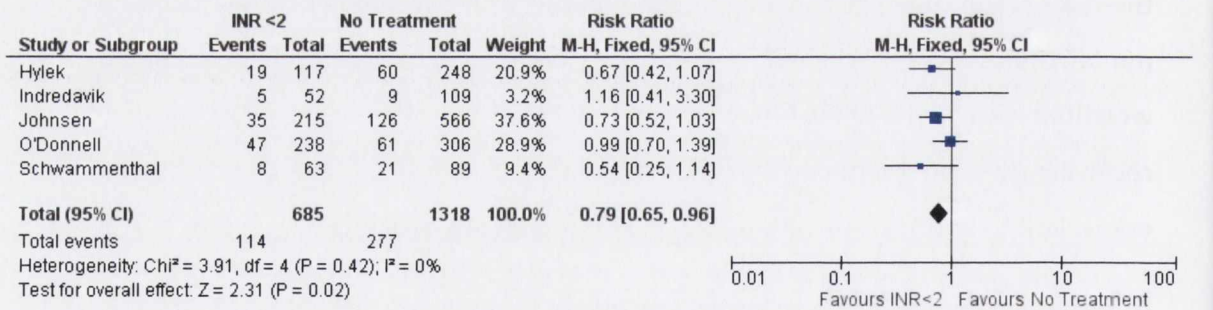
that functional outcomes at discharge are directly correlated with long term outcomes then this can be used to estimate the impact of prior treatment on stroke outcomes. As before the impact of warfarin on stroke severity was calculated as a weighted average using a TTR point prevalence of 60%, and in the absence of specific data on DOACs, it was assumed they were equivalent to therapeutic warfarin (INR $\geq$ 2). Figure 3.17 shows the results for non-AF strokes, as well as AF strokes with each type of prior treatment.

FIGURE 3.16 RELATIVE RISK OF FATAL STROKE IN PATIENTS WITH ATRIAL FIBRILLATION BY TYPE OF TREATMENT BEING RECEIVED PRIOR TO ONSET OF STROKE

Antiplatelet Therapy



Subtherapeutic Warfarin (INR<2)



Therapeutic Warfarin (INR $\geq$ 2)

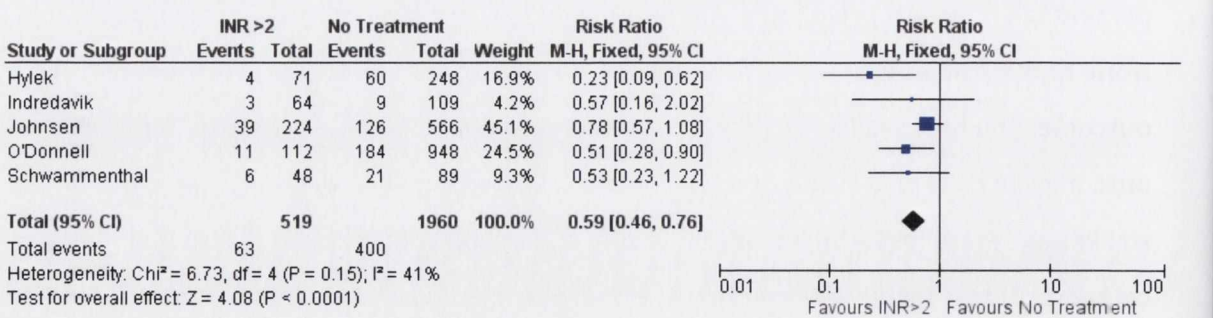
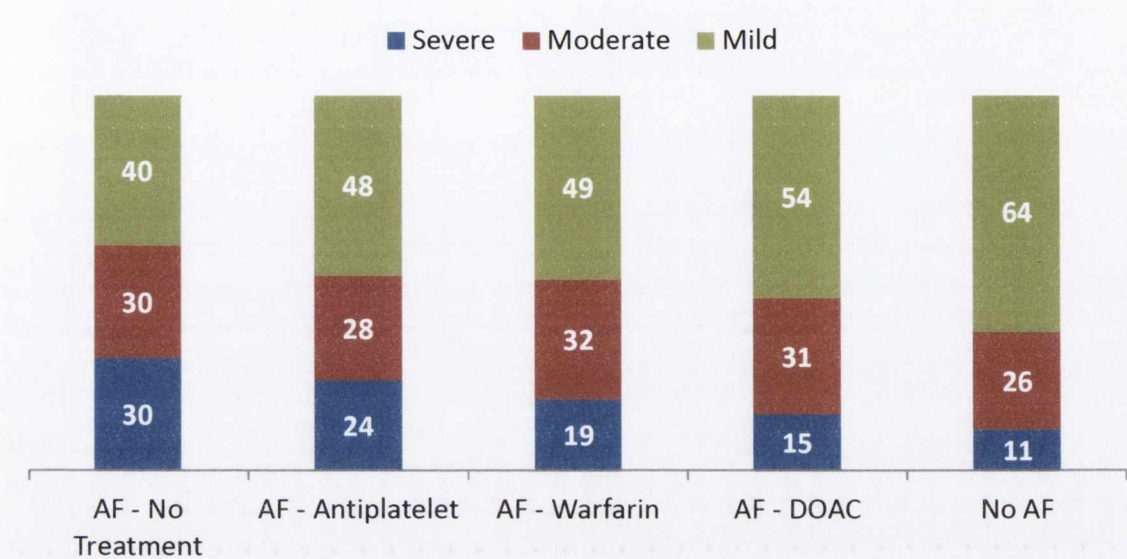


FIGURE 3.17 PERCENTAGE OF SURVIVORS WITH SEVERE, MODERATE OR MILD IMPAIRMENT POST-STROKE, BY TYPE OF PRIOR TREATMENT



Other effects of treatment

As well as changing the risk of ischaemic stroke and intracranial haemorrhage, antithrombotic treatment can also affect the risk of gastrointestinal bleeding and systemic embolism. In order to include this in the model, it was necessary to estimate the baseline risk of both these events in people with atrial fibrillation, as well as the relative risk associated with the three type of treatment included in the model (antiplatelet, warfarin, DOACs).

The average baseline risk of systemic (non-central nervous system [CNS]) embolism and major extracranial bleeds in untreated AF patients without a history of stroke was obtained from randomised trials that included a placebo control arm (see Table 3.7).^(203;204)

Confidence intervals were approximated using the formula:

$$95\% \text{ CI} = \frac{d}{N} \pm 1.96 \times \sqrt{\frac{\frac{d}{N} \times \left(1 - \frac{d}{N}\right)}{N}}$$

Where d = number of events and N = total number of cases

TABLE 3.7 RISK OF SYSTEMIC EMBOLISM AND MAJOR EXTRACRANIAL BLEED IN PATIENTS WITH ATRIAL FIBRILLATION NOT RECEIVING ANTITHROMBOTIC THERAPY

RCT	Systemic Embolism	Total	Major Extracranial Bleed	Total
AFASAK1	2	315	0	315
LASAF	0	91	NR	NR
SPAF1	4	527	8	527
BAATAF	0	201	8	201
CAFA	2	184	2	184
SPINAF	1	265	4	265
Total	9	1,583	22	1,492
Baseline Rate [95% CI]	0.006 [0.002, 0.009]		0.014 [0.009, 0.021]	

The relative risk of systemic embolism and major bleeding associated with warfarin, direct oral anticoagulants (DOACs) and antiplatelet therapy was obtained from Cochrane reviews of warfarin and antiplatelet therapy for preventing stroke in AF patients and a meta-analysis of all pivotal phase 3 trials of the four direct oral anticoagulants (dabigatran, rivaroxaban, apixaban and endoxaban) versus warfarin in non-valvular AF.⁽²⁰³⁻²⁰⁶⁾ Where only odds ratios were reported these were taken to be equivalent to relative risks, given the rarity of the outcomes being measured.⁽¹⁹⁵⁾ Table 3.8 shows the relative risk of embolism and bleeds for each of the three categories of treatment versus placebo.

TABLE 3.8 RELATIVE RISK OF SYSTEMIC EMBOLISM AND MAJOR BLEEDING ASSOCIATED WITH ANTITHROMBOTIC TREATMENT IN AF

	Gastrointestinal Bleeding	Systemic Embolism
Warfarin ⁽²⁰⁴⁾	1.07 [0.53, 2.12]	0.45 [0.13, 1.57]
Antiplatelet Therapy ⁽²⁰³⁾	1.14 [0.44, 2.98]	0.67 [0.19, 2.33]
Direct Oral Anticoagulants ⁽²⁰⁶⁾	1.34 [0.54, 3.29]	0.41 [0.11, 1.60]

As is evident from the wide confidence intervals around these relative risks, there is a high degree of uncertainty in relation to the relative risk of gastrointestinal bleeding and systemic embolism associated with the different antithrombotic treatment options for atrial fibrillation. There is also a lack of reliable evidence on the subsequent impact, if any, of these on mortality rates. These outcomes were therefore incorporated into the analysis

using estimates of their effect on health-related quality of life and the duration of that effect. These estimates are provided in Section 3.3.6.

3.3.4.6 EFFECTIVENESS OF SCREENING

Estimates of the effectiveness of screening at increasing the detection of new cases of AF are taken from the Cochrane review of this topic, which was described in section 3.2.⁽¹⁹¹⁾ The primary source of information is the UK SAFE trial, which compared opportunistic screening (by pulse palpation in GP practices followed by ECG if irregular) and systematic screening (by ECG) to routine care.⁽¹⁵¹⁾ They found that both types of screening programme were equally as effective at detecting new AF cases compared with usual care (OR 1.6), but that systematic screening costs substantially more. However, there were some important obstacles that prevented the overall odds ratio for the effect of screening being directly applied in the economic model. The SAFE study examined once-off screening, whereas the analysis of a prospective Irish programme had to take into account multiple years of successive screening rounds. In addition, there were other peculiarities that limit the transferability of the results. The baseline AF prevalence was 14% higher in the control group than the screened group (7.7% versus 6.9%). The differences in baseline prevalence are explainable in two ways; either AF was actually more common in the control group than the screened group (in which case randomisation failed), or routine practice in the control group was simply better at detecting AF than routine practice in the screened group. Either of these present problems for the transferability of the results as each would tend to overestimate the effect of screening (since there are more cases to find in the screening group). To overcome this the effect of screening was estimated using data from the same trial on the diagnostic accuracy of pulse palpation followed by ECG in this group, which is a valid outcome for estimating the effect on AF detection that is not affected by changes in disease prevalence. RCT data on the sensitivity and specificity of pulse palpation and ECG in AF detection, which varied depending on who carried the test and what type of ECG was performed (Table 3.9).^(151;221)

TABLE 3.9 SENSITIVITY AND SPECIFICITY OF PULSE PALPATION AND ECG

Test	Sensitivity	Specificity
Pulse palpation		
GP or Nurse	87.2	81.3
ECG		
12-Lead		
CDSS	83.3	99.1
GP	79.8	91.6
Nurse	77.1	85.1
GP & CDSS	91.9	91.1
Limb lead		
GP	82.5	88.5
Nurse	72	83.4
Chest lead		
GP	84.8	86.4
Nurse	68.7	82.8

CDSS – Clinical decision support system

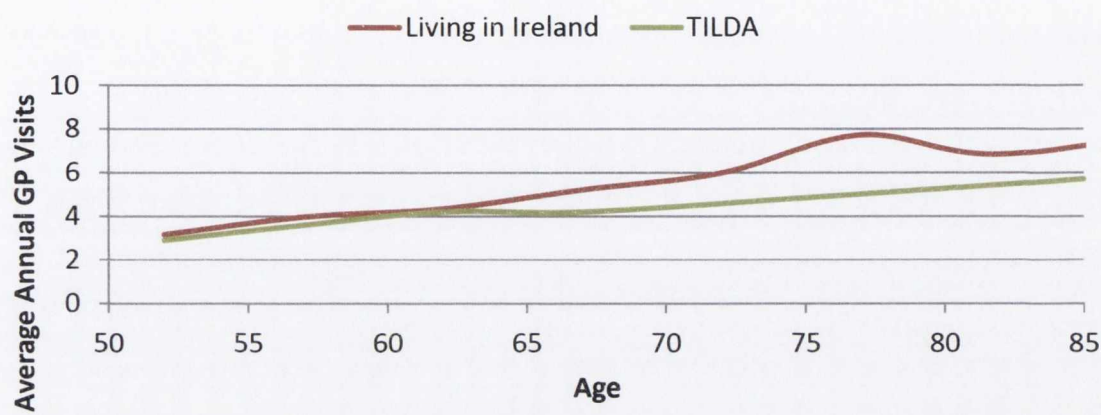
To evaluate the long term effectiveness of opportunistic screening for atrial fibrillation over multiple screening rounds within the screened cohort requires using the sensitivity of the test to estimate the rate of detection in the first and subsequent screens, rather than directly applying the results for AF detection in the screened group from the once-off screening study in all screening years. The sensitivity of screening needs to be combined with estimates of GP attendance and uptake rates, which dictate how often the average person with undiagnosed AF will get tested. Detection of the arrhythmia requires that an undiagnosed person attends a GP, agrees to screening and that the arrhythmia is successfully detected by the test. In terms of evaluating the impact of screening versus no-screening, the baseline detection rate of atrial fibrillation in the absence of screening as a result of routine care must also be estimated.

GP attendance rates

GP attendance rates for those aged 50 to 85 were obtained from TILDA (2011) and the Living in Ireland Survey (2004).^(222;223) There was some discrepancy between the two, with the earlier survey reporting higher frequency of attendance for those over 65 years (Figure

3.18). In the primary analysis, it was assumed that all those in the screening cohort attend a GP consultation at least once a year.

FIGURE 3.18 ANNUAL NUMBER OF GP VISITS BY AGE



Uptake of opportunistic screening

Data on uptake rates of opportunistic screening was obtained from the SAFE study. This found that 69.2% of patients consented to having their pulse palpated and 65.9% of patients found to have an irregular pulse agreed to have an ECG. Patients are considered to have accepted an offer of screening if they complete the two stages of the screening test. This reduces the combined uptake rate to 45.6%. However, of the people who declined an ECG, 45.5% already had a diagnosis of AF. When these were excluded from both the numerator and denominator then the rate of uptake of ECG is 79.0%, and the combined uptake rate is 54.7%.

Since pulse palpation by GPs is a recognised component of routine care it is likely that acceptance rates among a prospective screening cohort in a real life setting would be greater than that observed in an RCT, which required patients to provide formal consent as trial participants. It was therefore assumed that all patients will agree to have their pulse palpated and that all those with an irregular pulse will agree to have an ECG. A sensitivity analysis was carried out to examine the impact of significant numbers of patients either failing to attend at least one GP consultation per year or declining to be screening, by varying the uptake rate between 50% and 100%.

AF detection rates

National UK data on AF prevalence is routinely collected in each commissioning group as part of the NHS Quality Outcomes Framework (QOF). By comparing observed to expected cases in all GP practices, clinical commissioning groups and for the whole of the country, Public Health England recently estimated that overall diagnosis rates for AF in the absence of screening were approximately 65%.⁽²²⁴⁾ In Ireland the TILDA study screened approximately 5,000 people from a nationally representative sample of over 50s and found that approximately 40% of people with AF were unaware that they had the arrhythmia.⁽¹⁸⁵⁾ This difference is assumed to be as a result of the incentives in place to promote AF diagnosis in primary care in the UK. In the model, it was assumed that approximately 60% of incident AF cases are diagnosed by routine care, and the impact of uncertainty was examined using sensitivity analysis. The primary estimate is consistent with recent data collected from nine European countries in the EORP-AF Pilot registry, which reported that 40% of AF patients were asymptomatic.⁽²²⁵⁾

In this analysis it was assumed that opportunistic screening involves pulse palpation followed by an ECG read by a GP with the support of computer software, with a diagnosis requiring a positive result in both. Therefore the overall sensitivity of this two stage test is:

$$Sn_{test} = Sn_{pulse} \times Sn_{ecg}$$

Using values from Table 3.9, this gives a sensitivity of 80.1%.

The average person will attend a GP consultation more than once a year. If they are tested each time the overall sensitivity will increase, since a diagnosis is made if the person tests positive either time:

$$Sn_{total} = Sn_{test} + Sn_{test} - (Sn_{test} \times Sn_{test})$$

For example, if a person was tested twice a year the sensitivity increases from 80% to 96% and if tested every time they attend the probability of being detected approaches 100% (average attendance rate in screening cohort is >4 per year). However, the direct application of the sensitivity of the screening test in this way risks significantly overestimating the proportion of AF patients who would be detected with screening. The data are derived from

a trial that involved once-off pulse palpation during the course of one year, rather than repeat testing every time the patient attended, or annual testing over the course of multiple years. Therefore it is risky to assume that those who were not picked up in the first test have an 80% probability of being picked up in each subsequent test. Rather it is likely that factors such as whether asymptomatic AF is paroxysmal or persistent, or has atypical electrocardiographic presentation, make undetected cases more likely to remain undetected.

In this analysis it was assumed that people are opportunistically screened once a year when they attend their GP and that the sensitivity of the test in detecting incident cases is 80%. In the primary analysis the conservative assumption was adopted that false negatives are not detected in subsequent screening tests. A scenario analysis examined the impact of a screening test that has a consistent 80% sensitivity in detecting both incidence and prevalent cases every year. The sensitivity of the test itself was also varied to estimate the impact of uncertainty in the estimate of the effectiveness of pulse palpation and GP-based ECG.

Limitations associated with the approach to estimating the impact of screening in Ireland are that it may overestimate the increase in the detection of AF due to a lack of data on the impact of paroxysmal AF on detection rates. This would tend to make screening appear more effective. Results obtained using the proposed approach show a greater increase in detection compared with directly transposing the absolute difference in the percentage of new cases detected in the treatment and control arms of the SAFE study. Using this method would mean applying a 12% increase in observed prevalence in the screened cohort (absolute increase in AF cases was 22% in screening arm compared with 10% in control arm), giving observed prevalences of approximately 75% with screening (versus the model estimate of 80%). However, differences in the baseline prevalence of AF in the different arms of the trial, along with the fact that the majority of new AF cases in the treatment arm were detected outside of the screening programme, make such direct transposition to the absolute results problematic.

3.3.4.7 LONG-TERM STROKE SURVIVAL

Screening is primarily designed to detect AF prior to the occurrence of stroke, since investigating whether or not the arrhythmia is present after a stroke is standard practice for informing ongoing management of the patient. Therefore it is the incidence and severity of first-ever stroke that should differ between screened and unscreened populations, rather than the clinical outcomes after a stroke has occurred. For this reason the analysis estimates the overall average life expectancy and health-related quality of life after a stroke, by age and stroke severity. It does not separately model stroke recurrence or survival post-stroke by AF status or by type of treatment. There are some potential limitations of this approach. If screening and subsequent treatment were extremely effective then overall average survival would be improved because fewer patients with AF would have a stroke and given the association between AF strokes and worse outcomes, there would be fewer severe strokes. However given the challenges associated with detection and treatment, which mean that not all AF cases are detected and not all future strokes in detected cases are avoided through treatment, coupled with that fact that AF is implicated in a minority (~30%) of all strokes, overall population averages for stroke outcomes are unlikely to be significantly affected by screening. Another limitation is that by failing to model differences in post-stroke outcomes by treatment, the analysis will not be able to draw conclusions about the effectiveness and cost-effectiveness of competing treatment alternatives for those who experience a stroke. However this is beyond the scope of this project and the data required to carry out such an analysis are not readily available.

Ischaemic stroke

Survival by severity of initial stroke was reported from the Oxford Vascular Study between 2002 and 2012.⁽²²⁶⁾ Strokes were classified using the NIH stroke scale as minor (NIHSS≤3), moderate (NIHSS 4-10) or severe (NIHSS≥10). Survival to five years is shown in Figure 3.19. Their results show an initial drop in survival due to short term case fatality (at one month or hospital discharge), which was accounted for separately in this HTA as the incidence of fatal stroke. Therefore in the analysis it was necessary to adjust the UK data to estimate long-term survival by stroke severity for those who have survived to hospital discharge (Figure 3.20).

The results show that for patients who survive the initial insult, survival is not linear. Rather, a steeper reduction is observed in the first year compared with years' two to five. The increase in mortality in the first year increases with stroke severity, while the mortality rate after year one is similar for all strokes.

FIGURE 3.19 SURVIVAL TO FIVE YEARS BY SEVERITY OF ISCHAEMIC STROKE

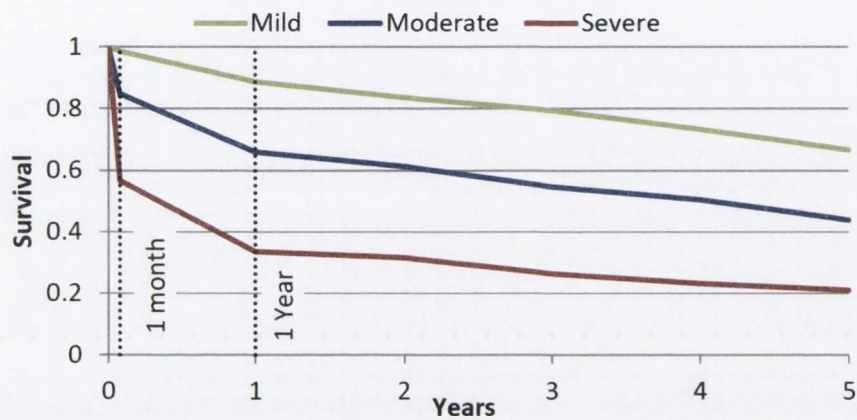


FIGURE 3.20 SURVIVAL TO FIVE YEARS BY SEVERITY OF STROKE FOR THOSE WHO SURVIVE THE INITIAL ISCHAEMIC STROKE



Using this data the annual probability of death by severity of stroke (in the first and subsequent years separately) was estimated as the slope of the survival curve (Table 3.10).

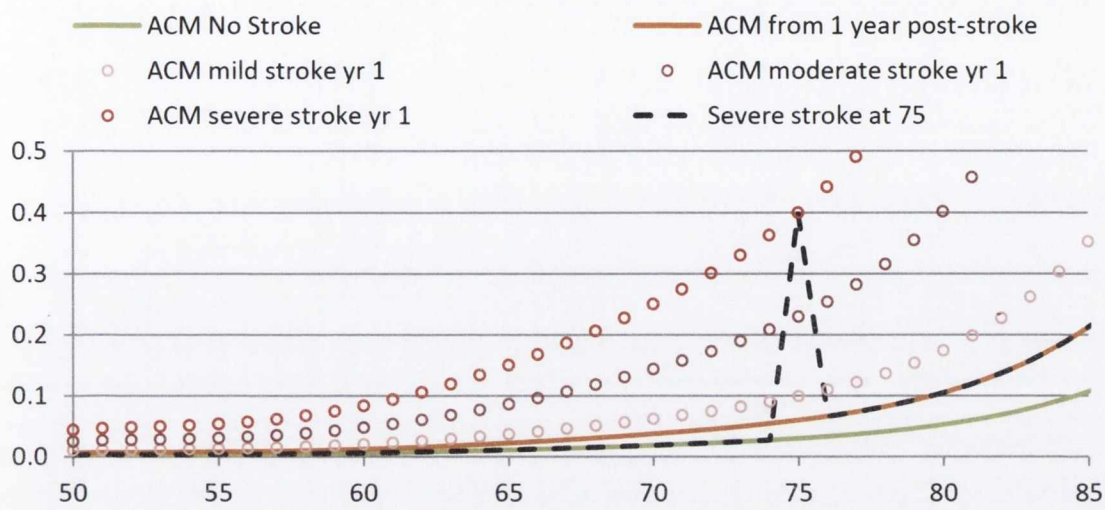
TABLE 3.10 ANNUAL PROBABILITY OF DEATH IN YEAR ONE AND SUBSEQUENT YEARS BY SEVERITY OF ISCHAEMIC STROKE

	Year 1	Subsequent years
Mild	0.10	0.06
Moderate	0.23	0.06
Severe	0.40	0.06

Care has to be taken when estimating rates from survival curves, since it is incorrect to say that the slope of the curve is equivalent to the annual mortality rate (which will vary over time with decreasing population).⁽²²⁷⁾ However in the Markov model, it was necessary to estimate the annual probability of death in each of the stroke states (mild, moderate, severe) if a person has survived the previous year, so the denominator is always one, making the probability of death equal to the slope of the survival curve for the corresponding time period.

The average age of patients in the Oxford Vascular Study was 75 years. To estimate survival by age the relative risk of death in year one and subsequent years was compared with the baseline mortality rate at that age without stroke (partial all cause mortality, see section 3.3.4.4 above). Figure 3.21 shows the annual probability of death in each stroke state by age. As an example, the dashed line shows annual mortality probabilities for a person who survives a severe stroke at age 75. They would have a normal annual risk of death prior to the stroke, which would be significantly elevated in the year following the (severe) stroke before decreasing after the first year to a level in excess of non-stroke mortality risk.

FIGURE 3.21 ANNUAL RISK OF DEATH BY AGE AND SEVERITY OF ISCHAEMIC STROKE



Haemorrhagic stroke

Long term survival from haemorrhagic stroke was estimated in a similar manner to ischaemic stroke. A 2014 systematic review⁽²²⁸⁾ identified three studies that reported haemorrhagic stroke survival at one and five years in the same study.⁽²²⁹⁻²³¹⁾ One of these studies reported a combined outcome of death or stroke recurrence rather than death alone.⁽²³¹⁾ Of the remaining two, one reported outcomes in the UK for both first ever subarachnoid haemorrhage (SAH) and primary intracerebral haemorrhage (PICH) and the other reported outcomes in Finland for PICH only.⁽²²⁹⁾ As shown in Figure 3.22, PICH results from both studies were similar and again a high initial drop in survival corresponding with fatal events was observed, followed by a relatively steep curve in year one when compared to subsequent years. The annual probability of death was calculated as the slope of the survival curve using the combined UK data on SAH and PICH (Figure 3.23 and Table 3.11).

FIGURE 3.22 SURVIVAL TO FIVE YEARS FOR HAEMORRHAGIC STROKE

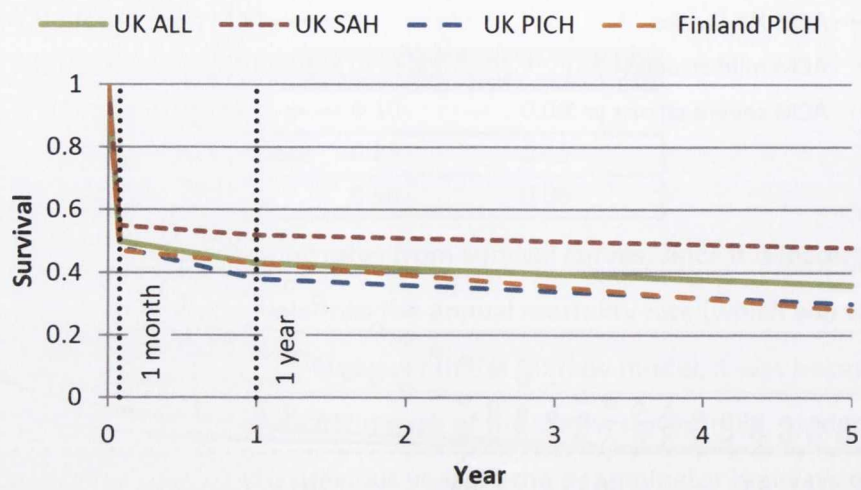


FIGURE 3.23 SURVIVAL TO FIVE YEARS FOR THOSE WHO SURVIVE THE INITIAL HAEMORRHAGIC STROKE

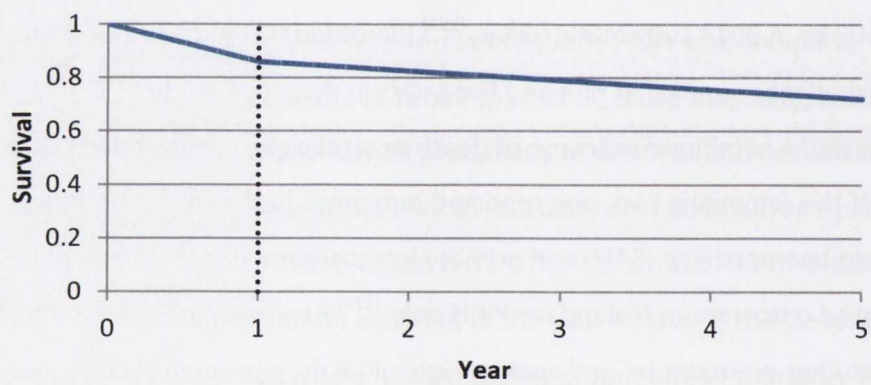


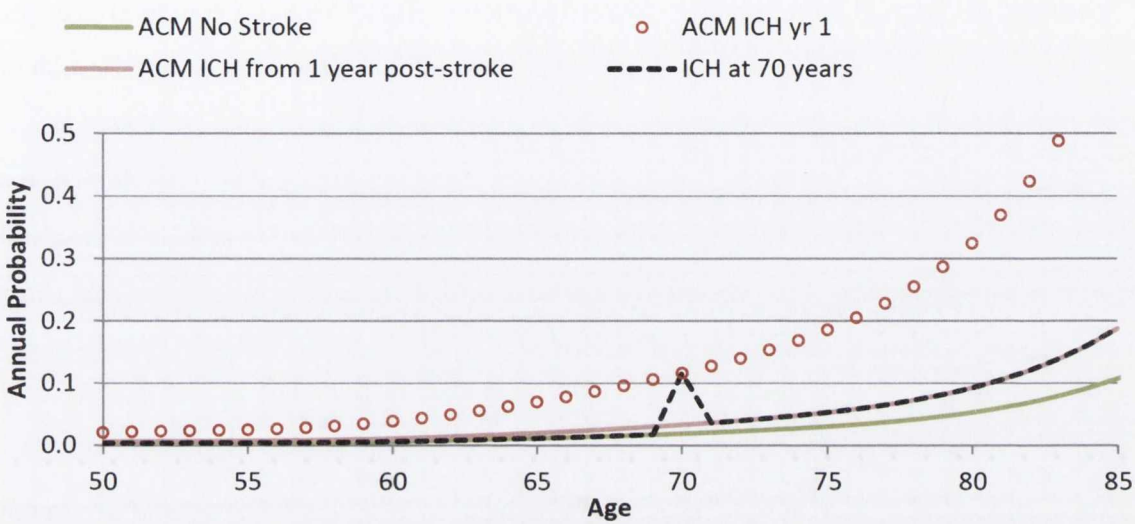
TABLE 3.11 ANNUAL PROBABILITY OF DEATH IN YEAR ONE AND SUBSEQUENT YEARS BY SEVERITY OF HAEMORRHAGIC STROKE

	Year 1	Subsequent years
Haemorrhagic Stroke	0.14	0.04

The average age of participants in the UK study was 72 years. As before the relative risk of death in year one and subsequent years compared with the baseline mortality rate at that age without stroke (partial all cause mortality) was calculated. Figure 3.24 shows the annual probability of death for survivors of haemorrhagic stroke by age, both in the first and

subsequent years. The dashed line shows annual mortality probabilities for a person who survives a haemorrhagic stroke at age 70.

FIGURE 3.24 ANNUAL RISK OF DEATH BY AGE AND SEVERITY FOR HAEMORRHAGIC STROKE



3.3.4.8 LIMITATIONS OF THE CLINICAL AND EPIDEMIOLOGICAL DATA

There are certain limitations to the approach adopted for estimating long term survival after stroke. While the outcomes for haemorrhagic stroke are taken exclusively from studies examining SAH and PICH, a minority (17%) of participant in the study used to estimate survival in ischaemic stroke had either SAH (5%), PICH (7%) or a stroke of unknown aetiology (5%). However, as outcomes were not reported separately the combined figure was used, which was assumed to be indicative of ischaemic stroke since these made up the majority of cases (>83%). There is also a risk that the relative risk of death calculated based on the mean age of the study cohorts may not be consistent across all age groups. However, in the absence of data on different age groups this is a better approach than directly applying results of the study to all people in the cohort, since this would produce counterintuitive results (chances of dying decreasing with advancing age) and there is evidence that mortality risk increases substantially with age.⁽²²⁹⁾ It was also assumed that stroke severity at admission (measured by NIHSS) is correlated with long term functional outcomes (measured by Barthel Index).⁽²³²⁻²³⁴⁾ There may also be differences in survival from iatrogenic stroke as a result of AF treatment compared with that of the overall haemorrhagic stroke population,

however the analysis models all those who survive a haemorrhagic stroke as a single group, so average survival rates are sufficient. There is also a risk that the treatment received by stroke survivors in the studies differs substantially from the current standard of care in Ireland, which would have implications for the applicability of the results. However both studies were carried out in a community setting in the UK, which has a comparable access to treatment, and results for ischaemic stroke are recent enough to justify an assumption of a comparable mix of available treatments for those who suffered a stroke (2002-2012). Finally, the analysis uses the best available Irish and international data on the detection rate of AF in routine care to estimate the proportion of cases diagnosed at any given time in the absence of screening. In the absence of any data by age group, it was assumed that the rate of undiagnosed AF is similar across all ages.

3.3.5 ESTIMATES OF COST

Relevant costs included in the analysis include the costs of AF case-finding and treatment, as well as costs associated with the clinical outcomes that may be impacted by AF screening. The primary analysis was carried out from the perspective of the publicly funded health and social care system. The cost-effectiveness of screening was also estimated using a societal perspective, as there are significant costs associated with informal care and lost productivity associated with stroke that are not borne by the health service. Therefore it was necessary to distinguish between costs that fall on the health service and those covered by private health insurers or out of pocket payments. Historical and international costs were converted to 2014 Euro using the relevant purchasing power parity and inflation rate.⁽¹⁰⁵⁾

3.3.5.1 COST OF SCREENING

Costs of screening include the incremental cost associated with pulse palpation during routine GP consultations and the cost of ECGs carried out in primary care. There may also be additional costs generated by the screening programme for specialist referral or additional tests beyond those normally required for a diagnosis of AF, or for further testing for incidental findings. However, as these costs are not directly associated with the screening programme they are not included in the primary analysis. The impact of including the cost of blood tests and an echocardiogram for each AF case diagnosed through screening is

examined in a sensitivity analysis and the number of additional specialist referrals due to a prospective Irish screening programme is estimated based on the available literature.

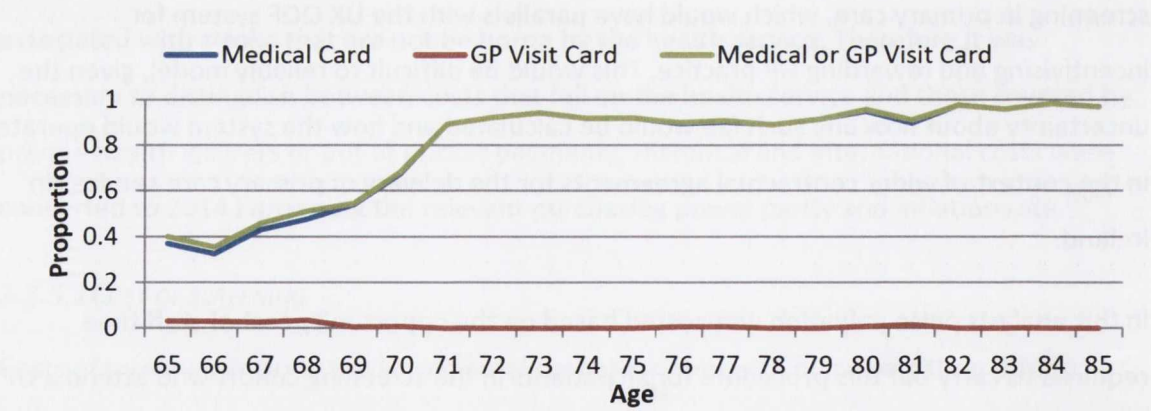
There are a number of approaches to costing opportunistic screening depending on how a prospective programme would be funded. The economic analysis carried out alongside the UK randomised controlled trial (RCT) of screening combined trial data on the average length of time it took to palpate the pulse and perform an ECG with labour costs by profession and the cost of ECG consumables to estimate average costs.⁽¹⁵¹⁾ However, there are differences in how GP practices are funded in Ireland and the UK, which may influence how the costs of screening are calculated. In Ireland, GPs are sole traders operating on a fee-per-service basis, who set their own fees for private consultations and receive a contract price for patients who qualify for a medical card or GP visit card. An alternative approach is cost screening using a fee per service, with set costs being assigned to some or all of the services provided. This could include a separate cost for pulse palpation and ECG, or simply assigning a fee for each new case of AF detected. The incremental costs of pulse palpation alone are likely to be minimal as it is a short procedure that does not require specialised equipment. Advertised prices for a resting ECG in Ireland range from €30 to €55.^(235;236) Paying a fee per new AF diagnosis would represent a departure from traditional methods of funding screening in primary care, which would have parallels with the UK QOF system for incentivising and rewarding GP practice. This would be difficult to reliably model, given the uncertainty about how any such fee would be calculated and how the system would operate in the context of wider contractual agreements for the delivery of primary care services in Ireland.

In this analysis pulse palpation was costed based on the opportunity cost of staff time required to carry out this procedure for all patients in the screening cohort who attend a GP consultation. Staff time was calculated using the schedule of fees and allowances payable to doctors participating in the General Medical Services (GMS) scheme and other community schemes provided through the Primary Care Reimbursement Service (PCRS). The cost of an ECG for those with an irregular pulse was taken as the set fee for this test under the GMS scheme and did not include the capital costs of equipment, since it is assumed that all GP practices are equipped to perform an ECG. The rationale for this is that the majority of

people in an over 65s screening cohort will have access to GP services paid for by the HSE, through either a medical card or a GP visit card, so the PCRS fees represents the best estimate of the marginal costs, as well as the opportunity cost of using that time for another purpose. However, GP care is not publicly funded for those without a medical card, apart from some tax relief on medical expenses, so a minority of people in the screening cohort will be required to pay out of pocket expenses at a higher rate to access a GP consultation. Also since screening is not part of the current GMS contract, its inclusion could put upward pressure on the existing schedule of fees and allowances. To assess the potential impact of this, a sensitivity analysis will be carried out to examine the impact of varying the cost of screening in the analysis.

Nationally representative TILDA data (n=8175) on the number of people with either a medical or GP card by age are shown in Figure 3.25.⁽²²²⁾ Coverage increases sharply once people reach 70, as this is the age at which people become eligible to apply for an over 70s medical or GP visit card, subject to a means test. The total percentage of people over 65 with access to free GP services is 81%.

FIGURE 3.25 PROPORTION OF PEOPLE OVER 65 WITH ACCESS TO FREE GP SERVICES, BY AGE



Pulse palpation and ECG

The SAFE RCT of opportunistic screening reported that the total time taken to perform pulse palpation during a GP consultation for some other reason was one minute.⁽¹⁵¹⁾ The annual GMS capitation fee for patients over 70 years is €271.62 (as of July 2013).⁽²³⁷⁾ Using TILDA

data on the average number of visits per year for this group (4.83, SD 0.85) and estimated average consultation times of approximately 10 to 15 minutes, the cost per minute of a HSE funded GP consultation in an older population was calculated to be approximately €4.50 (range €2.79 to €8.82). Many GP surgeries employ practice nurses, who can also perform pulse palpation in patients in the screening cohort. The subsidy paid to GPs through the PCRS towards the cost of employing practice nurses ranges from €30,945.86 to €37,822.72.⁽²³⁷⁾ Assuming a 39 hour working week and an annual leave entitlement of 24 days, this equates to a subsidy of €19.93 per hour, or €0.33 per minute (range €0.30 to €0.37).⁽²³⁷⁾ The UK trial of opportunistic screening in general practice reported that 62% of patients had their pulse palpated by a GP.⁽¹⁵¹⁾ If similar rates can be expected in Ireland than the weighted average for the cost to the health service for opportunistic pulse palpation as part of routine GP consultations in older patients would be approximately €2.88 (range €1.81 to €5.57). This is lower than the estimate obtained in the 2005 SAFE trial (€3.49 after inflation and conversion to 2014 Irish Euro).

The GMS capitation agreement provides a set fee in respect of a number of special items of service, including the performance and interpretation of ECGs. As of 2013 the fee paid to GPs for this procedure is €24.80.⁽²³⁷⁾ This is also lower than that reported in the UK trial, which was based on staff time and the cost of ECG consumables (€30.67 after inflation and conversion to Euro). However, it should be noted that GMS capitation fees have been reduced a number of times since 2008 due to budget cuts as a result of the economic recession, which accounts for some of the differences between current Irish costs and those reported in the UK study. The number of patients that will require ECG was estimated using data from the SAFE trial.⁽¹⁵¹⁾

3.3.5.2 COST OF AF TREATMENT

The average cost per patient for treatment was calculated as a weighted average based on the current standard of care for patients with a diagnosis of AF, estimated using TILDA data.

Antithrombotic medication

The percentage of AF patients receiving warfarin, DOACs and antiplatelet therapy was reported in section 3.3.4.5. For warfarin it is assumed that the average dose for long term maintenance of INR levels is 5mg per day. The cost of INR testing is estimated from a micro-costing study using Irish GP practice and Irish hospital data (€26 per GP INR and €56 per hospital INR), assuming a split of 50:50 for patients attending the hospital/GP setting every six weeks for well controlled INR levels.^(238;239) TILDA data showed that the majority (88%) of those reporting using DOACs were prescribed dabigatran (Pradaxa®) and a 2013 review by the HSE National Medicines Management Programme found that two thirds of patients prescribed dabigatran were prescribed the lower dose of 110mg/bid.⁽¹⁹⁹⁾ This does not affect the cost calculation as both dosages cost the same. The cost of dabigatran is comparable to that of rivaroxaban (Xarelto®) and apixaban (Eliquis®). Of those on antiplatelet treatment, the majority (74%) were receiving aspirin monotherapy. Aspirin dosages in atrial fibrillation range from 75mg/day to 325/mg day. In this cost calculation an average daily dose of 75mg of nu-seals aspirin was assumed. Drug costs were obtained from the PCRS database.⁽²⁴⁰⁾ Annual medication costs for each type of treatment based on these figures are shown in Table 3.12. Drug costs to the HSE were calculated per guidance provided by the National Centre for Pharmacoeconomics. A prescription fee of €2.50 per item, is only included in the analysis from the societal perspective.⁽²⁴¹⁾ It was assumed that all GMS prescriptions are dispensed once a month.

TABLE 3.12 ANTITHROMBOTIC MEDICATION COSTS (€)

	Warfarin	DOACs	Aspirin
Wholesale Price	24.26	856.29	45.38
Pharmacy Price	26.20	924.79	49.01
Dispensing fee	60.00	60.00	60.00
Wholesaler rebate	-0.97	-34.25	-1.82
Total price	85.23	950.54	107.19
INR Testing	355.33	0	0
Total annual cost	440.56	951.54	107.19

Rhythm and rate control medication

TILDA data on medications being taken by those who reported that they had a diagnosis of AF revealed that approximately 79% were receiving rate control treatment and 12% were receiving rhythm control treatment, with 9% reporting that they were receiving neither. That a higher proportion of patients are receiving rate control is consistent with published literature, but the degree of imbalance was greater than that reported elsewhere.⁽²⁴²⁾ The drug most commonly prescribed for rate control was bisoprolol, and the most commonly prescribed rhythm control drug was amiodarone. It is assumed that the maintenance dose of amiodarone in AF is 200mg daily and of bisoprolol is 5mg daily. The total annual cost for rhythm and rate control drugs is shown in Table 3.13.

TABLE 3.13 RHYTHM AND RATE CONTROL DRUG COSTS (€)

	Rate control	Rhythm control
Wholesale Price	23.66	99.82
Pharmacy Price	25.55	107.81
Dispensing fee	60.00	60.00
Wholesaler rebate	-0.95	-3.99
Total annual cost	84.60	163.82

Drug costs were obtained from the PCRS database, using prices for the most commonly reported brand prescribed for rate and rhythm control (Cardicor® and Cordarone X®, respectively). The average cost per patient was calculated as a weighted sum based on the proportion receiving each type of treatment. The cost of on-going blood and ECG testing associated with rhythm control is not included in the primary analysis. Sensitivity analysis was used to examine the potential effect of increasing the annual cost of rhythm control therapy to take account of testing.

3.3.5.3 COST OF STROKE AND ADVERSE EVENTS

The major direct costs associated with stroke include acute hospital care, rehabilitation and long term care. Indirect costs include informal care-giving and productivity losses due to mortality and morbidity. It was also necessary to estimate the cost associated with systemic embolism and adverse events, specifically major bleeding events.

Cost of in-patient treatment for stroke

The latest available data on inpatient costs for stroke in acute hospital in Ireland comes from the 2013 Casemix Ready Reckoner, which is based on HIPE data from 2011. This provides estimates of the cost of treatment for four different categories of stroke, based on the clinical complexity of the treatment received and the number of patients in each category (see Table 3.14). The weighted mean estimate of the cost of inpatient hospital care per patient treated based on this data is €8,939. This is consistent with the results of the Cost of Stroke in Ireland study, which estimated the cost of acute hospital care for stroke as €9,153 per patient, based on Casemix data from 2007.⁽¹³⁸⁾

TABLE 3.14 CASEMIX COSTS FOR STROKE IN IRELAND IN 2011

ADRG code	Description	Number of patients	Cost per patient
B70A	Stroke and other cerebrovascular disorders with catastrophic complication or comorbidity	949	€23,643
B70B	Stroke and other cerebrovascular disorders with severe complication or comorbidity	1513	€9,973
B70C	Stroke and other cerebrovascular disorders without either catastrophic or severe complication or comorbidity	2644	€4,883
B70D	Stroke and other cerebrovascular disorders with either death of transfer within 5 days	630	€1,325

This analysis requires estimates of the cost of acute hospital care by severity of stroke. Two Asian studies examined the impact of acute stroke severity (NIHSS) on inpatient hospital costs, comparing costs for those with mild, moderate and severe strokes to the overall average cost.^(243;244) While differences in the structure of health systems limit the transferability of cost data between countries, it was assumed that the relative impact of stroke severity on inpatient stroke costs should be consistent across different settings. Table 3.15 shows the results of combining data from these two studies on relative costs for mild, moderate and severe strokes compared with the overall average cost and applying it to inpatient stroke costs in Ireland. The average cost is applied to all fatal ischaemic stroke and all fatal and non-fatal haemorrhagic strokes. Based on the Cost of Stroke in Ireland study, it was assumed that 87% of acute hospital costs for stroke are borne by the public health system, 12% by private health insurers and 1% by out of pocket payments by patients.

TABLE 3.15 INPATIENT TREATMENT COSTS BY SEVERITY OF STROKE

Severity	Ratio	Irish costs
All	1	€8,939
Mild	0.80	€7,164
Moderate	1.09	€9,736
Severe	1.67	€14,894

Cost of in-patient and community rehabilitation care

The Cost of Stroke in Ireland study examined annual costs of inpatient rehabilitation for incident strokes in 2007, reporting an average cost per individual patient of €2,090 (range €1,407 to €3,056).⁽¹³⁸⁾ When this is inflated to the present day using the latest available data from the consumer price index (CPI) for health commodities (2014), the current value is €2,412 (range €1,623 to €4,244).⁽²⁴⁵⁾ It was assumed that the current standard of care for stroke rehabilitation is comparable to that in place in 2007. There is a lack of information on the cost of hospital rehabilitation by severity of stroke. However, there is data to suggest that in-hospital rehabilitation costs are directly correlated with stroke severity.⁽²⁴⁶⁾

Therefore the analysis assumes that the average is a weighted mean of the costs associated with mild, moderate and severe strokes, where there is a direct, linear correlation between costs and the severity of functional deficits on the Barthel scale. Using Irish National Audit of Stroke Care estimates on the percentage of mild, moderate and severe strokes included in the average figure, the cost of inpatient rehabilitation by stroke severity was estimated (Table 3.16).⁽¹⁹⁷⁾ Per the Cost of Stroke in Ireland study, it was assumed that 95% of acute hospital rehabilitation costs are borne by the public health system, 4% by private health insurers and 1% by out of pocket payments by patients.

The cost of community rehabilitation includes those associated with public health nursing, speech and language therapy, dietetics, physiotherapy and occupational therapy. The average cost per patient in the Cost of Stroke in Ireland study, inflated to 2014, is estimated at €904 (range €889 to €920). Using the same assumption as before (rehabilitation costs are directly correlated with severity of stroke), the cost of mild, moderate and severe stroke was estimated separately (Table 3.16). It is assumed that all costs associated with community rehabilitation apply in the first year only and are covered by public funding.

TABLE 3.16 INPATIENT AND COMMUNITY REHABILITATION COSTS BY STROKE SEVERITY

Stroke severity	Cost of inpatient rehabilitation (range)	Cost of community rehabilitation (range)
Mild	€1,117 (751 to 1,965)	€419 (411 to 426)
Moderate	€2,233 (1,503 to 3,929)	€837 (823 to 852)
Severe	€3,350 (2,254 to 5,894)	€1,256 (1,235 to 1,278)

Cost of in-patient treatment for systemic embolism and GI bleeds

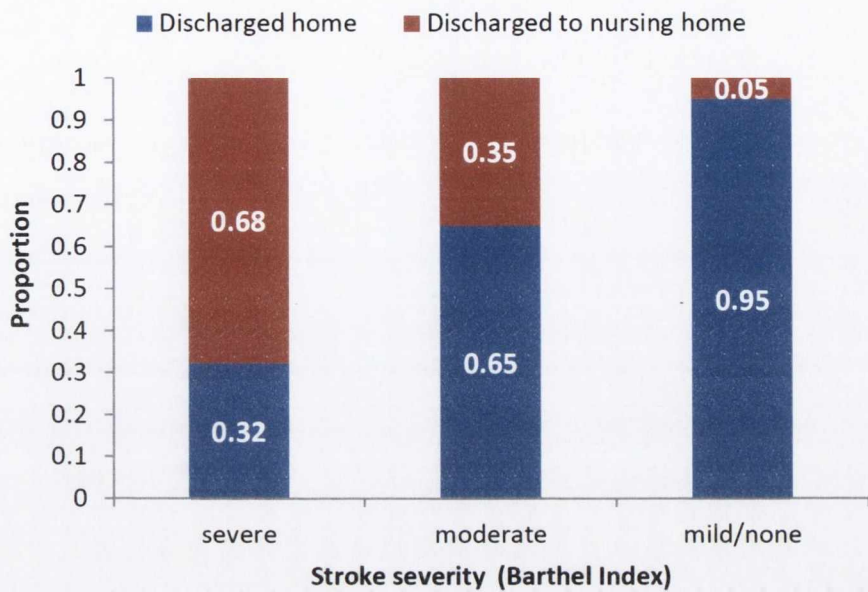
There is a lack of data on the cost of acute hospital treatment for systemic embolism and gastrointestinal bleeding in AF patients in Ireland. The best available estimates come from a technology appraisal carried out by the National Institute for Clinical Excellence in 2012 examining the use of DOACs in a UK setting.^(247;248) This estimated a cost of £2,603 (range £2,082 to £3,124) for non-fatal systemic embolism and £1,749 (range £1,399 to £2,099) for non-fatal GI bleeding. When these are converted to 2014 Irish Euro the equivalent costs are €3,698 (€2,956 to €4,436) and €2,483 (€1,988 to €2,982), respectively. It was assumed that the breakdown of costs between the public health system, private health insurers and out of pocket payments is the same as that for acute stroke care (87%, 12% and 1%, respectively).

Annual cost of care by severity of stroke

Direct long term care costs associated with stroke include nursing home care, ambulatory care, community rehabilitation, assistive technology and medications. Indirect costs include productivity losses as a result of morbidity and mortality, as well as the opportunity cost of informal care.⁽¹³⁸⁾

Data on the proportion of stroke survivors with mild, moderate and severe functional deficits who are discharged home or to residential care were obtained from the INASC study (Figure 3.26).⁽¹⁹⁷⁾ These estimates were calculated based on the total number of patients discharged to either of these destinations, excluding discharges coded as 'unknown' or 'other'. Costs associated with discharges to another hospital for inpatient rehabilitation are included separately.

FIGURE 3.26 DISCHARGE DESTINATION BY STROKE SEVERITY



The average cost per week for public and private institutions was calculated based on 2015 data from the HSE, which show that the average cost of care in public nursing homes is higher due to the increased proportion of patients with severe dependency in these (60%) compared with private institutions (35%).⁽²⁴⁹⁾ The annual cost of nursing home care by stroke severity is calculated as a weighted sum reflecting the fact that there are approximately twice as many patients with severe stroke included in the calculation of the average cost of public nursing homes, compared with private nursing homes. The cost of care for patients with moderate and mild stroke is assumed to be the same (Table 3.17).

TABLE 3.17 NURSING HOME COSTS BY SEVERITY OF STROKE

Nursing home	Weekly cost (95% CI)	Annual cost (95% CI) €
Private	€899 (614 to 1,185)	€46,760 (31,928 to 61,620)
Public	€1,245 (623 to 1,863)	€64,759 (32,396 to 96,876)
Weighted cost of severe stroke		€58,623 (32,237 to 84,889)
Weighted cost of moderate and mild stroke		€52,865 (32,087 to 73,607)

Previously published Irish data estimated that 73% of stroke-related nursing home costs in 2007 were funded from public resources.⁽¹³⁸⁾ However this was before the introduction of the Fair Deal Scheme in 2009, which changed the funding model to one where patients

contribute 80% of their assessable income and 7.5% of the value of any assets per annum, with the state paying the remainder. A person's principal residence is only included in the financial assessment for the first three years of care, and this payment can be deferred and collected from the person's estate if they wish. The latest available data from the HSE reported that in 2013 the level of patient contribution to nursing home care amounted to 6.4% of the total cost, with a marked difference in the percentage of costs paid for by the state between private (99%) and public nursing homes (84%).⁽²⁵⁰⁾ However, these figures do not include deferred payments so they are likely to be an underestimate of the true proportion of costs borne by patients. Uncertainty surrounding this estimate does not affect the economic analysis conducted using a societal perspective. For the analysis from the payer perspective, it was assumed that the HSE pays approximately 84% of the cost of nursing home care, based on 2013 data from public nursing homes only. This was varied in a sensitivity analysis.

Ambulatory care costs associated with outpatient visits and GP care were estimated from the Cost of Stroke in Ireland study (inflated to 2014) and applied to all stroke survivors (€726, range €637 to €815). GP care is a major component of this cost and the reported breakdown of public and out of pockets costs are 73% and 27%, respectively, for the overall stroke population. However, since the analysis models an older cohort, the proportion of people with a medical or GP card is likely to be higher. It was previously estimated that 81% of those over 65 years had a medical or GP card, so in the primary analysis of screening for over 65s it was assumed that 81% of the cost of ambulatory care is borne by the public health system. Total medication costs (including dispensing fees and rebates, but not prescription fees) associated with acute treatment are also taken from the Cost of Stroke in Ireland study, inflated to 2014 and applied to all stroke survivors (€1,849, range €1,649 to €2,049). As with ambulatory care, it was assumed that the 81% of these costs will be paid for by the health service through the GMS for medical card holders.

For stroke patients who are discharged home there may be costs associated with the provision of assistive technology and home modifications to allow them to live as independently as possible. The estimated total costs for aids, appliances and home modifications in 2007 was between €8 and €10 million.⁽¹³⁸⁾ National stroke audit data from

that year estimated that 56% of all patients were discharged home after a stroke.⁽¹⁹⁷⁾ Combining the available data on stroke incidence, discharge destination and costs (inflated to 2014) the average cost for assistive technology and home modification for patients discharged home was estimated to be €2,113 (range €1,761 to €2,642). Assuming that costs for those discharged home are directly correlated with stroke severity (per the Barthel scale) allowed estimation of the average cost per patient discharged home with mild, moderate and severe functional deficits, as well as the total average costs by stroke severity (Table 3.18).

TABLE 3.18 ASSISTIVE TECHNOLOGY AND HOME MODIFICATION COSTS, BY STROKE SEVERITY

Stroke severity	Average cost for patient discharged home	Overall average cost per patient
Mild	€1,504 (1,254 - 1,881)	€1,429 (1,191 - 1,787)
Moderate	€3,610 (3,009 - 4,514)	€2,346 (1,956 - 2,934)
Severe	€5,114 (4,262 - 6,394)	€1,636 (1,364 - 2,046)

The Cost of Stroke in Ireland study concluded that there was insufficient data available to estimate the proportion of these costs that were funded through the public health service. For the purposes of this analysis, it was assumed that 37% of costs are paid for by the HSE on the basis that items that are provided through the HSE aids and appliances funding account for 46% of the total cost and approximately 81% of patients have a medical card, which allows the holder to receive a prescribed aids and appliances free of charge.⁽²⁵¹⁾ The cost of aids and appliances were applied as a once-off charge in year one.

As well as direct costs for treatment, stroke is also associated with indirect productivity losses for those voluntarily providing informal care to stroke patients. The cost of informal care was previously estimated in Ireland using the human capital approach, which calculated the economic value of the time spent by caregivers using 2007 data on labour costs for those in employment and the value of leisure time (taken as one third the median hourly wage) for the unemployed.⁽¹³⁸⁾ Using international estimates of between nine and 20 hours of care being provided per week by informal caregivers, along with Irish data on average employment rates in under 65s and labour costs (€21.76 per hour), the average annual cost of informal care per stroke patient is estimated to be €10,938 (range €6,789 to

€15,087).^(138;252-257) In the analysis it was assumed that informal care is provided to all patients who are discharged home with moderate or severe dependency. The cost of informal care is only included in the analysis undertaken using a societal perspective.

The parameter estimates described above are used to estimate the total annual costs associated with haemorrhagic stroke and mild, moderate and severe ischaemic stroke from both a payer and societal perspective (Tables 3.19 to 3.22).

TABLE 3.19 LONG TERM AVERAGE ANNUAL COST OF CARE AFTER MILD STROKE

Description	Payer perspective	Societal perspective
Nursing home	€2220 (1348, 3092)	€2643 (1604, 3680)
Ambulatory care	€588 (516, 660)	€726 (637, 815)
Medication	€1498 (1336, 1660)	€1849 (1649, 2049)
Aids and appliances*	€529 (441, 661)	€1429 (1191, 1787)
Informal care	€0	€0
Total recurring annual cost	€4306 (3200, 5412)	€5216 (4090, 6544)

* cost applied as a once-off payment in year 1

TABLE 3.20 LONG TERM AVERAGE ANNUAL COST OF CARE AFTER MODERATE STROKE

Description	Payer perspective	Societal perspective
Nursing home	€15542 (9434, 21641)	€18503 (11230, 25762)
Ambulatory care	€588 (516, 660)	€726 (637, 815)
Medication	€1498 (1336, 1660)	€1849 (1649, 2049)
Aids and appliances*	€868 (724, 1086)	€2346 (1956, 2934)
Informal care	€0	€7394 (4590, 10199)
Total recurring annual cost	€17628 (11286, 23961)	€28472 (18106, 38825)

* cost applied as a once-off payment in year 1

TABLE 3.21 LONG TERM AVERAGE ANNUAL COST OF CARE AFTER SEVERE STROKE

Description	Payer perspective	Societal perspective
Nursing home	€33485 (18414, 48489)	€39864 (21921, 57725)
Ambulatory care	€588 (516, 660)	€726 (637, 815)
Medication	€1498 (1336, 1660)	€1849 (1649, 2049)
Aids and appliances*	€605 (505, 757)	€1636 (1364, 2046)
Informal care	€0	€3640 (2250, 5021)
Total recurring annual cost	€35571 (20266, 50809)	€46079 (26457, 65610)

* cost applied as a once-off payment in year 1

TABLE 3.22 LONG TERM AVERAGE ANNUAL COST OF CARE AFTER HAEMORRHAGIC
STROKE

Description	Payer perspective	Societal perspective
Nursing home	€11005 (5633, 16376)	€13101 (6706, 19495)
Ambulatory care	€588 (516, 660)	€726 (637, 815)
Medication	€1498 (1336, 1660)	€1849 (1649, 2049)
Aids and appliances*	€580 (483, 725)	€1567 (1306, 1960)
Informal care	€0	€5063 (3143, 6984)
Total recurring annual cost	€13091 (7485, 18696)	€20739 (12135, 29343)

* cost applied as a once-off payment in year one

3.3.5.4 PRODUCTIVITY COSTS

Productivity losses associated with stroke morbidity and mortality represent an important cost from a societal perspective. Both national and international studies have produced consistent estimates of the proportion of employed people who have to give up working as a result of stroke (45% to 65%).^(138;197;258-261) However, while there is evidence to show that functional ability is one of the main predictors of whether or not someone will return to work, there are conflicting estimates on the precise proportion of patients who will return to work after mild, moderate or severe stroke.⁽²⁶²⁻²⁶⁴⁾ In this analysis the simplifying assumption was made that no patients left with severe functional deficits or discharged to a nursing home return to work. For those with mild or moderate deficits the results of a previously published study, which found that 37% of patients with mild or moderate deficits who were employed prior to first-ever stroke fail to return to employment afterwards, were applied.⁽²⁵⁸⁾ Lost productivity was calculated using the human capital approach using Irish data from 2010 to 2014 on employment rates and average earnings by year of age within the modelled cohort (inflated to 2014, see Figures 3.27 and 3.28).^(265;266) Total productivity loss by age at death to 85 years is calculated using discounting to incorporate the time value of future earnings into the overall sum, which is itself discounted to reflect the year in which the productivity loss is incurred. Cumulative productivity losses by age at death or disability are shown in Figure 3.29.

FIGURE 3.27 EMPLOYMENT RATE BY AGE

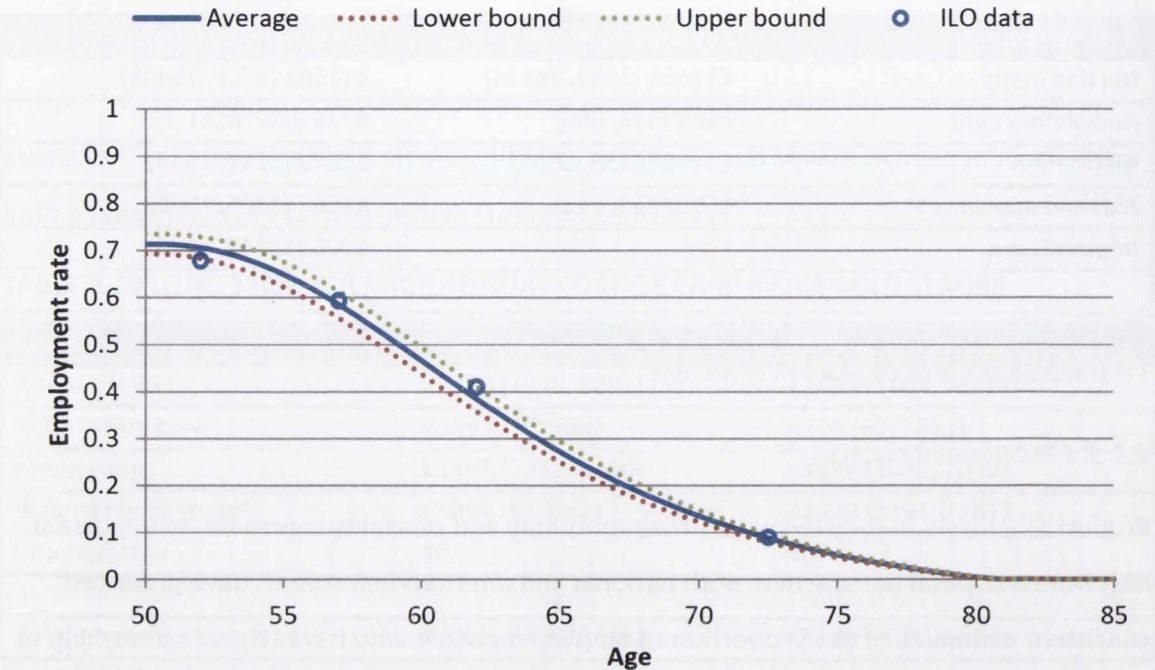


FIGURE 3.28 AVERAGE ANNUAL EARNINGS BY AGE

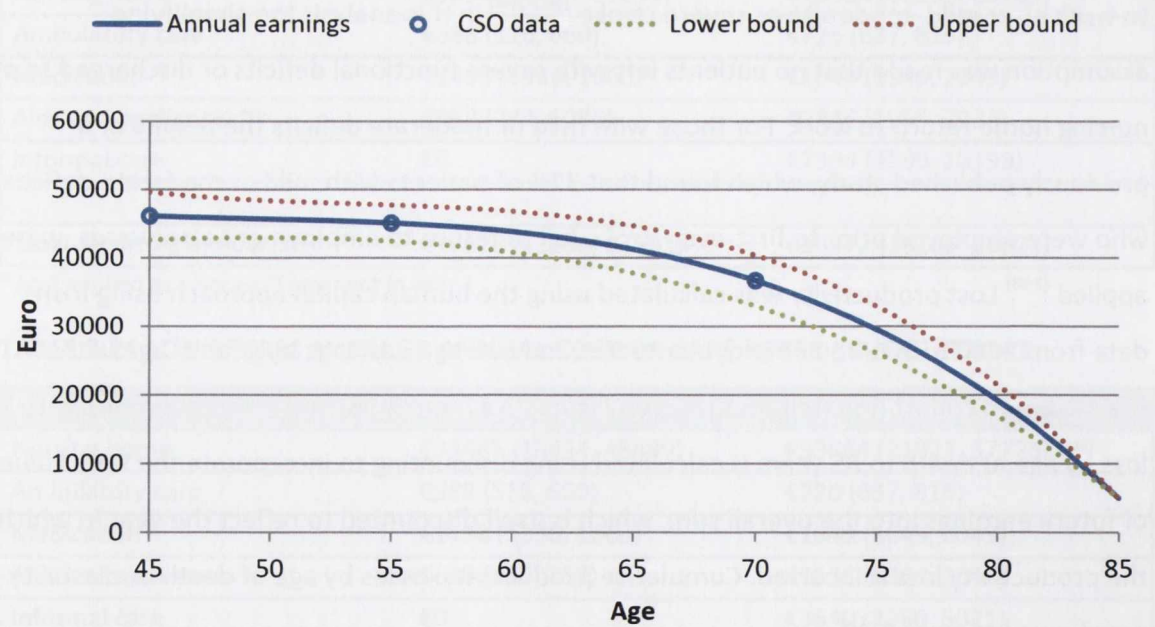
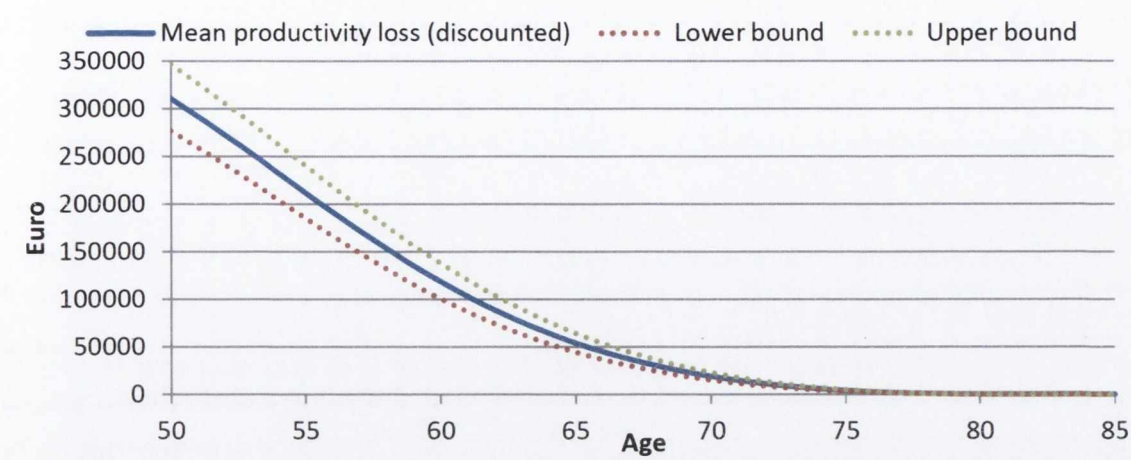


FIGURE 3.29 TOTAL DISCOUNTED PRODUCTIVITY LOSS BY AGE



3.3.5.5 LIMITATIONS OF THE COST DATA

There are a number of limitations associated with the estimation of the costs of screening for AF and treating stroke. Opportunistic screening, where a two stage test is designed to be carried out as part of a GP consultation when the patient is attending for some other issue, is more challenging to cost compared with traditional invitational programmes that offer screening at a dedicated centre. It was decided to cost the time needed to perform pulse palpation and to use a set fee for an ECG performed in primary care. It is possible that any future GP contract might regard screening as part of routine care that does not attract a fee. However, even if this were the case there would still be an opportunity cost associated with screening, which would be the value of the alternative use of that time during a consultation. Therefore the estimates outlined above are appropriate for the evaluation of the AF screening programme currently being considered.

Potential limitations in regard to the cost of stroke treatment include the fact that the most recent Casemix data on inpatient treatment costs is derived from 2011. However CSO data on inflation within the health sector between 2011 and 2014 was low (2.8%), so the impact of this should be minimal. Casemix provides the overall average costs for patients treated (weighted by the presence or absence of complications) rather than by severity of stroke. To estimate individual costs for those with mild, moderate or severe stroke it was assumed that treatment costs are directly correlated with acute severity. While the limited available

evidence on this issue supports this assumption, there is uncertainty about the relative cost differences.

There was a lack of Irish data on the hospital costs for systemic embolism and GI bleeds, so these costs were estimated using UK data (converted to 2014 Irish Euro). While there are caveats associated with using international data, given the similarities between Ireland and the UK in how hospitals are funded and access to treatment, this was considered to be the best available option for capturing these costs.

The analysis uses average costs for long term care for mild, moderate and severe stroke, which combines data on those for whom AF was or was not a contributing factor. This captures the cost implications of screening if the higher cost associated with AF stroke are assumed to be as a result of increased AF stroke severity, which increases the likelihood of death and significant long term functional impairment. While it is generally accepted that the reason AF strokes cost more to treat is because they are more severe, a recent Irish study found that AF was associated with substantially greater two-year costs in those with mild-moderate stroke (no difference was observed in severe stroke).^(267;268) The authors' did not discuss the reasons for this cost difference within the mild/moderate severity category, and acknowledge that confounding and lack of power may partially explain some of the findings. The analysis models mild and moderate stroke costs separately. The work carried out as part of the Irish National Audit of Stroke Care and the Cost of Stroke in Ireland study, both of which were based on data from 2007, are used to inform this analysis. All costs reported in these studies were inflated to 2014 and it was assumed that the overall findings in relation to stroke care are applicable to present day.

Estimates of the cost of informal care are associated with a high degree of uncertainty and are based on evidence showing an average of between nine and 20 caregiver hours being provided per week. In the absence of data on the difference in the mean number of hours provided for those with moderate and severe disability, the overall average was applied to both, rather than assuming that the level of informal care provided is directly correlated with the degree of dependency. Given the number of hours per week involved, it is likely that informal care compliments, rather than replaces, other support services. Uncertainty

about the relationship between the mix of formal and informal care prevented any assumptions about relative costs of informal care in moderate and severe stroke.

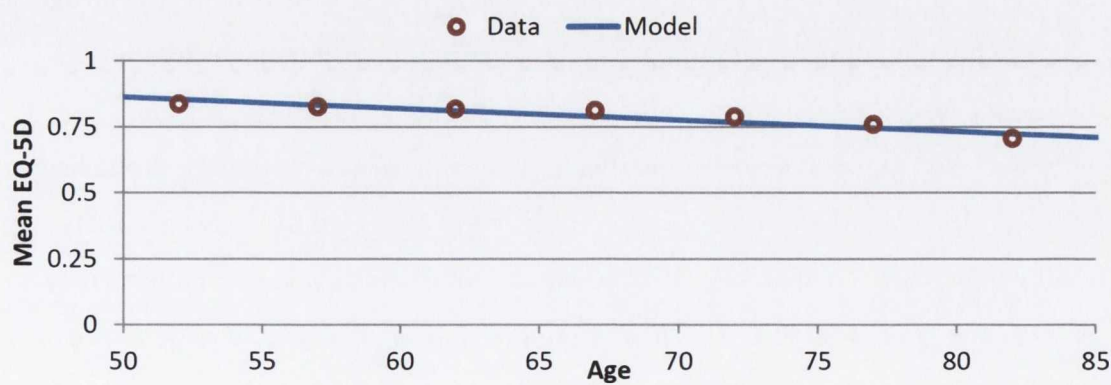
3.3.6 ESTIMATES OF UTILITY

The estimates of the impact of stroke on mortality enable calculation of the likely effect of screening in terms of life years lost or gained. What it does not take account for is any change in the quality of life for screened versus unscreened patients as a result of changes in functional status post-stroke, or treatment related adverse events, such as GI bleeds, that may not necessarily shorten life expectancy but are associated with significant morbidity. This information is included in the analysis using utility weights that measure the degree of impairment associated with each health state included in the model compared with full health.

3.3.6.1 BASELINE QUALITY OF LIFE BY AGE

Baseline data on mean utility weights for people without atrial fibrillation or stroke by age were taken from a previously published analysis of data from the Health Survey for England. This analysis estimated mean EQ-5D scores for the general population, as well as for those with and without heart problems other than myocardial infarction or hypertension.⁽²⁶⁹⁾ In the absence of comparable Irish data it is assumed that both populations are comparable. This parameter is modelled as a linear function (Figure 3.30).

FIGURE 3.30 BASELINE UTILITY WEIGHT ESTIMATES BY AGE FOR THOSE WITHOUT ATRIAL FIBRILLATION OR STROKE



3.3.6.2 QUALITY OF LIFE WITH ATRIAL FIBRILLATION

The model requires an estimate of the impact on quality of life for diagnosed and undiagnosed AF patients who have not suffered a stroke. It is generally accepted that AF is associated with a reduced quality of life due to symptoms such as weakness, fatigue and palpitations, which can be managed to varying degrees with rhythm or rate control medication.⁽²⁷⁰⁾ There is also evidence to suggest that those with undiagnosed AF experience a reduction in quality of life, despite the absence of overt symptoms, or because moderate symptoms are misattributed.^(143;271)

Previous studies have estimated a utility weight of 0.81 (95% CI 0.68, 0.91) associated with diagnosed AF, which was derived using EQ-5D data from a nationally representative sample of US AF patients without a history of stroke, adjusted for age, sex and co-morbidities.^(272;273) This is consistent with the estimate used in the economic evaluation of the UK SAFE trial.⁽¹⁵¹⁾ Although TILDA collected data on quality of life, the numbers of people who reported a diagnosis of AF were relatively low and quality of life was measured using the CASP-19 tool, rather than the EQ-5D, which is the tool that was used to estimate baseline utility weights for the general population in the absence of AF.

Estimating the utility loss associated with undiagnosed AF is more problematic as there is little evidence on the extent to which people in this cohort are genuinely asymptomatic, or are experiencing general symptoms such as dyspnoea or weakness, but lack a definite diagnosis. What evidence is available is derived from studies that compare diagnosed AF patients who are either asymptomatic or symptomatic.^(143;225) A UK study comparing quality of life (measured using SF-36) in symptomatic and asymptomatic AF patients (mean age 58 years), and healthy controls found significantly lower scores in all domains for the symptomatic AF group, and lower scores in one domain (general health) for the asymptomatic AF group. Compared with healthy controls, the asymptomatic group had average quality of life scores that were 6% lower than healthy controls, giving a utility weight of 0.94 (95% CI 0.86, 0.98).⁽²⁷⁴⁾ Applying this to all undiagnosed AF patients may underestimate the true utility loss, since it assumes that all undiagnosed patients are asymptomatic. However any adjustment for this risks overestimating this parameter. In the analysis the conservative estimate was used in the base case and the implications of

undiagnosed AF being associated with a greater utility loss was examined in a sensitivity analysis.

Limitations regarding the use of utility data for AF include applicability issues about using US data in an Irish population and uncertainty about the level of AF symptoms in the undiagnosed cohort. There are also some recent studies that would appear to challenge the idea that AF results in poorer quality of life in non-acutely ill older patient cohorts, finding little or no reduction associated with the arrhythmia in this population.^(275;276) It was also assumed that the quality of life reduction associated with undiagnosed AF does not decrease as a result of treatment after detection. This will tend to underestimate the effectiveness of screening if treatment does have a beneficial effect of the quality of life of previously undiagnosed AF patients. However in the absence of data for this group a conservative approach was adopted.

3.3.6.3 *QUALITY OF LIFE DECREASE ASSOCIATED WITH TREATMENT*

There is evidence to suggest that treatment for atrial fibrillation is associated with minor reductions in quality of life, unrelated to stroke or complications, as a result of the need for various degrees of ongoing monitoring, required changes in diet or lifestyle and the potential for adverse side effects. Warfarin, which requires regular blood tests to monitor INR levels, is associated with a greater degree of utility loss than antiplatelet or DOAC use. Estimates of the utility loss associated with each type of treatment are taken from published US survey data from patients with AF taking warfarin and aspirin, and a US physician survey of quality of life for patients on ximelagatran (Table 3.23).⁽²⁷⁷⁻²⁷⁹⁾

TABLE 3.23 QUALITY OF LIFE ESTIMATES FOR ANTITHROMBOTIC TREATMENT

Treatment	Utility Weight (95% CI)
Warfarin	0.987 (0.953, 1.00)
DOAC	0.994 (0.975, 1.00)
Aspirin	0.998 (0.994, 1.00)

3.3.6.4 *QUALITY OF LIFE AFTER A STROKE*

A meta-analysis of quality of life outcomes for stroke identified 20 studies that reported outcomes for mild, moderate and severe stroke separately.⁽²⁸⁰⁾ This found that severity of

stroke and the bounds of the scale used (death or worst possible outcome to normal, excellent or perfect health) predicted quality of life weights, but the elicitation method (time trade off, standard gamble, judgement) and type of respondent (patients, communities) did not. Time trade off elicitation from community members using a scale of death to perfect health produced pooled quality-adjusted life year (QALY) weights of 0.52 for major stroke, 0.68 for moderate stroke, and 0.87 for minor stroke. The same type of respondents, using the same type of elicitation method but a scale of death to normal health produced significantly lower pooled weights of 0.28, 0.45 and 0.64 for major, moderate and minor stroke, respectively. A previous cost-effectiveness study used data from this meta-analysis to group stroke severity by functional status post stroke according to whether the person was independent (0.65), moderately dependent (0.46) or totally dependent (0.30).⁽²⁷²⁾ These estimates are most closely aligned with the Framingham data on stroke severity used in the analysis, which used the modified Barthel Index to classify stroke survivors as severely dependent, moderately dependent or with mild to no dependence. The overall utility weight for haemorrhagic stroke was calculated as the average utility weight across all survivors using the same weights and functional outcomes as ischaemic stroke (average utility weight 0.57). A utility weight of zero was applied to fatal strokes.

3.3.6.5 QUALITY OF LIFE DECREMENTS FOR COMPLICATIONS AND ADVERSE EVENTS

It is assumed that non-central nervous system (CNS) bleeding events and systemic emboli result in a temporary reduction in quality of life. They are therefore included in the model as utility decrements that are incurred in the year that they happen. Previously published data estimated a utility decrement (calibrated to apply for one month) of 0.092 for major bleeding and 0.022 for pulmonary embolism.⁽²⁸¹⁾ These were applied to all major extra-cranial bleeding and systemic embolism events in the model, with a sensitivity analysis to estimate the impact of uncertainty in relation to these parameters on the overall cost-effectiveness results.

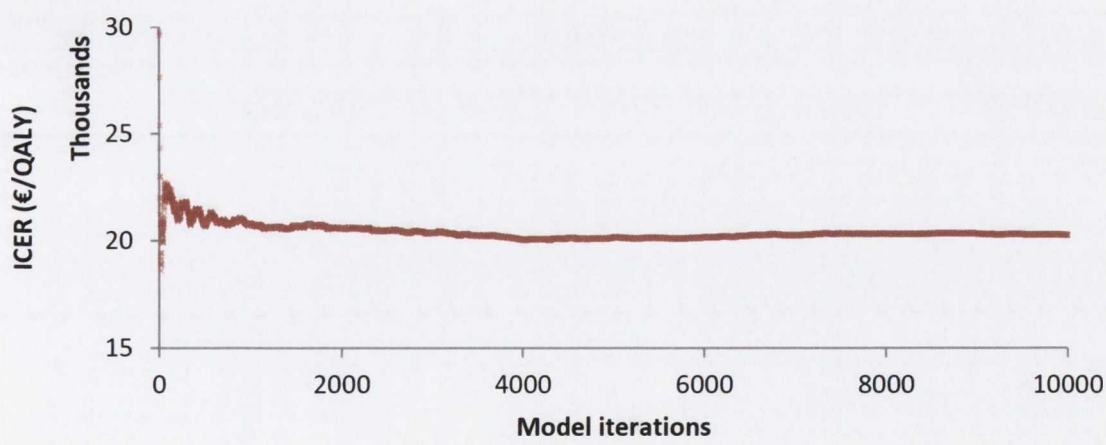
3.3.6.6 LIMITATIONS OF THE UTILITY DATA

The main limitation in regard to utility data is the lack of published Irish data on preferences for AF and stroke-related clinical outcomes. In the absence of Irish data, international estimates from the US and the UK were used, which may differ from the utility valuation that the Irish population would assign to the various health states. There is also a high degree of heterogeneity in the published literature for utility weights associated with mild, moderate and severe stroke. The estimates used in the model were chosen based on how closely the reported health states aligned with the categorisations employed in the clinical studies included in this analysis, and are consistent with those used in cost-effectiveness analyses elsewhere.

3.3.7 RESULTS OF THE ECONOMIC ANALYSIS

Convergence in the estimated cost-effectiveness of screening in the probabilistic model was achieved after approximately 4,000 iterations (Figure 3.31). All results presented here are based on the full 10,000 simulations comparing a strategy of opportunistic screening in primary care with no screening (routine practice).

FIGURE 3.31 CONVERGENCE OF ICER ESTIMATES IN MODEL



3.3.7.1 PAYER PERSPECTIVE RESULTS

Table 3.24 provides a summary of the absolute effects of screening and routine care, including the average undiscounted number of AF cases diagnosed, strokes avoided and life

years gained if screening was implemented within the current cohort of 65 year olds in Ireland (n=42,330). The model outputs indicate that one additional case of AF is diagnosed for every 22 people opportunistically screened for 25 years from the age of 65, and one stroke is avoided for every 270 people screened over the same period.

TABLE 3.24 ABSOLUTE OUTCOMES FOR SCREENING AND ROUTINE CARE BASED ON THE CURRENT IRISH POPULATION OF MEN AND WOMEN AGED 65 YEARS (N=42,330)

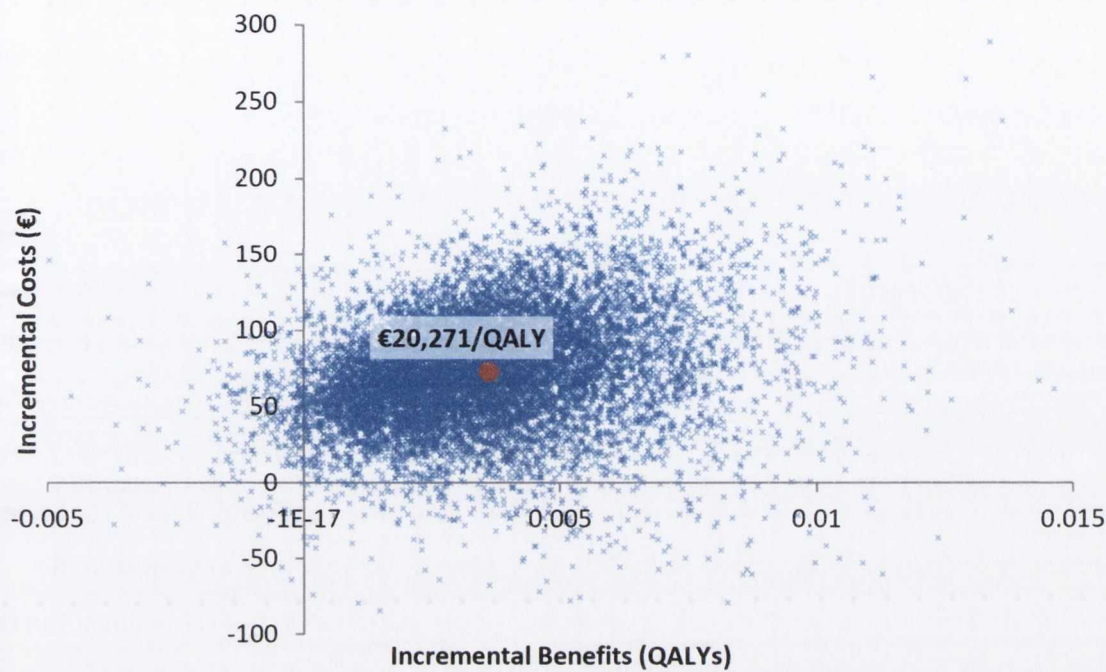
Outcome	Cases	Routine care	Screening	ICER (undiscounted)
AF cases detected	Total	5756	7700	€1,697 per additional AF case detected
	Incremental		1944	
Ischaemic strokes	Total	4293	4108	€54,203 per stroke avoided
	Incremental		-185	
Haemorrhagic strokes	Total	1285	1313	
	Incremental		28	

The incremental cost-effectiveness ratio (ICER) for AF screening in over 65s compared with routine care from the perspective of the HSE is €20,271/QALY (Table 3.25). The cost-effectiveness plane is shown in Figure 3.32.

TABLE 3.25 ICER CALCULATION (PAYER PERSPECTIVE)

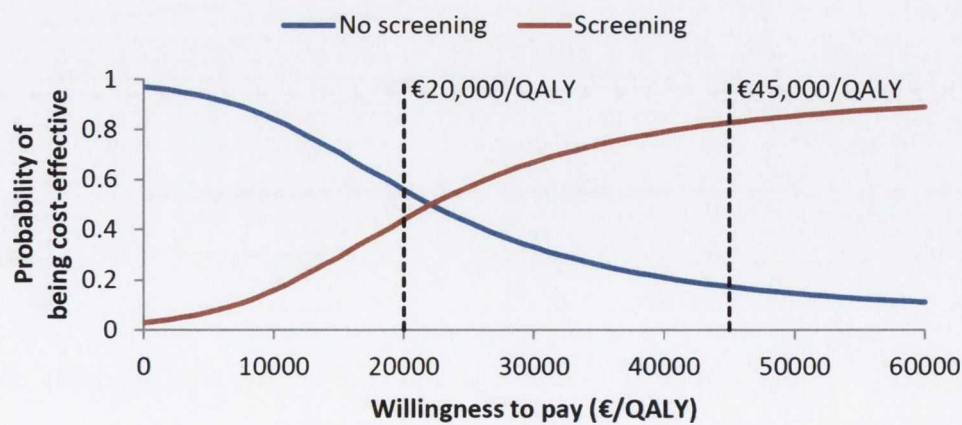
Strategy	Cost (€)	Incremental Cost (€)	Effect (QALYs)	Incremental Effect (QALYs)	ICER
No screening	3,854	-	7.8127	-	€20,271/QALY
Screening	3,927	73	7.8164	3.6012x10 ⁻³	

FIGURE 3.32 COST-EFFECTIVENESS PLANE (PAYER PERSPECTIVE)



The cost-effectiveness acceptability curve (CEAC) showing the probability of screening being the optimal strategy for a range of willingness-to-pay (WTP) thresholds is shown in Figure 3.33. Screening has a 44% probability of being cost-effective at a WTP threshold of €20,000/QALY and an 83% probability of being cost-effective at a WTP threshold of €45,000/QALY.

FIGURE 3.33 COST-EFFECTIVENESS ACCEPTABILITY CURVE (CEAC, PAYER PERSPECTIVE)



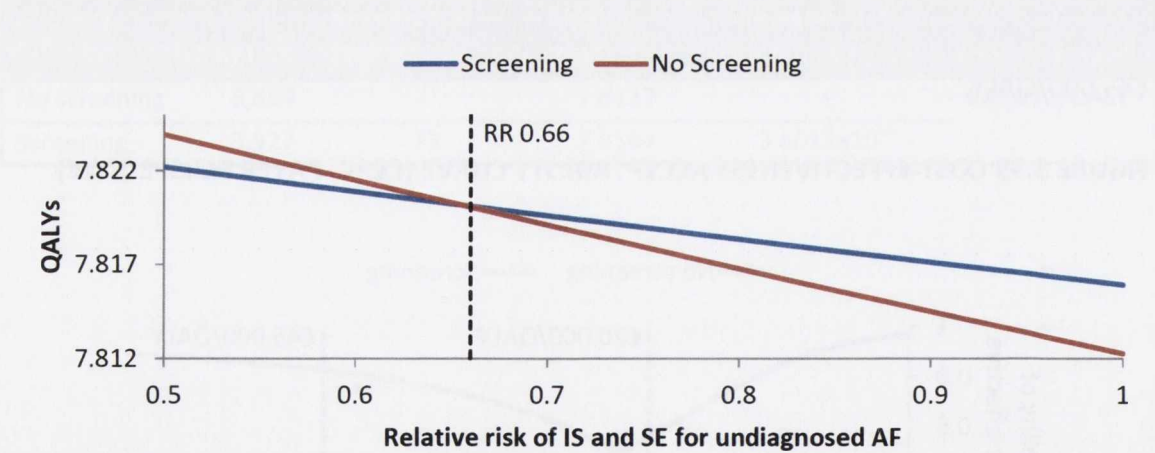
3.3.7.2 SENSITIVITY AND SCENARIO ANALYSIS

Given the uncertainty surrounding some of the key parameters in the model, extensive sensitivity and scenario analysis was carried out to examine what the impact of changes to these parameters would be on the overall cost-effectiveness results.

Stroke risk profile of asymptomatic AF patients

Uncertainty surrounding the benefits of early detection in asymptomatic AF patients was one of the main reasons why the UK National Screening Committee recommended that AF screening should not be offered by the NHS. While the CHA₂DS₂VAS_c tool for calculating the risk of stroke in atrial fibrillation does not distinguish between asymptomatic and symptomatic individuals, some studies in asymptomatic device-detected AF have suggested that the risk of stroke in asymptomatic AF may be 33% to 50% less than in symptomatic individuals. A sensitivity analysis was conducted to examine the effect of screening if the risk of stroke and systemic embolism in the additional people that would be detected by screening was less than in those detected through routine care (Figure 3.34).

FIGURE 3.34 IMPACT OF REDUCED RISK OF STROKE IN ASYMPTOMATIC AF ON EFFECTIVENESS OF SCREENING AND ROUTINE CARE

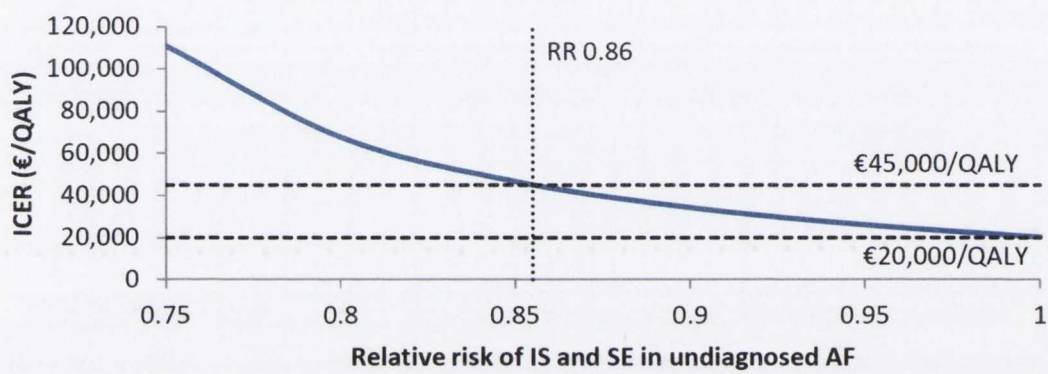


IS – Ischaemic Stroke, SE – Systemic Embolism, AF – Atrial Fibrillation, RR – Relative Risk, QALY – Quality Adjusted Life Year

This suggests that if the relative risk of stroke and systematic embolism in screen- detected patients is more than a third lower ($RR < 0.66$) than that of AF patients identified through

routine practice then the harms of screening outweigh the benefits. The impact on cost-effectiveness is shown in Figure 3.35, which shows that if the relative risk of stroke and systemic embolism is more than 14% lower in screen-detected patients compared with symptomatic patients, then screening would be considered not cost-effective using a willingness-to-pay threshold of €45,000/QALY.

FIGURE 3.35 IMPACT OF REDUCED RISK OF STROKE IN ASYMPTOMATIC AF ON COST-EFFECTIVENESS OF SCREENING



IS – Ischaemic Stroke, SE – Systemic Embolism, AF – Atrial Fibrillation, RR – Relative Risk, QALY – Quality Adjusted Life Year, ICER – Incremental Cost Effectiveness Ratio

Start ages for screening

The screening cohort in the primary analysis was men and women over 65 years. Table 3.26 shows the expected impact of varying the start age of screening between 50 and 70 years. The time horizon over which all programmes were evaluated was from the start of screening to age 90 years.

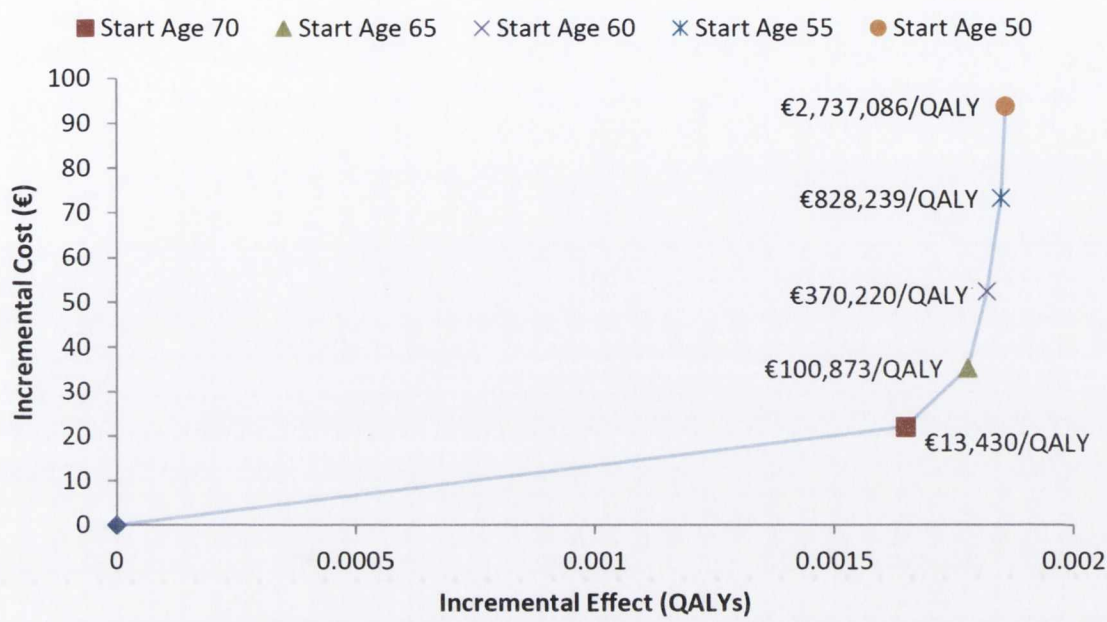
TABLE 3.26 ICERS FOR SCREENING VERSUS ROUTINE CARE AT START AGES BETWEEN 50 AND 70 YEARS

Start Age	Incremental Cost(€)	Incremental Effect (QALYs)	ICER compared to routine care*
50 Years	93.86	1.8585x10 ⁻³	€50,578/QALY
55 Years	89.03	2.3419x10 ⁻³	€38,004/QALY
60 Years	82.47	2.9276x10 ⁻³	€28,134/QALY
65 Years	73.66	3.6505x10 ⁻³	€20,271/QALY
70 Years	64.07	4.3854x10 ⁻³	€14,594/QALY

* Due to rounding error the ICER value calculated using the incremental cost and incremental effect values reported in this table may differ from the ICER value reported in the table. Where any such differences do occur please note that the ICER value reported in the table provides the most accurate estimate.

Comparing each start age to a comparator of routine care (as opposed to each other) found that reducing the start age of screening would tend to decrease the cost effectiveness of a prospective screening programme. This was expected given the sharp increase in the incidence of AF with advancing age. Increasing the start age is likely to improve the cost-effectiveness of the programme further. The ICER for each screening programme relative to the next best option (per Table 3.26) for a cohort of 50 year olds is shown in Figure 3.36. This shows that while the average cost of a QALY gained from annual screening starting at age 65 is well below a WTP threshold of €45,000/QALY, the average cost of an additional QALY generated by lowering the screening start age from 70 to 65 is over €100,000.

FIGURE 3.36 ICERS FOR ANNUAL SCREENING VERSUS NEXT BEST OPTION AT START AGES BETWEEN 50 AND 70 YEARS

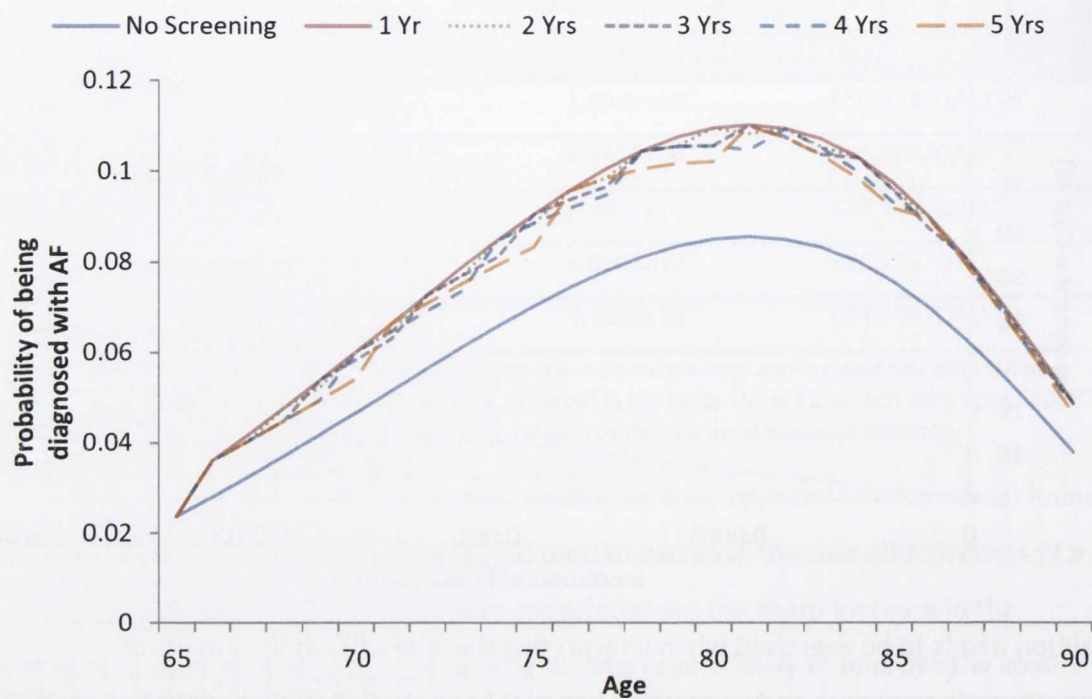


Caution needs to be exercised when interpreting these results, as the impact of opportunistic screening on AF detection has only been studied in a population of aged 65 years and over. Therefore any extension of the age range of screening requires an assumption that the clinical effectiveness estimates apply equally across all ages, which may not be the case.

Screening intervals

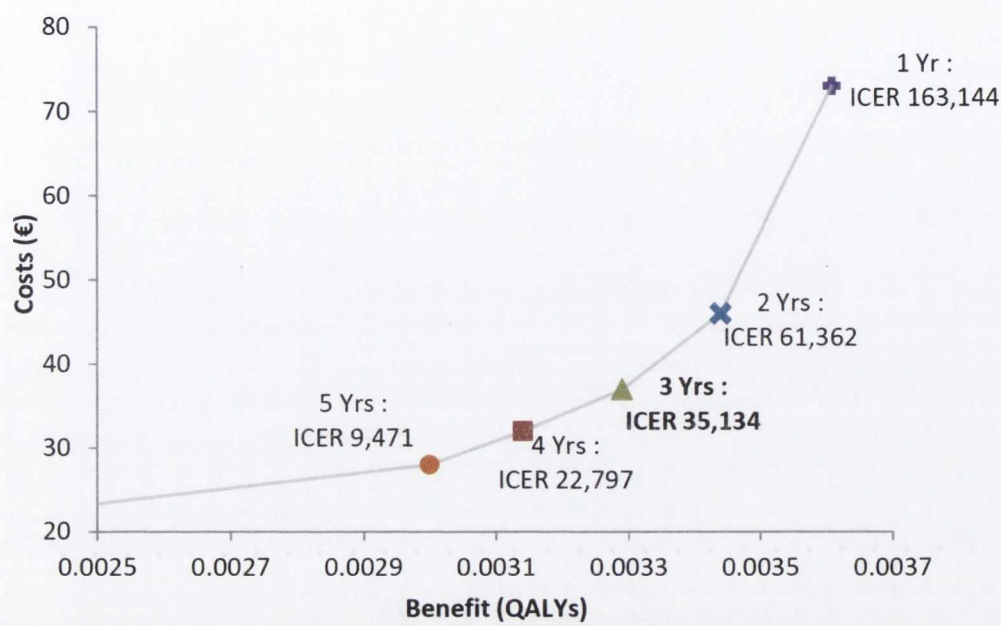
A scenario analysis was carried out to compare the annual screening programme evaluated in the primary analysis to programmes with an extended screening interval of between two and five years. In this scenario, incident AF cases in interval years have the same probability of being diagnosed as they do under routine care, whereas in screening years there is an increase in the detection of both incident cases and undetected prevalent cases from the interval period (Figure 3.37).

FIGURE 3.37 MODELLED PROBABILITY OF AF DIAGNOSIS BY AGE FOR DIFFERENT SCREENING INTERVALS



The cost-effectiveness plane comparing different screening intervals for a start age of 65 years is shown in Figure 3.38. This reveals that when the screening interval is lengthened, the rate of decrease in costs is greater than the rate of decrease in benefits, resulting in a lower ICER compared with no screening. It also shows that the ICER for annual screening compared with the next best option in the scenario analysis (screening every second year) far exceeds conventional willingness to pay thresholds used in Ireland. If extending the screening interval beyond one year is considered a realistic option, then at a willingness-to-pay threshold of €45,000/QALY the optimal screening strategy would be opportunistic screening every three years.

FIGURE 3.38 SCENARIO ANALYSIS COMPARING DIFFERENT SCREENING INTERVALS WITH A START AGE OF 65 YEARS



Caution needs to be applied when interpreting these results as the data on clinical effectiveness results were obtained from a once-off annual screen, raising questions as to whether or not they can be directly applied to longer screening intervals. Another important consideration is the feasibility of implementing extended screening intervals beyond one year in the context of an opportunistic programme requiring a one minute pulse palpation in patients who attend a GP consultation for a different reason.

Combining start ages and screening intervals

If it is assumed that the effect of screening is the same for every combination of start age and screening interval and that all assumptions in the primary analysis hold in every case then it is possible to compare all potential screening strategies in one cost-effectiveness plane (Figure 3.39). ICERs for all non-dominated strategies are shown in Table 3.27.

FIGURE 3.39 COMPARISON OF START AGES FROM 55 TO 75 AND SCREENING INTERVALS FROM ONCE-OFF TO EVERY 1 TO 5 YEARS (PAYER PERSPECTIVE)

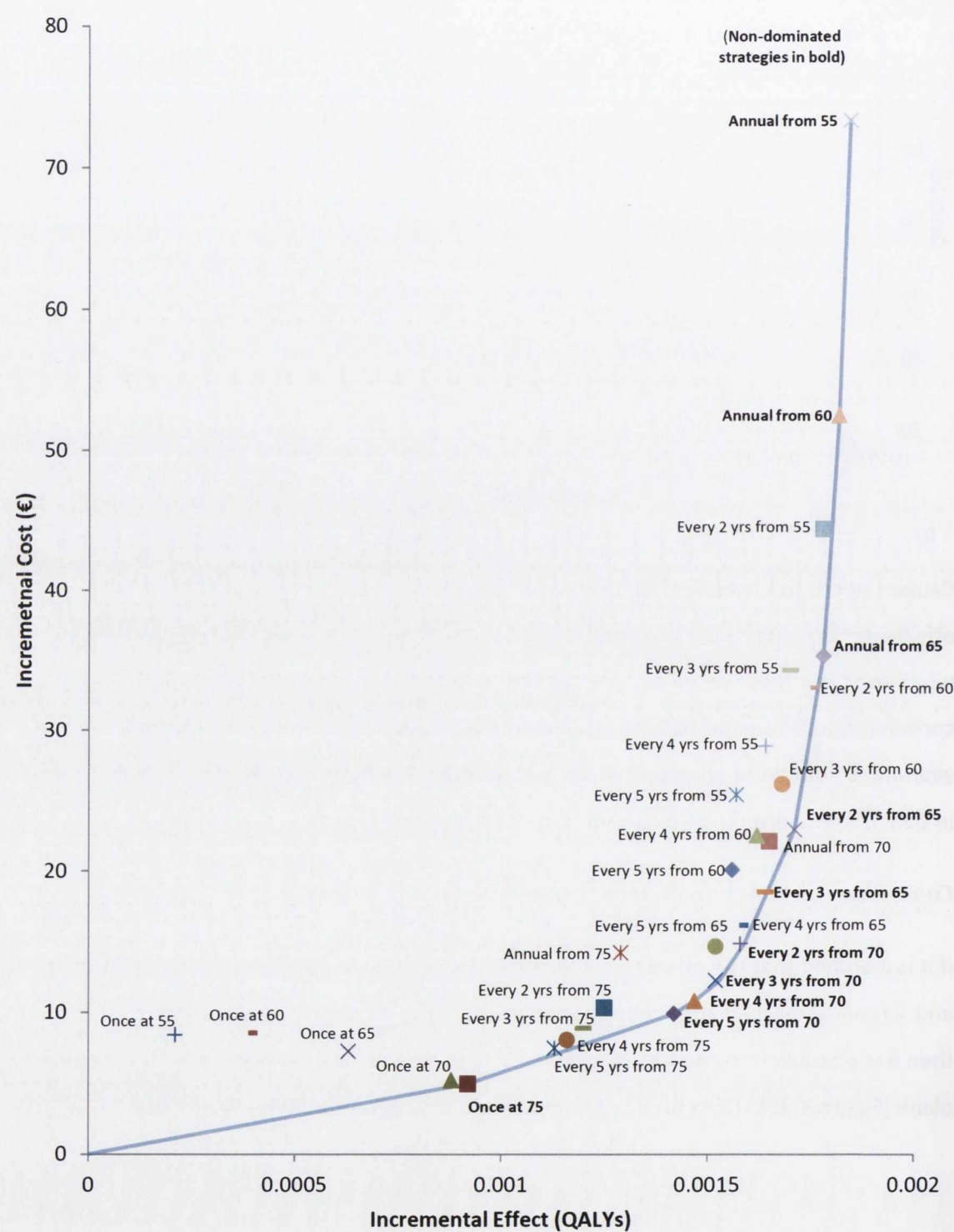


TABLE 3.27 INCREMENTAL COST EFFECTIVENESS RATIOS FOR ALL NON-DOMINATED STRATEGIES FOR START AGES FROM 55 TO 75 AND SCREENING INTERVALS FROM ONCE-OFF TO EVERY 1 TO 5 YEARS (PAYER PERSPECTIVE)

Strategy	Incremental Cost (€)	Incremental Effect (QALYs)	ICER* (€/QALY)
No screening	0	0	-
Once at 75	4.9615	9.1710x10 ⁻⁴	5,410
Every 5 yrs from 70	4.9447	4.9967x10 ⁻⁴	9,896
Every 4 yrs from 70	0.9075	5.2520x10 ⁻⁵	17,279
Every 3 yrs from 70	1.4483	5.5644x10 ⁻⁵	26,028
Every 2 yrs from 70	2.5874	5.9022x10 ⁻⁵	43,838
Every 3 yrs from 65	3.6782	5.8741x10 ⁻⁵	62,617
Every 2 yrs from 65	4.3919	6.5407x10 ⁻⁵	67,147
Annual from 65	12.3696	6.8478x10 ⁻⁵	180,637
Annual from 60	17.1824	4.6411x10 ⁻⁵	370,220
Annual from 55	20.8489	2.5173x10 ⁻⁵	828,239

* Due to rounding error the ICER value calculated using the incremental cost and incremental effect values reported in this table may differ from the ICER value reported in the table. Where any such differences do occur please note that the ICER value reported in the table provides the most accurate estimate.

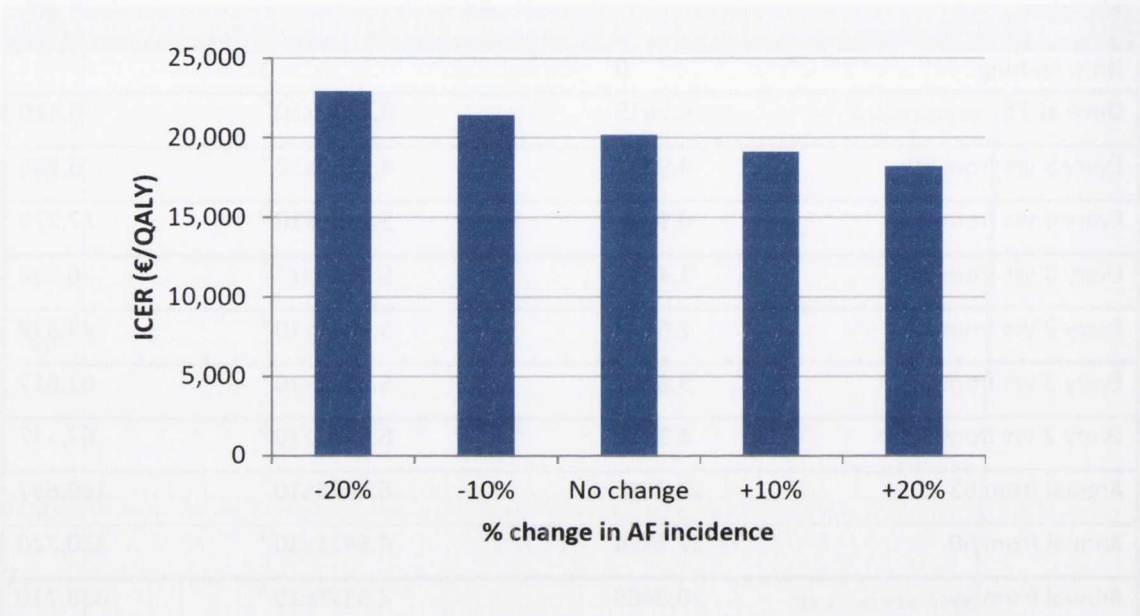
The results show that the most cost effective option is once-off screening at age 75, which has an ICER of €5,410/QALY. The cost of each additional QALY generated by moving to the next most cost-effective strategy (screening every 5 years from age 70) is approximately €10,000/QALY. In this analysis the ICER for annual screening from age 65 compared to the next best option (screening every two years from age 65) is over €180,000/QALY. At a willingness to pay threshold of €45,000/QALY the optimal strategy is biennial screening starting at age 70. However as outlined earlier, the validity of these comparisons is dependent on a number of untested assumptions being met, most notably the assumption that the effect of screening is the same across all age groups and screening intervals.

AF incidence

Accurate estimation of the total incidence of AF is difficult, as the arrhythmia may be intermittent or associated with nonspecific symptoms such as fatigue and dyspnoea. The

impact of uncertainty regarding AF incidence on the cost-effectiveness of screening was examined by varying incidence rates by $\pm 20\%$ (Figure 3.40).

FIGURE 3.40 ICER ESTIMATES WITH CHANGING AF INCIDENCE RATES



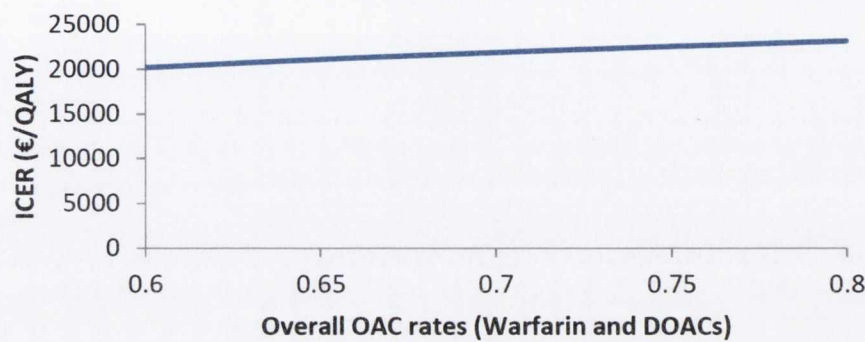
As expected, screening becomes more cost-effective as the estimated incidence of AF in the screening population increases, although the change is modest. The sensitivity analysis indicates the risk that the cost-effectiveness of screening is overestimated due to uncertainty about AF incidence is low, since the data used is more likely an underestimate rather than an overestimate of true AF incidence, and even a 20% overestimation would result in an ICER of less than €25,000/QALY.

Changes to OAC rates as a result of screening

In the primary analysis the conservative approach of assuming that the standard of care for AF will remain the same if a screening programme is introduced was adopted. However, as demonstrated in the STROKESTOP study, screening has the potential to increase treatment rates of AF both by identifying previously undiagnosed cases and by improving oral anticoagulation (OAC) rates among those with a prior diagnosis. Although definitive data on current OAC rates and direct oral anticoagulant (DOAC) use in AF patients is lacking, it was estimated that approximately 60% are anticoagulated and 35% of these are taking DOACs.

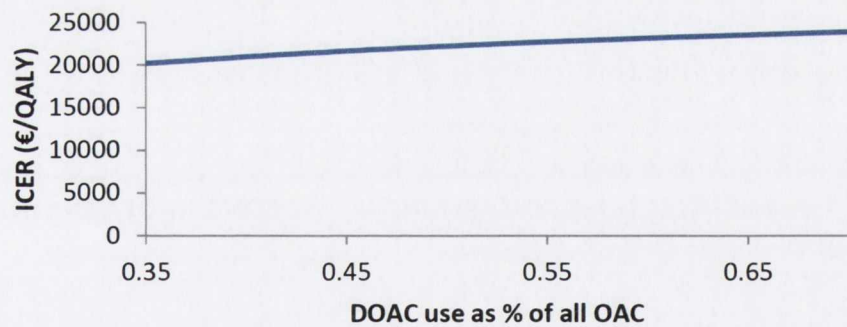
Figure 3.41 and 3.42 show the impact of increasing OAC rates and DOAC use as a result of screening on cost-effectiveness.

FIGURE 3.41 IMPACT OF INCREASING OAC RATES AS A RESULT OF SCREENING ON COST-EFFECTIVENESS



OAC – Oral Anticoagulant, DOAC – Direct Oral Anticoagulant, ICER – Incremental Cost Effectiveness Ratio

FIGURE 3.42 IMPACT OF INCREASING DOAC USE AS A RESULT OF SCREENING ON COST-EFFECTIVENESS



OAC – Oral Anticoagulant, DOAC – Direct Oral Anticoagulant, ICER – Incremental Cost Effectiveness Ratio

Results show that the marginal increase in benefits from greater OAC and DOAC use is matched by the marginal increase in costs, so there is no major change in the incremental cost effectiveness ratio (ICER) estimate even with large increases in DOAC use.

Recent analysis of DOAC use in Ireland suggests that a significant proportion of patients are prescribed doses that are non-inferior to warfarin. To examine the impact of suboptimal DOAC prescription a worst-case scenario was examined where all those on DOACs had the

same reduction in risk of ischaemic stroke and systemic embolism as those on warfarin, while retaining the same risk of bleeding (and costs). Results are shown in Table 3.28, which indicates that the impact on the overall cost-effectiveness of screening versus routine care is minimal (approximately 3% increase in ICER).

TABLE 3.28 EFFECT OF SUBOPTIMAL DOAC DOSING ON ICER FOR SCREENING

Strategy	Cost (€)	Incremental Cost (€)	Effect (QALY)	Incremental Effect (QALY)	ICER*
No screening	3,855	-	7.80914	-	€20,789/QALY
Screening	3,930	74	7.81272	3.5783x10 ⁻³	

* Due to rounding error the ICER value calculated using the incremental cost and incremental effect values reported in this table may differ from the ICER value reported in the table. Where any such differences do occur please note that the ICER value reported in the table provides the most accurate estimate.

Recent UK guidelines for the management of AF recommend against offering aspirin monotherapy solely for stroke prevention for people with atrial fibrillation.⁽²⁸²⁾ The most recent Irish and UK data suggests that aspirin is currently being used for this purpose in up to a third of patients. As this is likely to reduce over time in light of the UK guidelines, a sensitivity analysis was carried out to estimate the cost-effectiveness of screening being introduced into an environment with very high OAC rates, using the extreme case of 100% DOAC use. The results of this scenario analysis (Table 3.29) show that this would not significantly affect the cost-effectiveness results.

TABLE 3.29 EFFECT OF INTRODUCING SCREENING IN THE CONTEXT OF VERY HIGH RATES OF DOAC USE

Strategy	Cost (€)	Incremental Cost (€)	Effect (QALY)	Incremental Effect (QALY)	ICER*
No screening	4,091	-	7.81706	-	€21,795/QALY
Screening	4,234	143	7.82363	6.5661x10 ⁻³	

* Due to rounding error the ICER value calculated using the incremental cost and incremental effect values reported in this table may differ from the ICER value reported in the table. Where any such differences do occur please note that the ICER value reported in the table provides the most accurate estimate.

Screening sensitivity and the effectiveness of routine practice

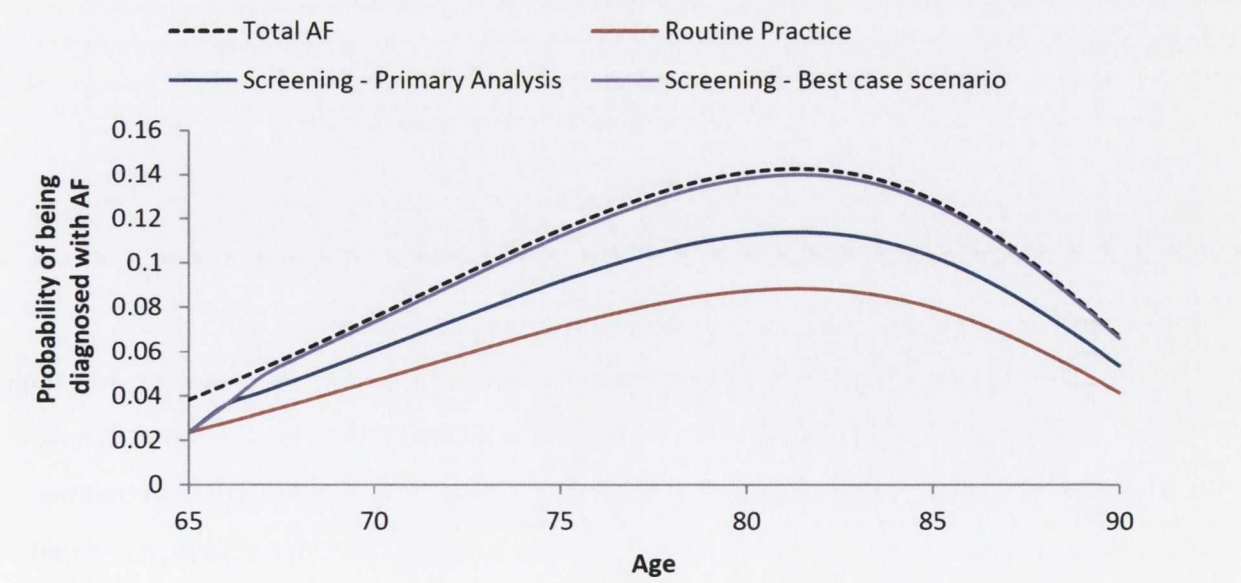
In the primary analysis it was conservatively assumed that incident cases that are not detected the first time the person with AF is screened will remain undetected in subsequent years. Results of a sensitivity analysis of the effect of a screening programme where latent cases have the same probability of being detected each year are shown in Table 3.30. Figure 3.43 shows the difference in the proportion of AF cases diagnosed over time in this scenario compared with the primary analysis. As anticipated it results in a higher rate of case-detection and an increase in the cost-effectiveness of screening (lower ICER).

TABLE 3.30 ICER CALCULATION FOR BEST CASE SCENARIO FOR EFFECTIVENESS OF OPPORTUNISTIC SCREENING

Strategy	Cost (€)	Incremental Cost (€)	Effect (QALY)	Incremental Effect (QALY)	ICER*
No screening	3,846	-	7.80987	-	€12,809/QALY
Screening	3,940	94	7.81718	7.3146×10^{-3}	

* Due to rounding error the ICER value calculated using the incremental cost and incremental effect values reported in this table may differ from the ICER value reported in the table. Where any such differences do occur please note that the ICER value reported in the table provides the most accurate estimate.

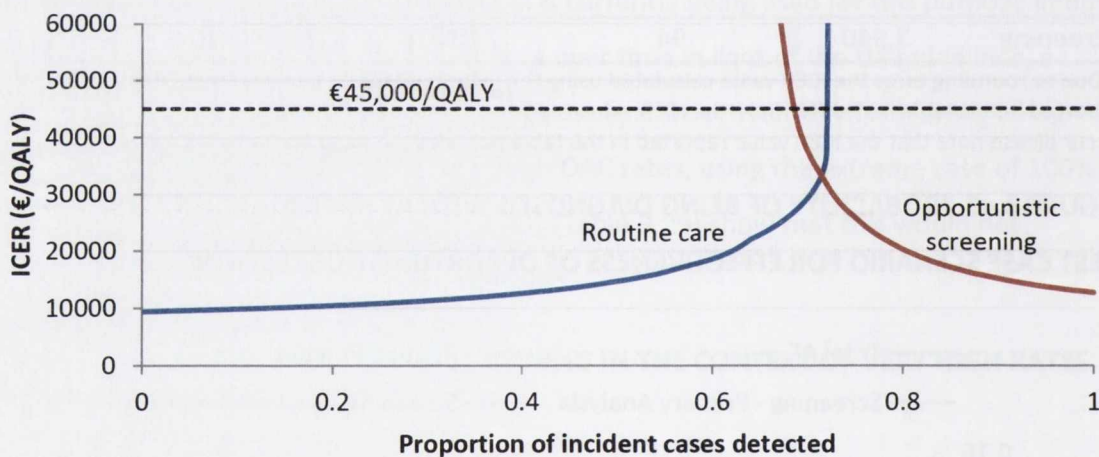
FIGURE 3.43 PROBABILITY OF BEING DIAGNOSED WITH AF IN PRIMARY ANALYSIS AND BEST CASE SCENARIO FOR EFFECTIVENESS OF OPPORTUNISTIC SCREENING



In the absence of data on the effect of disease progression on detection rates of latent AF this was not modelled separately. Rather, it was assumed that disease progression is similar across comparators and does not contribute to significant differences between groups.

Figure 3.44 shows the impact of varying the effectiveness of routine care and opportunistic screening on the overall cost-effectiveness estimate. This shows that given current estimates of the proportion of cases identified by routine care (62%), opportunistic screening would be cost-effective at a willingness-to-pay of €45,000/QALY as long as it increased the rate of AF detection to at least 70%. Conversely, if the sensitivity of pulse palpation and ECG at detecting incident cases is 80%, then screening would be cost-effective as long as the rate of AF detection in routine practice was less than 72%.

FIGURE 3.44 UNIVARIATE SENSITIVITY ANALYSIS OF THE IMPACT OF THE EFFECTIVENESS OF ROUTINE PRACTICE AND OPPORTUNISTIC SCREENING ON COST-EFFECTIVENESS



Uptake of screening and the cost of pulse palpation

Uncertainty relating to the uptake of screening has implications for both the clinical effectiveness and costs associated with screening. In the SAFE trial 69% of patients had their pulse taken, and 81% of those without a previous diagnosis of AF who were found to have an irregular pulse consented to having an ECG.⁽¹⁵¹⁾ In this analysis it was assumed that the overall uptake of opportunistic screening is likely to be higher than that observed in a trial setting due to the absence of the requirement for formal consent and the fact that pulse

palpation is a well known and accepted part of routine GP care. However, a worst case scenario could see significantly decreased AF detection in opportunistic screening due to a low acceptance rate of screening among patients. Costs of pulse palpation may also be higher than that included in the primary analysis, due to a higher proportion of tests being carried out by GPs rather than practice nurses, or due to underestimation of practice nurse costs from failing to include GP contributions to nurse salaries in the calculation of the cost of staff time. An Irish study of GP attendance rates reported that estimates derived from practice data are likely to be higher than self reported estimates, the kind collected by TILDA.^(222;283) If the TILDA data is an underestimate then as well as lending further support to the assumption that all those in the screening cohort attend a GP consultation at least once a year, it may reduce the estimated opportunity cost of pulse palpation, which is based on the GMS capitation fee.

To examine the impact of this uncertainty, a sensitivity analysis was conducted that varied uptake between 50% and 100%, and varied the cost of pulse palpation between €2.88 and €14.40 (Figures 3.45 and 3.46).

FIGURE 3.45 IMPACT OF DECREASING UPTAKE OF SCREENING ON COST-EFFECTIVENESS

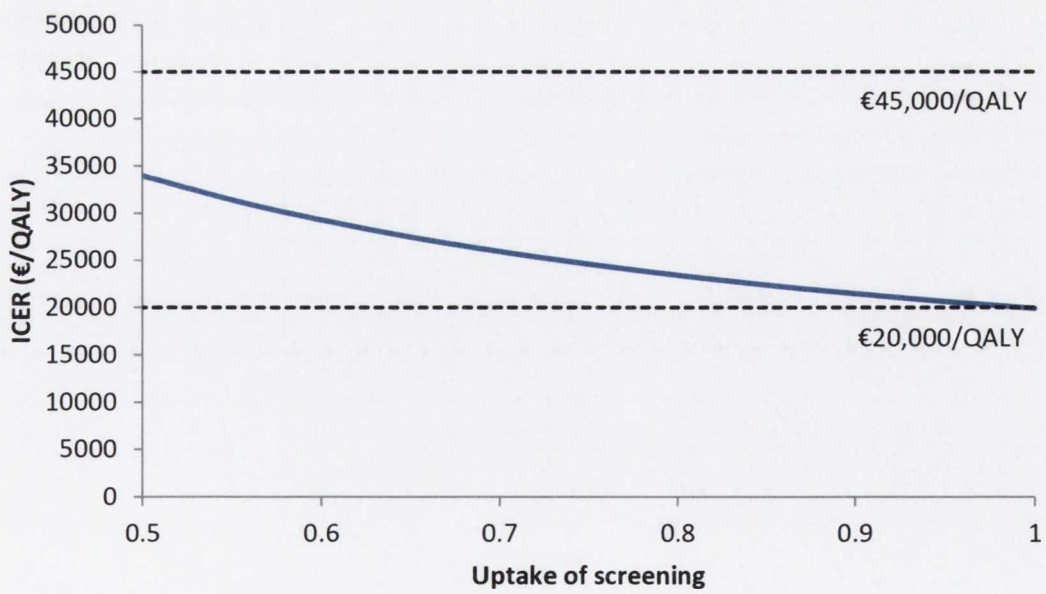
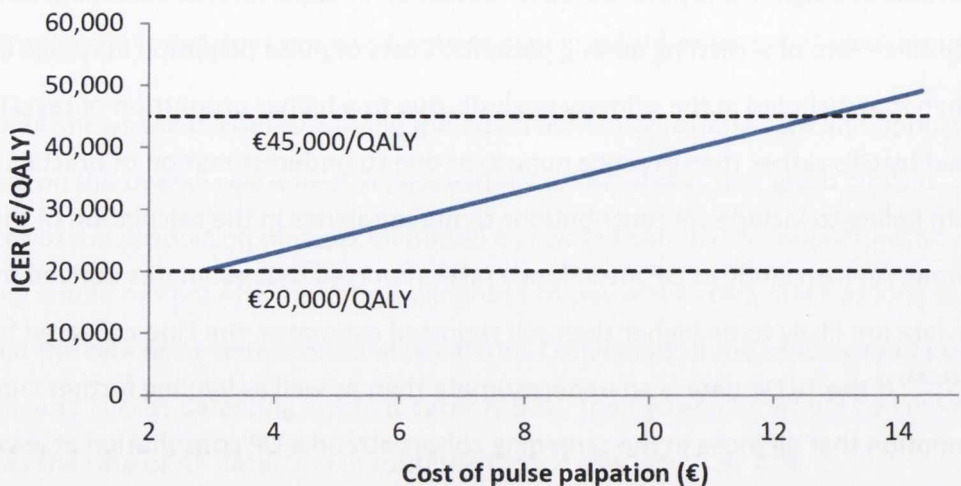
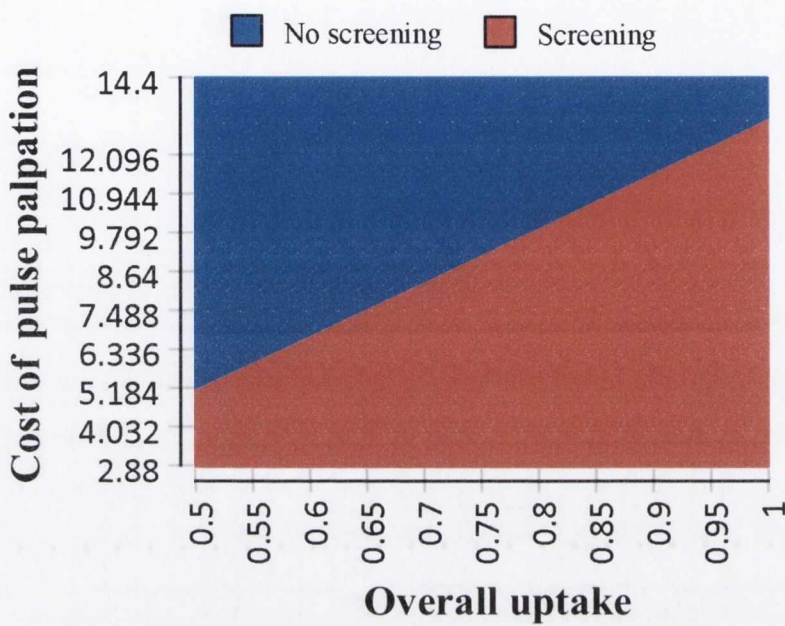


FIGURE 3.46 IMPACT OF INCREASING COST OF PULSE PALPATION ON COST-EFFECTIVENESS



Results of univariate sensitivity analysis showed that the overall results were relatively insensitive to changes in the uptake of screening or the opportunity cost of pulse palpation, with the ICER for screening remaining cost-effective at a willingness-to-pay threshold of €45,000/QALY. A two-way sensitivity analysis examining the impact of simultaneous changes in both these parameters is shown in Figure 3.47. This shows that the intervention is likely to be cost-effective at a willingness-to-pay threshold of €45,000/QALY unless the opportunity cost of pulse palpation during a routine GP visit is greatly underestimated and uptake rates are significantly overestimated.

FIGURE 3.47 TWO-WAY SENSITIVITY ANALYSIS OF SCREENING UPTAKE AND COST OF PULSE PALPATION (WTP = €45,000/QALY)



Inclusion of costs of additional testing as part of an AF diagnosis

The draft AF care pathway developed by the HSE specifies that blood tests and an echocardiogram should be carried out in patients diagnosed with AF.⁽¹⁴⁰⁾ The costs of additional tests for structural heart disease were not included in the primary analysis because the benefits associated with diagnosing and treating these concomitant conditions were not included. Including the incremental costs, but not the incremental utility associated with these tests would bias the analysis in favour of routine care. However, the potential impact of these additional costs was examined in a sensitivity analysis. In the absence of HSE cost data for echocardiography and blood testing prices were obtained from private health clinics. Prices for echocardiography ranged from €81 to €250, and prices for blood testing ranged from €20 to €30.⁽²⁸⁴⁻²⁸⁶⁾ For the purposes of the sensitivity analysis a conservative (high) estimate of a combined cost of €250 for additional testing for each new diagnosis of AF was used. The results of the cost-effectiveness analysis that includes these costs are presented in Table 3.31, which show that their inclusion increases the ICER by approximately 16%.

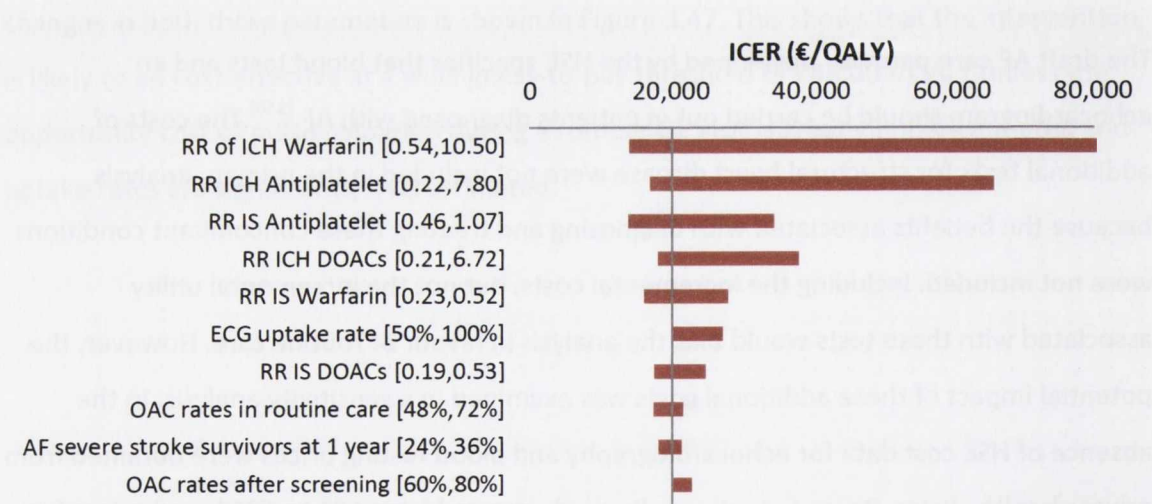
TABLE 3.31 INCLUSION OF COSTS OF BLOOD TESTING AND ECHOCARDIOGRAPHY FOR EACH DIAGNOSED AF CASE

Strategy	Cost (€)	Incremental Cost (€)	Effect (QALY)	Incremental Effect (QALY)	ICER
No screening	3,886	-	7.81185	-	€23,423/QALY
Screening	3,971	85	7.81548	3.6289×10^{-3}	

Deterministic sensitivity analysis

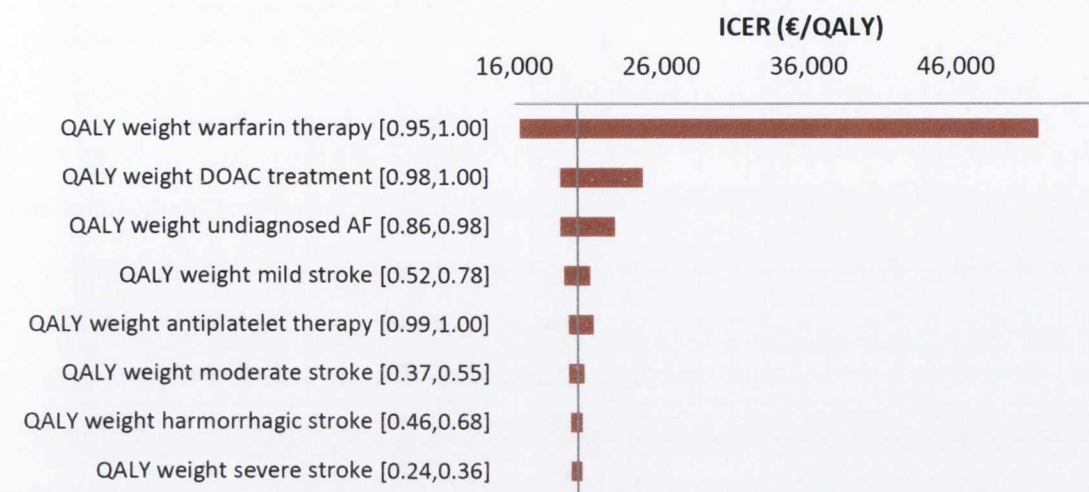
In addition to the scenarios examined in detail above, deterministic univariate sensitivity analysis was carried out for all the parameters in the model by varying them within their 95% confidence bounds or by $\pm 20\%$, to assess the sensitivity of the overall results to individual parameter uncertainty. Separate tornado plots showing the potential impact of uncertainty regarding transition probabilities, utilities and costs on the overall ICER for screening are shown in Figures 3.48, 3.49 and 3.50.

FIGURE 3.48 TORNADO PLOT FOR TRANSITION PROBABILITIES



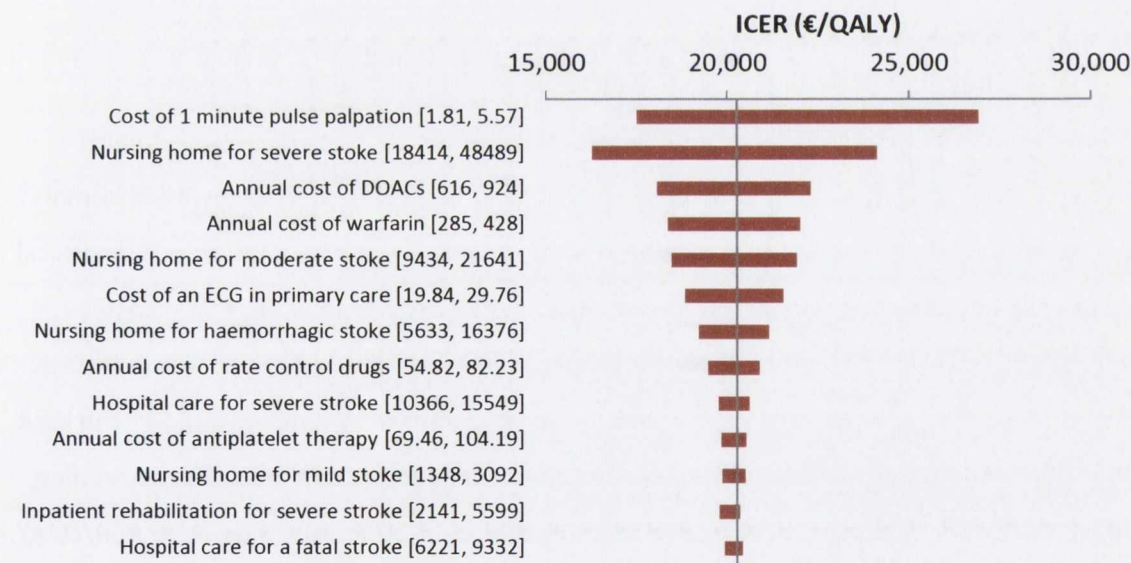
RR – Relative Risk; ICH – Intracranial Haemorrhage; IS – Ischaemic Stroke; DOAC – Direct Oral Anticoagulant; AF – Atrial Fibrillation; ECG – Electrocardiogram; OAC – Oral Anticoagulant

FIGURE 3.49 TORNADO PLOT FOR UTILITIES



QALY – Quality Adjusted Life Year; DOAC – Direct Oral Anticoagulant; AF – Atrial Fibrillation; ICH – Intracranial Haemorrhage; GI – Gastrointestinal

FIGURE 3.50 TORNADO PLOT FOR COSTS



DOAC – Direct Oral Anticoagulant; ECG – Electrocardiogram; ICH – Intracranial Haemorrhage;

The high degree of uncertainty regarding the impact of antithrombotic therapy on haemorrhagic stroke risk is evident from the tornado plots for transition probabilities. Due to the relative rarity of this outcome, the bounds around the pooled estimate in the Cochrane review of the effectiveness of warfarin and aspirin were extremely wide ([0.54 to

10.50] and [0.22, 7.80], respectively). Uncertainty in relation to the impact of being prescribed warfarin on quality of life also has the potential to significantly affect the overall ICER - the lower bound for warfarin anticoagulation was 0.953, which when combined with the high usage rates represents a potentially significant utility loss. The results also show that any potential reversal of reductions in the GMS fee for ECGs that were introduced in the last number of years due to the economic recession are unlikely to significantly alter the results of the analysis. Sensitivity analysis of the impact of increasing the cost of rhythm control treatment to take into account the cost of blood and ECG testing every three months, and increasing the cost of DOACs by adding the cost of renal function tests every three months does not significantly impact the overall cost-effectiveness results for the comparison of AF screening to routine practice. Similarly, any decreases in the annual cost of warfarin through the use of near patient testing in primary care, or increases in warfarin effectiveness by achieving higher TTR rates is unlikely to significantly affect the overall results.

3.3.7.3 SOCIETAL PERSPECTIVE RESULTS

The analysis from the societal perspective includes the same benefits as the payer perspective along with the total cost of treatment whether it falls on the public health service, patients or private health insurers. It also includes costs associated with informal care and lost productivity due to stroke morbidity and mortality. The ICER from the societal perspective for screening versus routine care is €23,004/QALY (Table 3.32). The cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC) are shown in Figures 3.51 and 3.52. The average cost per patient for both comparators is increased, but the ICER is comparable to that of the payer perspective. From the perspective of society, screening has a 79% chance of being cost-effective at a willingness-to-pay threshold of €45,000/QALY.

TABLE 3.32 ICER CALCULATION (SOCIETAL PERSPECTIVE)

Strategy	Cost (€)	Incremental Cost (€)	Effect (QALY)	Incremental Effect (QALY)	ICER*
No screening	14,529	-	7.81643	-	€23,004/QALY
Screening	14,613	84	7.82007	3.6441x10 ⁻³	

* Due to rounding error the ICER value calculated using the incremental cost and incremental effect values reported in this table may differ from the ICER value reported in the table. Where any such differences do occur please note that the ICER value reported in the table provides the most accurate estimate.

FIGURE 3.51 COST-EFFECTIVENESS PLANE (SOCIETAL PERSPECTIVE)

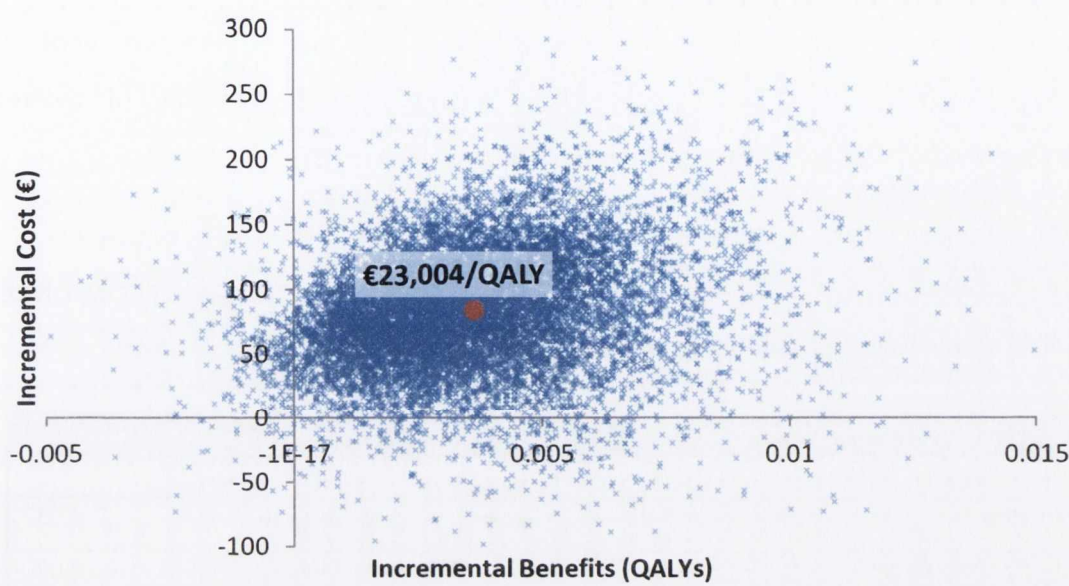
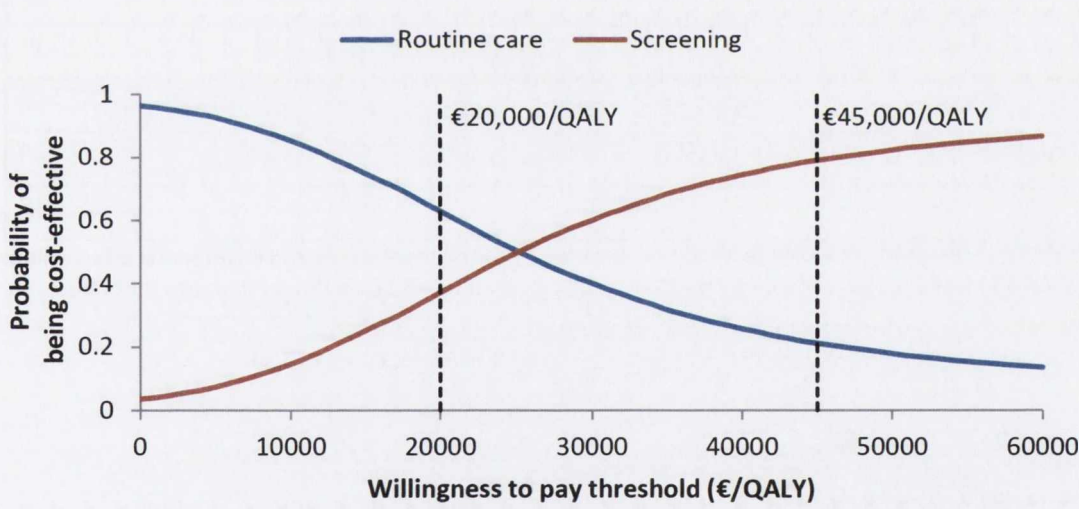


FIGURE 3.52 COST EFFECTIVENESS ACCEPTABILITY CURVE (CEAC, SOCIETAL PERSPECTIVE)



Comparing all combinations of start age between 55 and 75 and frequencies from once off screening to screening every one to five years yields similar results to those obtained using a health service perspective (see Figure 3.53 and Table 3.33). The most cost effective strategy is once off screening at 75, which has an ICER of approximately €8,000, and the incremental cost of the primary comparator of annual screening from age 65 compared with the next best option (screening every two years from 65) is approximately €180,000/QALY. The ICER

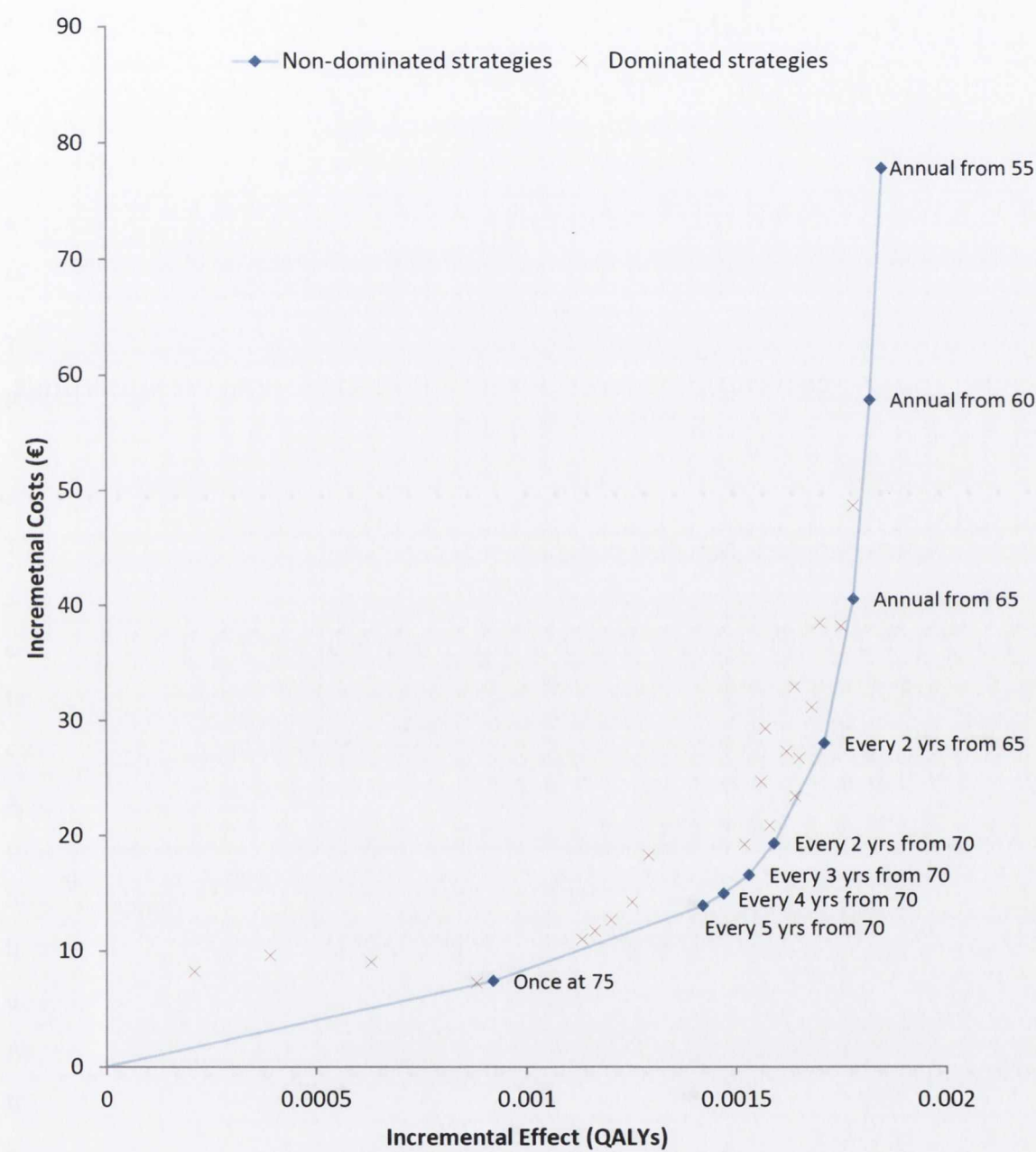
for screening every two years from 70 slightly exceeds the conventional willingness to pay threshold used of €45,000 for publicly funded health interventions. Once again it is important to note that the validity of these comparisons is dependent on a number of untested assumptions being met, most notably the assumption that the effect of screening is the same across all age groups and screening intervals.

TABLE 3.33 INCREMENTAL COST EFFECTIVENESS RATIOS FOR ALL NON-DOMINATED STRATEGIES FOR START AGES FROM 55 TO 75 AND SCREENING INTERVALS FROM ONCE-OFF TO EVERY 1 TO 5 YEARS (SOCIETAL PERSPECTIVE)

Strategy	Incremental Cost (€)	Incremental Effect (QALYs)	ICER *(€/QALY)
No screening	0	0	-
Once at 75	7.3706	9.1708x10 ⁻⁴	8,037
Every 5 yrs from 70	6.5057	4.9967x10 ⁻⁴	13,020
Every 4 yrs from 70	1.0391	5.2520x10 ⁻⁵	19,785
Every 3 yrs from 70	1.6018	5.5641x10 ⁻⁵	28,788
Every 2 yrs from 70	2.7402	5.9020x10 ⁻⁵	46,428
Every 2 yrs from 65	8.7083	1.2415x10 ⁻⁴	70,144
Annual from 65	12.5673	6.8477x10 ⁻⁵	183,525
Annual from 60	17.2893	4.6411x10 ⁻⁵	372,524
Annual from 55	19.9522	2.5172x10 ⁻⁵	792,619

* Due to rounding error the ICER value calculated using the incremental cost and incremental effect values reported in this table may differ from the ICER value reported in the table. Where any such differences do occur please note that the ICER value reported in the table provides the most accurate estimate.

FIGURE 3.53 COMPARISONS OF START AGES FROM 55 TO 75 AND SCREENING INTERVALS FROM ONCE-OFF TO EVERY 1 TO 5 YEARS (SOCIETAL PERSPECTIVE)



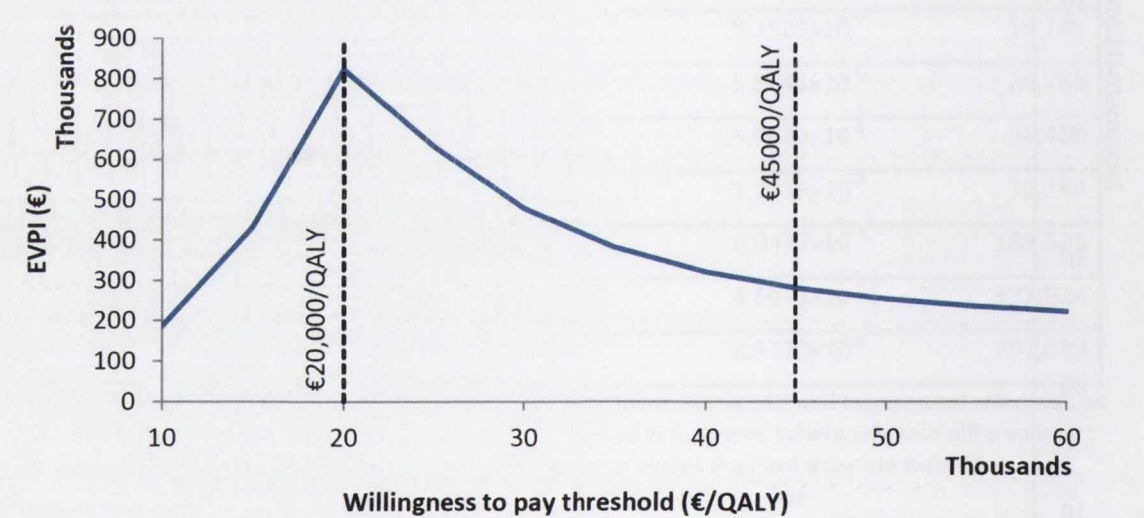
3.3.7.4 VALUE OF INFORMATION ANALYSIS

Expected value of perfect information (EVPI) analysis provides a way to investigate the value of acquiring more evidence before deciding whether or not to introduce opportunistic

screening for AF. It examines both the probability that a decision based on existing evidence will be wrong and the consequences of a wrong decision, and uses this to calculate the monetary value of acquiring perfect information, thus eliminating the possibility of taking the wrong option.

The EVPI calculation for opportunistic AF screening versus routine practice is shown in Figure 3.54. This shows that the value of perfect information to inform decision making at a WTP threshold of €45,000/QALY is approximately €280,000. This relatively low EVPI estimate reflects the low level of uncertainty about the cost-effectiveness of screening, which has an 83% chance of being cost-effective at this WTP threshold.

FIGURE 3.54 EXPECTED VALUE OF PERFECT INFORMATION (EVPI) FROM THE PERSPECTIVE OF THE HSE



3.4 DISCUSSION

This analysis combined the best available data on the effect of antithrombotic treatment on stroke outcomes with a conservative estimate of the increase in AF detection associated with repeated annual pulse palpation, which assumed that incident cases that are not detected by screening remain undetected in subsequent screening rounds. The results indicate that opportunistic screening for AF in over 65s in primary care is likely to be cost-effective using conventional willingness-to-pay thresholds in Ireland, with an incremental cost-effectiveness ratio (ICER) of approximately €20,271/QALY compared with routine care.

The results of the economic analysis are sensitive to potential changes in a number of parameters used in the analysis. Among the most important of these is the risk profile of screen-detected patients. The undiagnosed cohort includes those that are completely asymptomatic as well as those in whom AF symptoms are unexplained or misattributed. This analysis found that if the relative risk of ischaemic stroke and systemic embolism in screen-detected patients is more than 14% lower than that of cases detected in routine care, then screening would not be considered cost-effective using conventional willingness-to-pay thresholds. No differentiation is made between these groups for the purposes of calculating AF stroke risk per the CHA₂DS₂-VASc score, but there are some studies in asymptomatic device-detected AF that have suggested that the risk of ischaemic stroke could be up to 50% lower in asymptomatic AF.⁽¹⁹³⁾ However, recent analysis of data from nine European countries in the EORP-AF Pilot General Registry found that asymptomatic AF had a higher one-year mortality than symptomatic AF.⁽²²⁵⁾ Two studies are currently underway to examine the balance of benefits and harms of OAC treatment in asymptomatic AF.⁽²⁸⁷⁾ The STROKESTOP study, which has already posted interim results for AF detection in the screened group (see section 3.2), will follow screen-detected AF patients in whom OAC was used, to measure the impact of treatment on stroke rates.⁽¹⁶⁰⁾ The study is expected to be completed in 2019. The ARTESiA trial is examining the benefits of DOAC treatment for people with implantable device detected atrial high rate episodes (AHREs).⁽²⁸⁸⁾ The primary outcomes are stroke and major bleeding events and results are also expected to be available in 2019. Of these two studies the STROKESTOP trial is more suited to answering the question of interest in this analysis, as it includes those who may have been

experiencing mild, unrecognised symptoms, rather than being limited to those who have completely asymptomatic AF.

Decreasing the age at which screening starts reduces the cost-effectiveness of any prospective programme. Starting annual screening at age 50 is unlikely to be cost-effective at a willingness to pay threshold of €45,000/QALY, and ICERs for start ages between 55 to 70 years range from €38,000/QALY to €15,000/QALY compared to no screening. Comparing different start ages for annual screening to each other, it was found that the marginal cost of every additional QALY generated by lowering the screening start age from 70 to 65 is over €100,000. The length of the screening interval also has a significant impact on cost-effectiveness. In a scenario analysis that varied the frequency of opportunistic pulse palpation between once every year to once every five years for all over 65s, the ICER for screening once every three years compared to once every four years was over €35,000/QALY, with ICERs for shorter intervals exceeding a €45,000/QALY threshold. Given the fact that AF prevalence increases with age it is unsurprising that later start ages are more cost-effective. What the results also show is that as the start age increases the optimal screening interval decreases. Given a willingness to pay of €45,000/QALY, the optimal screening intervals for start ages of 55, 60, 65 and 70 years are 5, 4, 3, and 2 years, respectively. When all start ages are combined with all screening intervals the most cost-effective strategy from the perspective of a health service with a willingness to pay threshold of €45,000/QALY is biennial screening from age 70. However, these results need to be interpreted with caution, as all the available evidence on the effectiveness of screening comes from studies carried out in people aged 65 years and over, and no studies have as yet compared the results of using different screening intervals. Another feature of this analysis is that it only examines screening strategies in a previously unscreened population. While it may be the case that a three year interval is the most cost effective for a start age of 65 and a two year interval is the most cost effective for a start age of 75, this does not imply that a two year interval for 70 year olds who have been screened every three years since 65 is the optimal strategy. By modelling the impact of different screening intervals at particular ages for a cohort that that is already being screened, it may be possible to identify an adaptive screening algorithm that varies the screening interval

depending on age and screening history that could improve the cost effectiveness of a prospective programme further, allowing it to be provided to a broader target population. For instance it may be possible to extend the age range of screening if the initial screening interval is long, and decreases as AF incidence increases as the screened population ages, therefore differing depending on the person's screening history. Further research is required to examine the feasibility of such an adaptive screening algorithm and the potential increases in cost effectiveness achievable.

Other influential parameters include the rate of AF detection in routine care and the sensitivity of the two stage screening test. The analysis found that screening is likely to be cost-effective if it increases the rate of AF detection by at least 8%. The cost-effectiveness estimates were not greatly altered by plausible changes in the baseline incidence of AF or changes to the proportion of people who are prescribed DOACs, warfarin or antiplatelet therapy. The results were also relatively insensitive to changes in the opportunity cost of pulse palpation and the intervention remained cost-effective when uptake rates were lowered to represent a worst case scenario for opportunistic screening.

Among the limitations of this analysis is that while both Irish and UK data sources indicate that the proportion of AF cases detected by routine care is approximately 60%, there is a lack of data on the effect of age on AF detection. In this analysis it was assumed that the rate of undiagnosed AF was consistent across all ages. If it were the case that incident AF had a higher probability of remaining undiagnosed in younger or older age groups this may have implications for the optimal start age of screening. Another limitation is the lack of studies involving multiple AF screening rounds over a period of years, as all studies to date have evaluated once off screening in a particular age group. A conservative approach was adopted in the primary analysis, by assuming that prevalent cases that are undetected in the initial screening round remain undetected in subsequent screening rounds. This is likely to underestimate the clinical effectiveness of multiple rounds of screening. The opposite approach of assuming that undiagnosed AF has an equal chance of being detected in each round risks overestimating the impact of screening, since it is likely that factors such as whether asymptomatic AF is paroxysmal or persistent, or has atypical electrocardiographic presentation, make undetected cases more likely to remain undetected. However as the

results show, AF screening is likely to be cost effective even using a conservative approach to estimating the impact of multiple screening rounds.

While the analysis reported here shows the value of the intervention in terms of cost per QALY gained, it does not show how much should be budgeted in the short term for the introduction of the programme. This information is of relevance to policymakers seeking to estimate the affordability of the intervention in terms of the direct costs of screening and treatment that will be incurred from the start of the programme, as well as any potential cost savings associated with any reduction in stroke incidence or severity that can be expected in the future. Major direct costs to the health service provider (Health Service Executive [HSE]) include the cost of screening ECGs for those found to have an irregular pulse, as well as the cost of rhythm and rate control treatment for the management of AF and antithrombotic therapy for stroke prophylaxis. Of particular importance would be the costs associated with increased use of direct oral anticoagulants, which are more expensive than warfarin, and could put significant strain on existing budgets. The increase in expenditure on direct oral anticoagulants is likely to be especially pronounced in the first year of the programme, due to the increased detection of AF in the prevalent screen (first screening round) compared with subsequent screening rounds. In this analysis pulse palpation was not associated with a set fee, since it was considered part of routine care, but the opportunity cost of the time needed to perform the procedure was included in the cost effectiveness analysis. If a decision was made to pay GP's a fee for pulse taking in the context of an opportunistic screening programme then that would need to be included in the budget impact analysis also. Cost reductions that are anticipated to accrue once the impact of screening on stroke outcomes has had time to materialise include decreased costs associated with acute hospital treatment for stroke, post-stroke rehabilitation and nursing home care.

A review of previously published economic analyses identified two studies that examined the cost-effectiveness of AF screening using pulse palpation in primary care, both of which concluded that it was likely to be cost-effective compared with routine practice. However, no country was identified as having a national AF screening programme currently in place. In July 2014, the UK National Screening Committee recommended against offering screening

for all those aged 65 years and over, due to a lack of evidence demonstrating that those identified as at risk of stroke through screening would benefit from early diagnosis.⁽¹⁹³⁾ This decision is due to be reviewed in 2017. More recently, the Swedish Dental and Pharmaceutical Benefits Agency, whose remit is to determine which pharmaceutical and medical devices shall be subsidised by the state, has concluded that the benefits of primary preventive screening with thumb ECG (per the STROKESTOP trial) justifies the costs of screening. The cost effectiveness study based on STROKESTOP, which involved intermittent ECG recording over two weeks rather than opportunistic pulse palpation with ECG confirmation, reported an ICER of €4,313/QALY, which is slightly lower than the ICER for once-off screening at 75 using pulse palpation with ECG confirmation reported in this study (€5,410/QALY).⁽¹⁸⁴⁾

3.5 CONCLUSION

An economic analysis comparing the costs and benefits of annual opportunistic screening of men and women aged 65 years and older in primary care in Ireland found that the intervention is likely to be cost-effective using conventional willingness-to-pay thresholds, assuming that those detected through screening have a comparable stroke risk profile as those detected through routine practice. Increasing the start age of screening or the screening interval may improve the cost-effectiveness of a prospective screening programme.

4. BREAST CANCER SCREENING

4.1 BACKGROUND

Mammographic breast screening aims to reduce breast cancer mortality by detecting and treating cancers at an early stage before they present clinically, when treatment is more effective. The main risk associated with screening is overdiagnosis, which is the detection and treatment of cancers that would never otherwise have become clinically significant if they had not been detected by screening. In the absence of a way to reliably identify which true-positive screening test results will result in illness or death, all detected cancers are treated. For overdiagnosed women, the significant, life-long psychological and physical consequences of breast cancer diagnosis and treatment are incurred unnecessarily.⁽²⁸⁹⁾

Although national screening programmes are in place throughout the developed world, there is continued debate about whether or not the anticipated breast cancer mortality reductions are being realised and also about the degree of overdiagnosis that is occurring.⁽²⁹⁰⁻²⁹²⁾ In response to this controversy the UK Department of Health established an independent review panel to assess the benefits and harms of screening. Their report concluded that invitation to breast cancer screening delivers approximately a 20% reduction in breast cancer mortality.⁽²⁹³⁾ This estimate is based on pooled RCT evidence from studies conducted 20 to 50 years ago, which have been questioned due to concerns about the risk of bias in some of the original trials and the fact that they predate important advances in treatment.⁽²⁹⁴⁾ In the absence of new RCTs, the best evidence comes from contemporary screening programmes in real life settings that were introduced in such a way as to produce comparable screened and unscreened groups for long enough for an effect of screening to be observable. Previous studies of this type have generated diverse findings, with some showing no benefit and others finding disease-specific mortality reductions in excess of those reported in the original RCTs. This diversity in results is mirrored by considerable heterogeneity in methods. Studies have variously compared average mortality rates or mortality trends, using incidence-based or prevalence-based outcomes. Effect size has been measured as the difference between groups after the introduction of screening

(geographical comparison) or as the difference in the change in each group before and after screening (geographical-historical comparison).

There is also considerable diversity in estimates of overdiagnosis as a result of screening. Previous estimates from observational studies range from 5% to over 50%.⁽²⁹⁵⁻²⁹⁹⁾ Much of this heterogeneity is as a result of using different assumptions, screening populations and analytical methods.⁽²⁹⁶⁾ The UK independent review report describes a range of different methods that have been used to calculate overdiagnosis.⁽³⁰⁰⁾ Their preferred method for expressing the percentage overdiagnosis during the screening period (as opposed to over the lifetime of women invited to screening) is as the number of excess cancers as a proportion of cancers diagnosed during the screening period in women invited for screening. Using this approach they report an overdiagnosis rate of 19% based on pooled RCT data.

Ireland first introduced biennial mammographic screening of women aged 50 to 64 years in February 2000. The phased geographical implementation of the programme created a natural experiment, where screening was rolled out to approximately half the total screening population in Ireland eight years before screening was offered in other parts of the country. In 2015 the Irish government announced that it intends to extend the upper age limit of the national breast screening programme to 69 years.⁽¹³⁾ The aim of this study was to estimate the impact of the Irish breast screening programme on breast cancer mortality and overdiagnosis and to examine the cost effectiveness of the existing programme, as well as the extended programme which would see women screened for a further five years.

4.2 CLINICAL EFFECTIVENESS OF BREAST SCREENING

4.2.1 INTRODUCTION

The best evidence for the impact of service-level screening programmes comes from countries where screening was introduced in such a way as to produce comparable screened and unscreened groups for long enough for an effect of screening to be observable. So far this has occurred to varying degrees in six countries (Sweden, Norway, Denmark, Finland, the Netherlands and the United Kingdom).⁽³⁰¹⁾ Studies examining these programmes have reported disease specific mortality reductions ranging from 7% to 42%. However, none of these countries had such fortuitous circumstances for the evaluation of screening as pertained in Ireland, due to the availability of large, balanced groups comprising over 90% of the entire national population of women aged 50-64 all of whom had the same history and access to treatment, a single cut-off point separating screening and comparison groups (rather than gradual introduction requiring multiple group-year comparisons), and the availability of comprehensive, high-quality data on breast cancer incidence, with long-term patient level follow up.

The aim of this research was to estimate the impact of the Irish breast screening programme on breast cancer mortality and overdiagnosis, and compare the results of adopting different analytical approaches that have been used previously to estimate these outcomes in other countries. This includes comparing the results of:

- Using prevalence-based and incidence-based mortality outcomes
- Estimating overdiagnosis using stage at diagnosis and mode of presentation
- Using a controlled before and after design compared with a controlled interrupted time series analysis to estimate the impact of screening on breast cancer mortality

4.2.2 METHODS

THE SCREENING PROGRAMME

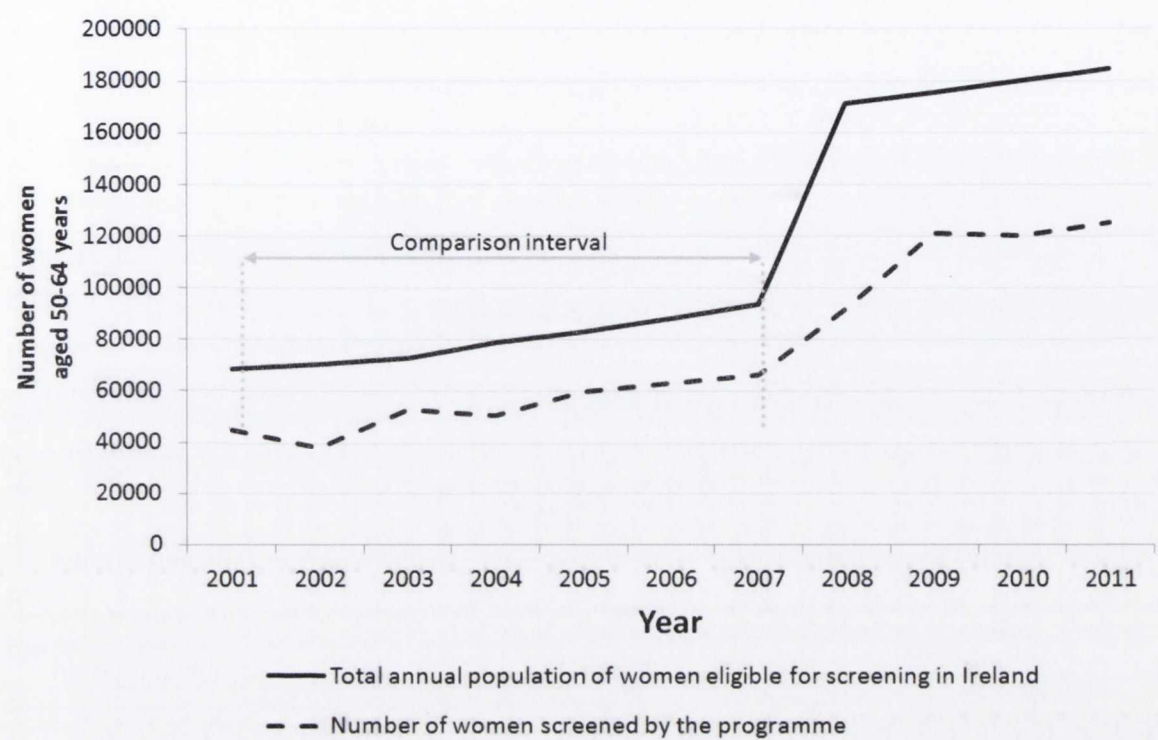
The Irish breast screening programme invites all women between 50 and 64 years for two-view mammography (cranio-caudal and mediolateral oblique) every two years. Invitation

letters with a prearranged appointment are sent to all women in the target population, giving at least seven days notice. If an appointment is missed a reminder invitation is sent before the end of the screening round. The average uptake of screening is 73.9% (range 71.6% to 76.3%).

Ireland has a population of approximately 4.5 million people and is divided into 26 counties. Screening began in 11 counties in the eastern part of the country in February 2000 (screening group). The programme was gradually extended to four other counties between 2001 and 2006, before being introduced in the remaining 11 counties in the south and west of the country in December 2007 (comparison group). The average annual population of the screening group was 150,000, compared to 132,000 in the comparison group.

The incidence of asymptotically detected cancers is the outcome that is most sensitive to the introduction of screening. As Figure 4.3 shows (see results Section 4.2.3), asymptomatic incidence rates started to rise sharply in 2000, coinciding with the introduction of the programme, but it was not until 2001 that incidence rates reached the levels that they would eventually be maintained at following the initial prevalence screen. This is consistent with reports from the screening programme indicating that the first screening round was completed by year two of the programme.⁽³⁰²⁾ Thus in this analysis 2000 is considered the 'wash-in' period for the intervention, with the post-screening period starting in 2001. Figure 4.1 shows the annual number of screening mammograms carried out by the screening programme over the study period, compared with the total annual target population for screening, confirming that the screening programme maintained good coverage within the target population over the study period.

**FIGURE 4.1 ELIGIBLE SCREENING POPULATION AND TOTAL NUMBER OF WOMEN
SCREENED BY THE PROGRAMME BY YEAR, FROM 2001 TO 2011**



CLINICAL OUTCOMES

Breast cancer mortality

The impact of screening on breast cancer mortality is estimated using both prevalence-based and incidence-based outcome measures. Prevalence-based, or death certificate mortality, is the more commonly used outcome generally, but it is complicated by the need to distinguish between deaths that occurred in the study period from cancers diagnosed before screening was in place from deaths from cancers diagnosed after screening was available. Since the majority of breast cancer deaths in the screening cohort in the years immediately after the introduction of the programme will be from cancers diagnosed before it was introduced, a lead time adjustment is required to try to isolate the effect of screening. In contrast, incidence-based mortality separates those who were diagnosed before and after screening started, and compares the death rates in screened and unscreened areas by the end of the follow up period.⁽³⁰³⁾ Therefore incidence-based outcomes provide a more reliable estimate of effect since they avoid the need to incorporate an uncertain lead time

adjustment to minimise contamination from deaths that occurred in the screening population in the screening era from cancers diagnosed before screening started.

Any changes in incidence-based outcomes should be observable in the screening group (50-64 year olds) in the interval immediately after the introduction of screening to the end of the follow up period. In this analysis, breast cancer deaths in both groups were partitioned into those that were first diagnosed before screening was in place from 1994 to 1999, and those that were diagnosed after screening was in place in the treatment group in 2001 and before screening was started in the control group in 2008.

Prevalence-based mortality outcomes are also estimated for the purposes of comparison. Reports from trials with long follow-up suggest that it takes five years for the benefit of screening on breast cancer mortality to be observable.⁽³⁰⁰⁾ Therefore the impact of screening those aged 50 to 64 years on prevalence-based breast cancer mortality should begin to become apparent in the 55 to 69 year old group five years after the start of screening. However, even after five years there will still be a good deal of contamination present, which will gradually decline over time.

Overdiagnosis by stage at diagnosis

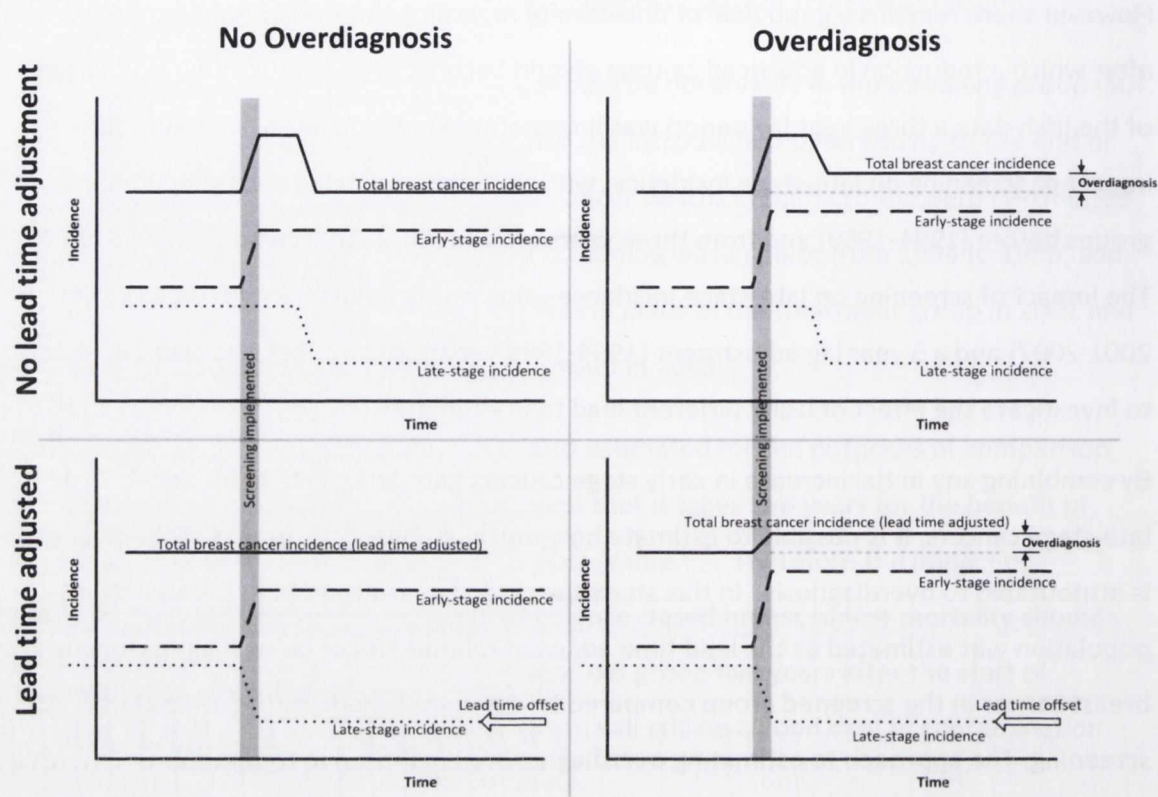
Since the aim of screening is to move forward the time of diagnosis, screening is expected to be associated with an initial increase in early stage cancers, followed by a subsequent decrease in late stage cancers. Early stage cancers were defined as those diagnosed at TNM stage 0, I and II, and late-stage cancers as those first diagnosed at TNM stage III and IV. For early-stage cancers the pre-screening and post-screening comparison intervals for both groups were 1994-1999 (when there was no screening in either group) and 2001-2007 (when screening was in place in the treatment group but not in the control group).

The full impact of screening on late-stage incidence is not anticipated to become apparent until such time as the excess incidence of early stage cancers associated with screening would have presented at a later stage if they had not been detected through screening. Previous analyses of public screening programmes have reported a reduction in the incidence of advanced cancers after three years of screening, which is in agreement with RCT data indicating that the lead time associated with screening (that is how long it would

have taken a screen detected cancer to present clinically) is 40 months on average.^(304;305) However there remains a good deal of uncertainty regarding the appropriate lag period after which a reduction in advanced cancers should become apparent.^(306;307) In the analysis of the Irish data a three year lag period was incorporated in the primary analysis of the impact of screening on late-stage incidence, with this outcome being compared in both groups before (1994-1999) and from three years after (2004-2010) screening was in place. The impact of screening on late-stage incidence using no lag adjustment (1994-1999 versus 2001-2007) and a 5 year lag adjustment (1994-1999 versus 2006-2011) was also calculated, to investigate the effect of using different lead time estimates.

By combining any initial increase in early stage cancers with any subsequent decrease in late-stage cancers, it is possible to estimate how much, if any, of the excess cancer incidence is attributable to overdiagnosis. In this study the rate of overdiagnosis in the target population was estimated as the lead time adjusted relative risk of being diagnosed with breast cancer in the screened group compared to the unscreened group during active screening. The approach to estimating overdiagnosis is illustrated in Figure 4.2.

FIGURE 4.2 APPROACH USED TO ESTIMATE OVERDIAGNOSIS AS A RESULT OF SCREENING



Overdiagnosis by type of presentation

As well as the early-stage/late-stage dichotomy, the impact of screening on breast cancer incidence and overdiagnosis can also be examined by separating cancers into those that are screen-detected and those that are detected clinically (through symptoms or incidentally). Screening should be associated with an immediate increase in asymptotically detected cancers, followed by a subsequent decrease in cancers that are detected clinically, since in an ideal screening programme every asymptotically detected cancer is one less that will present clinically later on. As with the early-stage/late-stage analysis, there is no definitive estimate of the amount of time it takes for increased asymptomatic detection to fully translate into decreased clinical detection. However since screening is based on an assumption that symptomatic detection is associated with later stage at diagnosis, any reduction in clinical presentation rates should at least be apparent by the time any reduction in late-stage incidence has occurred, and probably sooner since in the absence of screening 80% of clinically detected cancers are diagnosed symptomatically at an early stage

(TNM 0,I,II) in Ireland. Therefore a three year lag period should be sufficient to examine the impact of screening on clinical presentation rates. A secondary analysis using no lag adjustment was also carried out.

As with the analysis by stage at diagnosis, combining any initial increase in asymptotically detected cancers with any subsequent decrease in clinically detected cancers provides an estimate of how much, if any, of the initial rise in cancer incidence is attributable to overdiagnosis. Using data on the type of presentation (asymptomatic or clinical), the rate of overdiagnosis was estimated during active screening as the lead time adjusted relative risk of being diagnosed with breast cancer in the screened group compared to the unscreened group.

STUDY DESIGNS AND STATISTICAL METHODS

A controlled before and after (CBA) design was used to estimate the impact of screening on breast cancer mortality and overdiagnosis. The impact of screening on prevalence-based breast cancer mortality was also evaluated using a controlled interrupted time series (ITS) analysis which decomposed the overall average effect into the change in level and slope, providing an indication of the relative changes in prevalence-based breast cancer mortality between groups over time. Incidence-based mortality was not included in the ITS analysis, since this is a measure of the number of deaths by the end of the follow up period rather than multiple measurements at different time points.

The comparison method used in both designs tests the interaction of geographical and historical differences between the screening and comparison groups, which controls for a range of potential unmeasured confounders that may have arisen due to the lack of true randomisation, such as geographical differences in contraceptive use, or the prevalence of genetic risk factors.

Controlled before and after (CBA) analysis

In the CBA analysis the standardised rate ratio (SRR) between both groups after screening had been implemented (geographical comparison) was calculated, as well as the difference between the SRR within each group before and after screening (interaction of historical and geographical comparison). Table 4.1 shows the statistical methods used in the CBA in detail.

TABLE 4.1 CONTROLLED BEFORE AND AFTER ANALYSIS METHODS

Standardised rate ratios (SRR) and 95% confidence intervals (CI) were calculated as follows,⁽³⁰⁸⁾

$$\text{Standardised rate ratio (SRR)} = \frac{ASR_1}{ASR_2}$$

$$95\%CI = \left(\frac{ASR_1}{ASR_2} \right)^{1 \pm (z/x)}$$

where

$$x = \frac{(ASR_1 - ASR_2)}{\sqrt{s.e(ASR_1)^2 + s.e(ASR_2)^2}}$$

$$z = 1.96 \text{ (at the 95\% level)}$$

The standard error of all age-adjusted mortality rates was calculated using the binomial approximation. P-values were calculated per Altman 2011.⁽³⁰⁹⁾

European age-standardised rates were calculated for the following groups;

	Before screening	After screening
Screening group	ASR _{scr-before}	ASR _{scr-after}
Comparison group	ASR _{comp-before}	ASR _{comp-after}

The SRR between groups in the geographical comparison (SRR_{geo}) was calculated as;

$$SRR_{geo} = \frac{ASR_{scr-after}}{ASR_{comp-after}}$$

The SRR within groups for the screening (SRR_{wg-scr}) and comparison (SRR_{wg-comp}) group was calculated as;

$$SRR_{wg-scr} = \frac{ASR_{scr-after}}{ASR_{scr-before}} \text{ and } SRR_{wg-comp} = \frac{ASR_{comp-after}}{ASR_{comp-before}}$$

The ratio of SRRs (based on the difference in the change in breast cancer mortality between the screening and comparison group) in the geographical- historical comparison (SRR_{geo-hist}) was calculated as:

$$SRR_{geo-hist} = e^d$$

Where

$$d = \ln(SRR_{wg-scr}) - \ln(SRR_{wg-comp})$$

Test of interaction (z) and 95% confidence intervals for SRR_{geo-hist} were calculated using the method described in Altman 2003.⁽³¹⁰⁾

Time series analysis

In the controlled ITS analysis, segmented regression was used to compare the annual percentage rate change (APC) in breast cancer mortality in both groups using a log-linear model, with the breakpoint set at the point at which the impact of screening is expected to become apparent (i.e. five years after screening first introduced). Table 4.2 describes the statistical methods used in the ITS analysis in detail.

TABLE 4.2 INTERRUPTED TIME SERIES ANALYSIS METHODS

The regression model used to compare annual percentage rate change (APC) in each group after screening was;^(311;312)

$$\ln(ASR) = \beta_0 + \beta_1 time + \beta_2 screening + \beta_3 timeAfterScreening + e_t$$

Where β_0 is the baseline level, β_1 is trend prior to screening, β_2 is change in level after screening, β_3 is change in trend after screening and e_t is the error term. *Time* is the time in years from the start of the study period, *screening* indicates before (0) or after (1) the start of screening and *timeAfterScreening* is the time since the start of screening.

The annual percent change in each of the groups after screening is given by;

$$Annual\ percent\ change\ (APC) = (e^{\beta_3} - 1) * 100$$

The model used to compare the difference between groups in change in trend before and after screening was;

$$\ln(ASR) = \beta_0 + \beta_1 time + \beta_2 screening + \beta_3 timeAfterScreening + \beta_4 group + \beta_5 group.time + \beta_6 group.screening + \beta_7 group.timeAfterScreening$$

Where β_4 is the difference between groups in baseline level, β_5 is the difference between groups in prior trend, β_6 is the difference between groups in change in level, β_7 is the difference between groups in change in trend. *Group* is the groups variable (1 for screening group, 0 for comparison group).

The difference between groups in annual percent change in trend after screening is given by;

$$Difference\ in\ annual\ percent\ change\ (APC_{diff}) = (e^{\beta_7} - 1) * 100$$

The regression model estimates the average age-standardised population-based mortality rate in each group over time. Fitted age-standardised mortality rates in each group by the end of the study period (2011) are used to calculate the standardised rate ratios for the between groups (geographical) comparison and for the comparison based on the difference in the change in breast cancer mortality between the screening and comparison group (historical-geographical comparison).

Absolute Effects

Relative reductions in breast cancer mortality associated with screening were expressed in absolute terms using data on average age-standardised mortality rates in the study period. The reciprocal of the absolute difference provides an estimate of the number of person-years of invitation to screening required to prevent one death from breast cancer;

$$\text{Number needed to invite (NNI)} = \frac{1}{|ASR_{WithScreening} - ASR_{WithoutScreening}|}$$

Similarly the relative risk of being diagnosed with breast cancer in the screened group compared with the comparison group during active screening was used to calculate the absolute effect of screening on overdiagnosis, based on incidence rates in the screened group over the course of the study period, using the following formula;

$$\text{Number needed to invite (NNI)} = \frac{1}{|BCI_{WithScreening} - BCI_{WithoutScreening}|}$$

Study data

All data on breast cancer incidence by stage at diagnosis (TNM 0, I, II, III, IV), type of presentation (screening, symptomatic, incidental), age at diagnosis, year of diagnosis, survival and cause of death for women in both groups was collected prospectively by the National Cancer Registry Ireland (NCRI) and the Central Statistics Office (CSO). As neither of these organisations play a role in the provision of screening, knowledge of exposure to the intervention did not affect data collection. All incidence rates were directly standardised using the European standard population. All statistical analysis was carried out in Stata 12 and all graphs were produced in Excel.^(107;313) For all outcomes the mean estimate of effect was reported, along with the corresponding 95% confidence intervals (CI).

4.2.3 RESULTS

Figure 4.3 shows breast cancer incidence rates for all outcomes over the course of the study period. The total number of cases, person-years and European age-standardised rates for all outcomes in both groups before and after screening are provided in Table 4.3.

FIGURE 4.3 BREAST CANCER INCIDENCE RATES FOR EARLY-STAGE, LATE-STAGE, ASYMPTOMATICALLY AND CLINICALLY DETECTED CANCERS

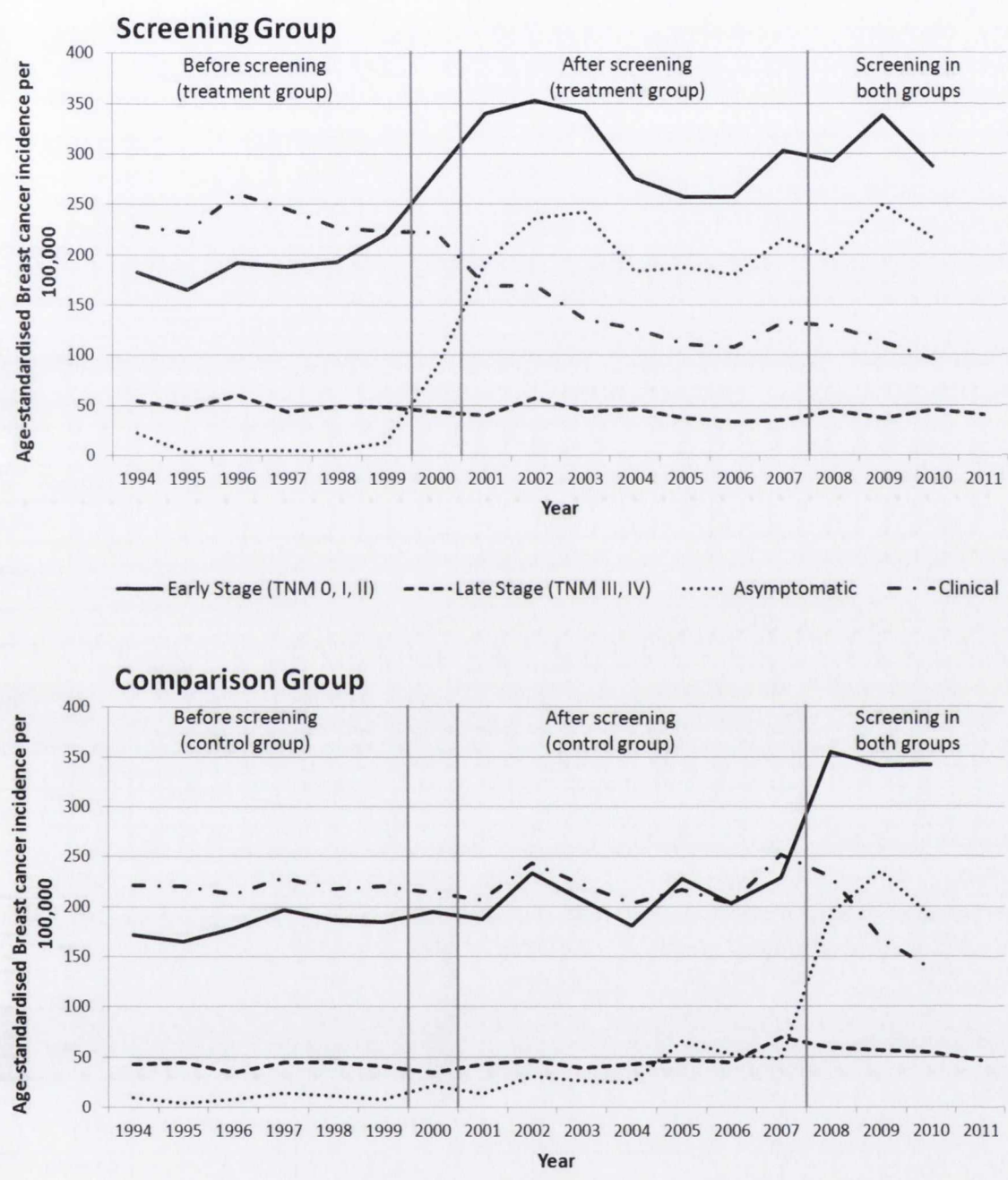


TABLE 4.3 CASES, PERSON-YEARS, EUROPEAN AGE-STANDARDISED RATES AND STANDARDISED RATE RATIOS FOR ALL OUTCOMES IN BOTH GROUPS BEFORE AND AFTER SCREENING

Incidence-based Breast cancer mortality	Screening Group		Comparison Group	
	Before	After	Before	After
Breast cancer deaths	651	464	535	471
Person years	725707	1048048	623441	927079
Age-standardised rate per 100,000 (ASR)	89.69	44.3	85.83	50.72
Standardised rate ratio (SRR)	0.49 (95%CI 0.44 to 0.56)		0.59 (95%CI 0.52 to 0.67)	
Ratio of relative risks (RRR)	0.84 (95%CI 0.70 to 1.00)			
p value	0.0495			
Prevalence-based Breast cancer mortality*	Screening Group		Comparison Group	
	Before	After	Before	After
Breast cancer deaths	1454	604	1267	598
Person years	1534123	856500	1368656	776389
Age-standardised rate per 100,000 (ASR)	94.38	70.50	91.46	76.77
Standardised rate ratio (SRR)	0.75 (95%CI 0.68 to 0.82)		0.84 (95%CI 0.76 to 0.92)	
Ratio of relative risks (RRR)	0.89 (95%CI 0.78 to 1.01)			
p value	0.08			
Overdiagnosis by stage at diagnosis**	Screening Group		Comparison Group	
	Before	After	Before	After
Breast cancers (TNM 0, I, II, III, IV)	1750	3615	1387	2491
Person years	725707	1048048	623441	927079
Age-standardised rate per 100,000 (ASR)	241.27	345.47	222.43	268.55
Standardised rate ratio (SRR)	1.43 (95%CI 1.36 to 1.51)		1.21 (95%CI 1.13 to 1.29)	
Ratio of relative risks (RRR)	1.19 (95%CI 1.09 to 1.29)			
p value	<0.0001			
Overdiagnosis by type of presentation**	Screening Group		Comparison Group	
	Before	After	Before	After
Breast cancers (Asymptomatic and clinical)	1765	3465	1428	2411
Person years	725707	1048048	623441	927079
Age-standardised rate per 100,000 (ASR)	243.27	331.24	229.04	259.94
Standardised rate ratio (SRR)	1.36 (95%CI 1.29 to 1.44)		1.13 (95%CI 1.06 to 1.21)	
Ratio of relative risks (RRR)	1.20 (95%CI 1.10 to 1.31)			
p value	<0.0001			

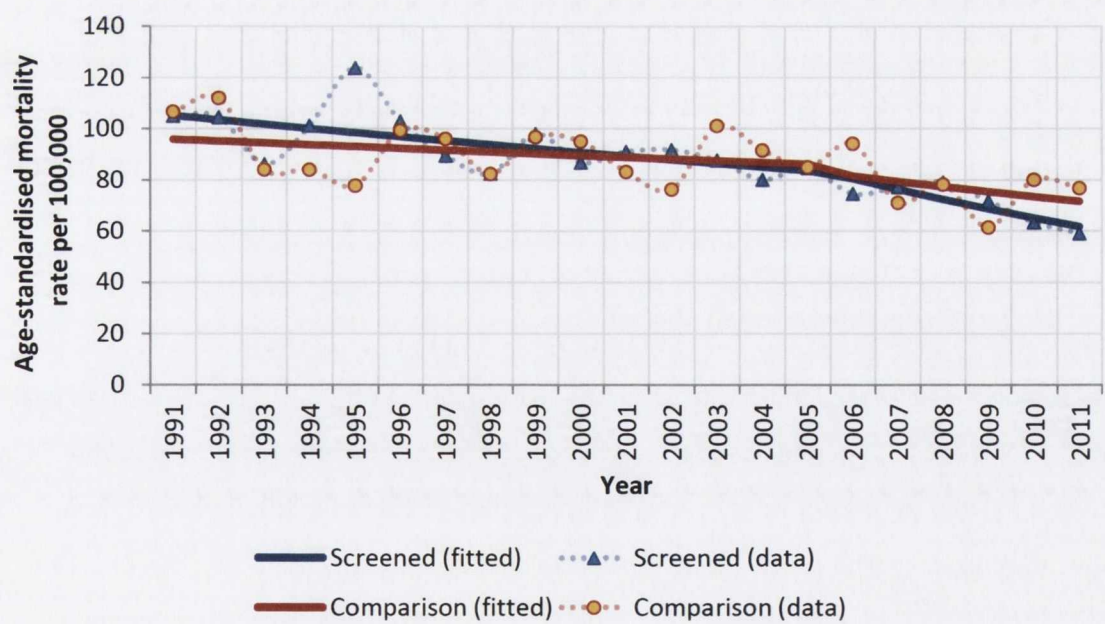
*With 5 year lead time adjustment; **With 3 year lead time adjustment

Breast cancer mortality

Controlled before and after analysis of incidence-based mortality found a 16% reduction in the relative risk of dying of breast cancer in the screened group compared with the unscreened group (RR 0.84, 95% CI 0.70 to 1.00, $p=0.0495$). This is equivalent to an average of one breast cancer death avoided for every 741 women invited to screening in Ireland over the study period.

CBA analysis of prevalence-based mortality found a lower mean reduction of 11% in breast cancer mortality in the screened group (RR 0.89, 95%CI 0.78 to 1.01, $p=0.08$). Prevalence-based breast cancer mortality rate trends before and after the impact of screening is expected to be observable are shown in Figure 4.4.

FIGURE 4.4 SEGMENTED REGRESSION OF PREVALENCE-BASED BREAST CANCER MORTALITY BEFORE (1991-2005) AND AFTER (2006-2011) THE IMPACT OF SCREENING IS EXPECTED TO BECOME OBSERVABLE



Comparing trends in both groups before and after 2006 (allowing for a five year delay in when screening could have an impact), an APC of -3.59% was found in the screening group (95%CI -7.95 to 0.98, $p=0.12$), and an APC of -1.80% in the unscreened group (95%CI -7.90 to 4.71, $p=0.59$). The mean difference in the change in trend after 2006 in the screening

group, controlling for contemporaneous changes in the comparison group (APC_{diff}), was -1.82% (95%CI -9.03 to 5.95, $p=0.65$). Fitted breast cancer mortality rates in each group just before screening could begin to affect prevalence-based breast cancer mortality (2005) and at the end of the study period (2011) are shown in Table 4.4.

TABLE 4.4 FITTED PREVALENCE-BASED BREAST CANCER MORTALITY RATE AT BEGINNING AND END OF COMPARISON INTERVAL

	Screening group (55-69 years)	Comparison group (55-69 years)
Fitted mortality rate per 100,000 at end of pre-screening period (2005)	83.56 (95%CI 63.74, 109.53)	86.09 (95%CI 59.18, 125.25)
Fitted mortality rate per 100,000 at end of post-screening period (2011)	61.69 (95%CI 27.34, 139.22)	71.55 (95%CI 23.18, 220.93)

The difference in these fitted rates at the start and end of the comparison interval, which were estimated using the difference in change in trend between the screening and comparison groups (geographical-historical comparison) as opposed to as the average over the comparison interval (as was the case with the CBA analysis), is equivalent to a non-significant reduction of 11% in prevalence-based breast cancer mortality (RR 0.89, 95%CI 0.55, 1.40, $p=0.65$).

Overdiagnosis

Combining the increased incidence of early-stage cancers with the subsequent three year lagged decrease in late-stage cancers, an overdiagnosis rate of 19% was found in the screened group during active screening (RR 1.19, 95% CI 1.09 to 1.29). If no lead time adjustment is used, the overdiagnosis estimate increases to 23% (RR 1.23, 95% CI 1.13 to 1.34). If the lead time adjustment is extended to 5 years the overdiagnosis estimate is similar to that of the three year lagged estimate (RR 1.19, 95% CI 1.10 to 1.30).

When overdiagnosis is examined by combining the increased incidence of asymptotically detected cancers with the subsequent three year lagged decrease in clinically detected cancers, the estimated overdiagnosis rate in the screened group during active screening was

20% (RR 1.20, 95% CI 1.10 to 1.31). If no lead time adjustment in the rate of clinically detected cancers is incorporated then the overdiagnosis estimate is 23% (RR 1.23, 95%CI 1.13 to 1.34).

The average age-standardised breast cancer incidence rate in the screened group in the post-screening interval was 346 per 100,000. Applying the overdiagnosis results to calculate the counterfactual incidence rate, it is estimated that over the course of the programme to date, for every 1,734 person-years of invitation to screening one breast cancer was overdiagnosed. This is equivalent to an average of one overdiagnosed cancer for every 173 women invited to screening for ten years in Ireland.

Balance of benefits and harms of screening

Based on the results reported in this thesis, it is estimated that for every breast cancer death avoided through screening, an average of 4.3 cancers were overdiagnosed over the study period. For a cohort of 100,000 50 year old women screened for 10 years this equates to 567 overdiagnosed cancers and 134 breast cancer deaths averted.

If the fitted breast cancer mortality rate by the end of the study period (62 per 100,000) is used instead of the average mortality rate over the entire screening period (71 per 100,000), then for every one breast cancer death avoided 4.9 cancers are overdiagnosed during active screening. For a cohort of 100,000 50 year old women screened for 10 years, this is the equivalent of 567 cancers overdiagnosed and 117 breast cancer deaths averted.

4.2.4 DISCUSSION

Our study took advantage of a natural experiment created by the phased introduction of screening in Ireland, to calculate the impact of screening within the overall target population, rather than just those who attended for screening. The circumstances surrounding the introduction of screening in Ireland arguably provides the best opportunity so far available in the literature to examine the impact of a population breast screening programme, due to the availability of large, balanced groups comprising over 90% of the entire national population of women aged 50-64 all served by the same national health system, a single cut-off point separating screening and comparison groups (rather than

gradual introduction requiring multiple group-year comparisons), and the availability of comprehensive, high-quality data on breast cancer incidence, with long-term patient level follow up. Based on this data, the Irish screening programme was associated with a 16% relative reduction in breast cancer mortality. It was also estimated that the overdiagnosis rate during active screening was 19%, which is equivalent to one in every six cancers detected when screening is in place. Based on average breast cancer mortality and incidence rates over the course of the study period, for every one death averted through screening, 4.3 cancers were overdiagnosed.

The implications of using prevalence-based, rather than incidence-based, breast cancer mortality outcomes and analytical methods that calculate changes in trends over time rather than average effects over the study period were also examined. Prevalence-based (or death certificate) mortality is routinely used to estimate the impact of screening programmes. However, population-based observational studies of prevalence-based mortality need to incorporate a lag period to account for the time it takes for mortality reductions as a result of screening to become apparent in the target population and are likely to underestimate the total mortality reduction as a result of screening unless sufficient data is available. The results of this study show that even a decade after the introduction of screening in Ireland, the full impact of screening is not observable using routinely reported (prevalence-based) breast cancer mortality. Furthermore, the findings show that the mean estimate of benefit calculated using a time series approach is consistent with average outcomes over the entire study period, but because of the relatively few time points available the confidence intervals around this estimate are extremely wide and are unlikely to yield a statistically significant result even with more years of data.

Despite these limitations, time series approaches do have the advantage of taking into account the fact that the breast cancer mortality rate has been decreasing in Ireland since the early 90's, mirroring international trends as a result of improvements in treatment, increased disease awareness and better organisation of services.^(314;315) A decreasing background trend in breast cancer mortality reduces the absolute benefit associated with the relative reduction in mortality delivered by screening. Therefore any decrease in breast cancer mortality rates as a result of better management of symptomatic patients that has

occurred between the study period (2001-2007) and the present day would tend to increase the ratio of overdiagnosed cases to breast cancer deaths averted. Our analysis shows that if the fitted breast cancer mortality rates at the end of the study period are used instead of the average, the balance of benefits and harms of screening increases from 4.3 to 4.9 overdiagnosed cases per deaths avoided. This highlights the need for continuous reappraisal of the overall balance of benefits and harms of modern population-based screening programmes.

Comparison with other studies

A recent systematic review of quasi-experimental studies identified seven unique reports of breast cancer screening programmes for women aged between 50 and 70 years that were introduced in such a way as to produce a comparison group against which to estimate the impact of screening.⁽³⁰¹⁾ All of these studies reported incidence-based breast cancer mortality. Five studies used the same geographical-historical comparison method used in this thesis, and gave a pooled RR of 0.87 (95%CI 0.78 to 0.97) when adjusted for person years and RR 0.84 (95%CI 0.76 to 0.94) when adjusted for population size, which is consistent with the estimate reported here. However the age-range of the study population in this analysis of the Irish programme (50-64 years) is narrower than those of the pooled review studies, which include women aged 50-69 years.

The challenges associated with estimating the degree of overdiagnosis as a result of screening are well known and there are acknowledged limitations to all the methods used so far.^(14;296;316) Observational studies tend to produce higher estimates of overdiagnosis (22% to 54%) than studies that use statistical modeling to adjust for lead time (<5%).⁽¹⁴⁾ There is also no consensus on the most appropriate denominator to use, with previous analysis showing that various selections can produce overdiagnosis rates ranging from 19% to 46% using the same data.⁽¹⁴⁾ The estimate of overdiagnosis in this thesis is based on the fundamental principal of screening; that mammography in healthy women detects early stage asymptomatic cancers before they would have presented clinically at a more advanced stage, which was calculated as the lead-time adjusted relative risk of being diagnosed with cancer in the screened group, compared to the unscreened group.

Expressed as a percentage, this represents the excess cancer incidence associated with screening as a proportion of total cancer incidence in the absence of screening. The preferred method for expressing the percentage overdiagnosis during the screening period (as opposed to over the lifetime of women invited to screening) in the UK independent review is as the number of excess cancers as a proportion of cancers diagnosed during the screening period in women invited for screening.⁽²⁹³⁾ Using this approach they report an overdiagnosis rate of 19% (or one in five cancers) based on pooled RCT data. When the results of the present analysis are calculated using the denominator specified in the Marmot report (total cancer diagnosed in the screened group), the overdiagnosis estimate is 16.7% (equivalent to one in six cancers), slightly lower than the Marmot estimate. The Canadian National Breast Screening Study recently published 25 year follow up results of their RCT of annual screening of a younger cohort of women (40-59) than are screened in Ireland (50-64) and reported that screening was associated with an overdiagnosis rate of 22%.⁽³¹⁷⁾

Limitations

As highlighted previously, the use of statistical adjustments for lead time has a major bearing on the results and the validity of these adjustments is unclear.⁽³¹⁸⁾ Given the variability in growth rates for different types of breast cancer, it is unlikely that an overall average lead time is highly representative of different subgroups, some of whom may be more or less likely to be detected through screening. However in the absence of definitive evidence on how much screening advances the time of diagnosis in non-overdiagnosed people in Ireland, previously reported results showing a mean sojourn time of 3 years in comparable populations were used.^(304;305) A sensitivity analysis using shorter (0 years) and longer (5 years) lead time adjustments was also carried out. If three years was too short then one would expect a five year lead time adjustment to find a lower estimate of overdiagnosis. The analysis showed that comparable results were obtained for both, indicating that a three year lead time is sufficient to capture the majority of the effect of screening. It is believed, therefore, that while adjusting for a mean lead time does introduce bias, this approach provides the best possible estimate of the overall impact of the screening programme on overdiagnosis in Ireland given the available data.

Although the highest quality study designs possible were used to examine the effectiveness of screening in a real-life setting (NHMRC evidence level III-2⁽³¹⁹⁾), there is a risk of selection bias due to the lack of truly randomised allocation. This is mitigated by using a geographical-historical comparison, but at the cost of exposure to regression bias, since it adjusts for differences that may be solely due to chance and therefore may not be present in the post-screening period as a result of regression to the mean. As all results are based on directly age-standardised rates for each outcome, any impact of differences in the age-related risk profile between groups is minimised. Also since the analysis uses cross sectional data from before and during screening, rather than longitudinal data from screened and unscreened groups before, during and after screening, it was impossible to estimate the rate of overdiagnosis over the lifetime of screened women. As discussed in the UK independent review, this is likely to be lower than the rate of overdiagnosis during active screening.⁽³⁰⁰⁾

A pilot programme was initiated in 1989 to assess the feasibility of a national breast screening programme.⁽³²⁰⁾ As part of this almost 18,000 women were screened from the 1925-1940 birth cohort from areas that would go on to become part of the screening group. This means that by the time the national screening programme for 50-64 year olds was first introduced in 2000, up to 8% of the target population may already have received an invitation to screening during the pilot project. However given that the potential prior exposure at the start of the programme was small, decreased rapidly over time as the youngest in the pilot project cohort moved beyond the upper age limit of the national programme, and the fact that no appreciable effect of the pilot programme was found over the course of the study period on the most sensitive outcome (incidence of asymptomatic cancers, see Figure 4.3), the risk of bias from prior exposure to an invitation to screening is considered to be low.

The Irish screening service switched from film-screen to digital mammography in April 2008, shortly after the end of the comparison interval in 2007. Prior to this, digital mammography had been used in a limited number of areas as part of a pilot project that began in 2005.⁽³²¹⁾ As a result there is a threat from differences in instrumentation if the same technology had not been used in both groups. The impact of any such bias is not thought to be significant

because although digital mammography is more sensitive than film-screen mammography, it has a similar positive predictive value.⁽³²²⁾

Perhaps the most significant risk of bias arises from the potential for contamination in the unscreened population as a result of raised awareness due to the introduction of the programme in other parts of the country, leading to more opportunistic screening. Figure 4.3 shows that the incidence of asymptotically detected cancers in the unscreened group did rise over the course of the study period. However not all of this is likely to be attributable to contamination, as some of the increase would reflect natural changes in practice and behaviours over time as a result of greater disease awareness and increased vigilance, which would also have been occurring in the screened population. Any contamination as a result of opportunistic screening would tend to underestimate both the benefits (decrease in breast cancer mortality) and the harms (overdiagnosis) of screening.

4.2.5 CONCLUSION

The Irish breast screening programme has resulted in a significant decrease in breast cancer mortality within the target population, but has also led to the diagnosis and treatment of a substantial proportion of cancers that may not otherwise have become clinically significant. Continued improvements in the management of symptomatic patients are likely to decrease the absolute benefits of screening, highlighting the need for continuous reappraisal of the balance of benefits and harms of screening within the target population.

4.3 COST-EFFECTIVENESS OF BREAST SCREENING

4.3.1 INTRODUCTION

More than a decade after the European Parliament adopted a resolution calling for every woman to have access to high-quality breast screening mammography, state funded national and regional programmes are in place throughout Western Europe.^(129;323) The majority of these programmes screen women between the ages of 50 and 69 at two-year intervals, with the exception of the UK, which screens women aged 50 to 70 every three years, and Ireland, which screens women aged 50 to 64 years every two years. The Irish government recently announced that it intends to extend the upper age limit of the national breast screening programme to 69 years.⁽¹³⁾

Evaluating the impact of these national programmes has proved controversial. Conflicting evidence on the clinical effectiveness of screening was reviewed by an independent UK panel in 2012, which concluded that since observational studies examining the performance of service-level screening programmes all share the common problem of potential lack of comparability of screened and unscreened women, the best available evidence came from RCTs carried out 20 to 30 years ago showing that screening reduces breast cancer mortality by 20%, but at the cost of the overdiagnosis of one in five cancers detected during active screening.⁽³⁰⁰⁾ However, the original RCTs were conducted prior to advances in the management of symptomatic disease that have reduced the baseline breast cancer mortality rate in the absence of screening, thereby decreasing the benefit of earlier detection. The phased introduction of screening in Ireland in 2000 created a natural experiment, where approximately half of the target population was screened for seven years while no screening was offered in other parts of the country. Using ten years of individual patient follow-up data, it was previously estimated that screening in Ireland was associated with a 16% reduction in breast cancer mortality and an overdiagnosis rate of one in six cancers detected during active screening (Section 4.2).

Estimating the overall balance of benefits and harms of a contemporary, population-based screening programme based on these results is problematic, since nobody can definitively say what level of overdiagnosis would tip the scales against the mortality reduction

delivered by screening. Consideration also needs to be given to the opportunity cost of the healthcare resources required to provide breast screening in the context of the wider provision of public health interventions, to ensure that the cost of the programme is economically balanced in relation to possible expenditure on medical care as a whole.⁽¹⁴⁵⁾ The aim of this analysis is to examine the overall benefit of screening by comparing the utility gained as a result of decreased breast cancer mortality and earlier diagnosis, with utility losses associated with the detection of cancers that would never have been diagnosed in the absence of screening. The cost-effectiveness of the current Irish screening programme for women aged 50-64 and the incremental costs and benefits of the proposed extension of the age range to include women aged up to 69 years were also evaluated.

4.3.2 METHODS

4.3.2.1 MODEL STRUCTURE AND PRIMARY ANALYTICAL METHODS

A cost-utility analysis was carried out using a life table model implemented as a probabilistic two state (alive-dead) Markov chain, to simulate breast cancer incidence and mortality, health related quality of life and healthcare utilisation within a cohort of 50 year old women in Ireland over a 35 year time horizon. Using this model the existing Irish screening programme for women aged 50 to 64 years and an extended screening programme for women aged 50 to 69 years was compared to strategy of no screening.

A utility analysis was conducted to examine the overall balance of benefit and harms of screening by comparing the utility gains (in QALYs) from earlier detection and decreased breast cancer mortality as a result of screening, with the utility loss associated with overdiagnosis. No discounting was used in this analysis, which sought to examine the absolute benefit of screening a cohort of 50 year old women in Ireland, irrespective of when that benefit accrued.

An economic analysis was carried out to examine the cost-effectiveness of screening, using both a payer perspective (that of the publicly funded health service) and a limited societal perspective that included productivity losses associated with breast cancer mortality, calculated using the human capital approach. In the economic analysis a discount rate of 5% was applied to benefits (in QALYs), and costs, which were inflated to 2014 Euro.

4.3.2.2 SENSITIVITY AND SCENARIO ANALYSIS

Probabilistic sensitivity analysis was used to account for uncertainty in the parameters values used in the model. Individual values from each parameter distribution were randomly sampled over the course of 10,000 model simulations to generate an overall average result. A cost-effectiveness acceptability curve (CEAC) was generated to show the probability of each comparator being cost effective at a given willingness to pay (WTP) threshold.

In the primary analysis the average breast cancer mortality rate over the study period (2001-2007) was used to estimate the absolute benefit derived from the relative reduction in breast cancer mortality delivered by screening. However, the breast cancer mortality rate has been decreasing in Ireland since the early 90's, mirroring international trends as a result of improvements in treatment, increased disease awareness and better organisation of services.^(314;315) To examine the impact of a background decreasing trend in breast cancer mortality on the cost-effectiveness of screening, a sensitivity analysis was carried out by calculating individual ICERs for the existing screening programme using the baseline breast cancer mortality rate in the unscreened population each year between 1996 and 2007. Linear regression was then used to estimate the ICER trend corresponding to the change in baseline breast cancer mortality in the absence of screening.

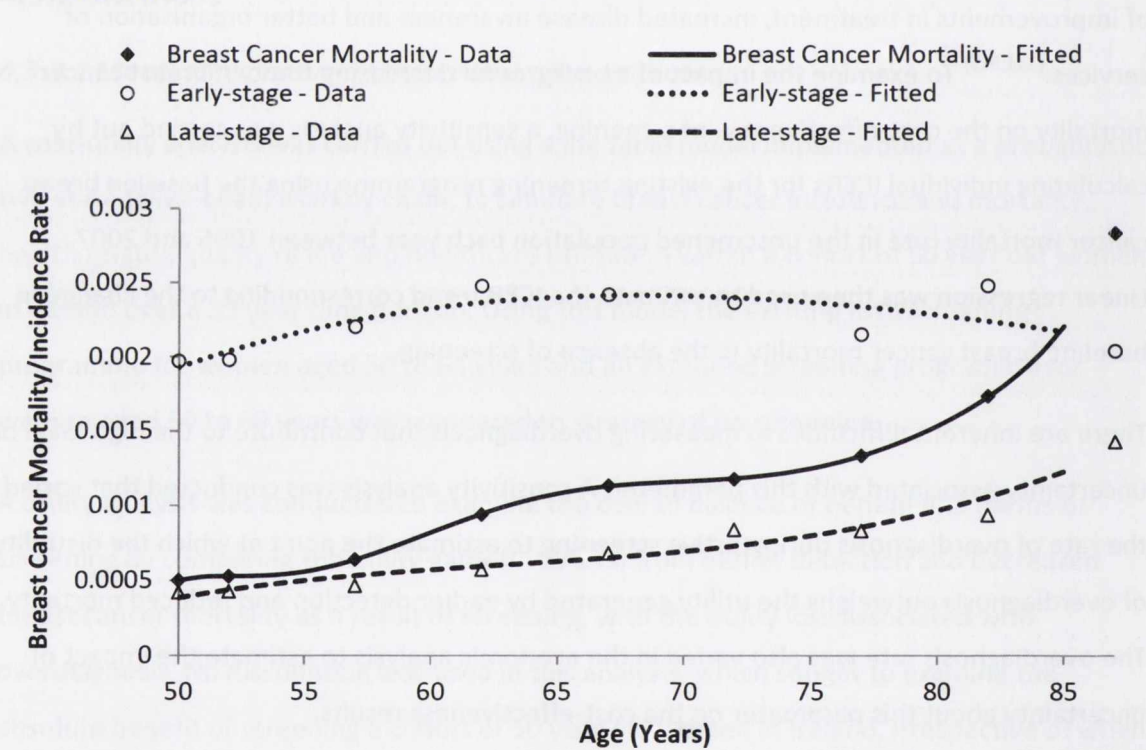
There are inherent difficulties in measuring overdiagnosis that contribute to the high level of uncertainty associated with this parameter. A sensitivity analysis was conducted that varied the rate of overdiagnosis during active screening to estimate the point at which the disutility of overdiagnosis outweighs the utility generated by earlier detection and reduced mortality. The overdiagnosis rate was also varied in the economic analysis to estimate the impact of uncertainty about this parameter on the cost-effectiveness results.

4.3.3 ESTIMATES OF EFFECT

The impact of the Irish breast screening programme was estimated from a controlled before and after study estimating the impact of the Irish breast screening programme (Section 4.2). This study used data from contemporaneous screened and unscreened areas of the country to compare the baseline breast cancer incidence and mortality rate in the absence of screening, with breast cancer incidence and mortality rates in screened areas, using ten

years of individual patient follow up data. It found that screening was associated with a statistically significant 16% reduction in breast cancer mortality and a lead-time adjusted overdiagnosis rate of 19% during active screening. This study also provided data on the proportion of early-stage (TNM 0, I, II) and late-stage (TNM III, IV) cancers with and without screening and showed that increases in early-stage incidence associated with screening occur immediately after screening starts, while subsequent decreases in late-stage presentation are observed after a lead time of three years. Figure 4.5 shows Irish breast cancer mortality and incidence rates in the absence of screening and Table 4.5 shows the clinical effectiveness parameters used in the analysis.

FIGURE 4.5 BREAST CANCER INCIDENCE AND MORTALITY RATES BY AGE IN THE ABSENCE OF SCREENING



Based on the conclusions of the UK Independent Review of Breast Screening, it was assumed that the effect of screening on breast cancer mortality would not become apparent within the screened population until five years after the start of screening, and that this would continue for ten years after screening ended.⁽²⁹³⁾ Female mortality rates by year of age from all causes other than breast cancer were estimated using data from Irish life tables for all cause mortality, minus breast cancer mortality.⁽²⁶⁶⁾

4.3.4 ESTIMATES OF UTILITY

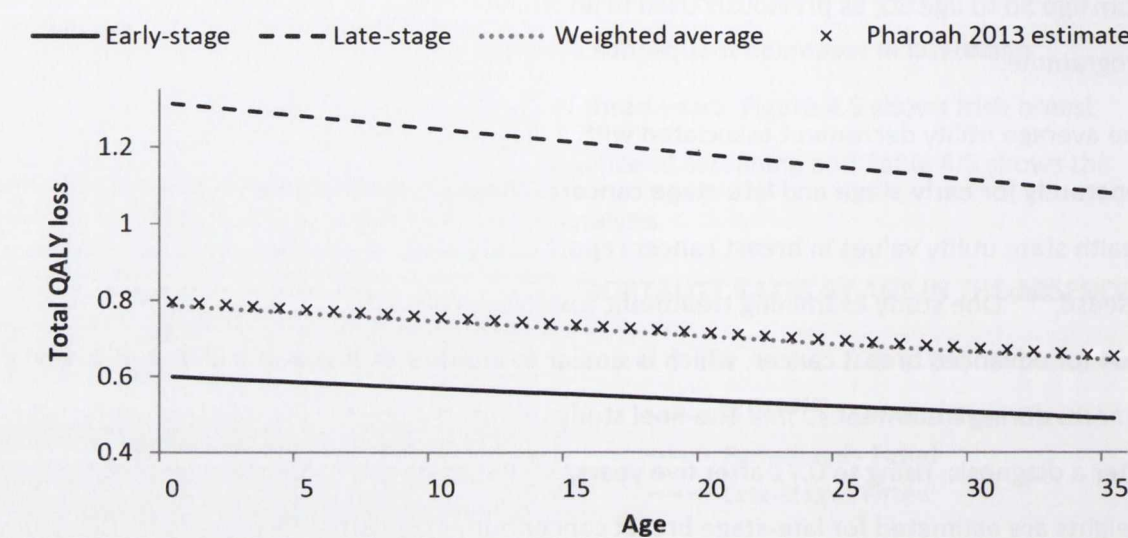
In the absence of data on age-specific health related quality of life in Ireland, baseline utility weights by year of age were taken from UK population data showing an average health-related utility weight in the general population of 0.85, declining by 0.0043 units per year from age 50 to age 80, as previously used in an analysis of the UK breast screening programme.⁽³²⁴⁾

The average utility decrement associated with a diagnosis of breast cancer was estimated separately for early-stage and late-stage cancers. Three studies identified in a review of health state utility values in breast cancer report utility weights associated with late-stage disease.⁽³²⁵⁾ One study examining treatment toxicology calculated a baseline utility weight of 0.64 for advanced breast cancer, which is similar to another estimate of 0.63 for advanced cancers during treatment.^(326;327) The final study reported a utility weight of 0.62 in the year after a diagnosis, rising to 0.71 after five years.⁽³²⁸⁾ Based on this evidence, average utility weights are estimated for late-stage breast cancer during and after treatment of 0.64 and 0.70 respectively. Using Irish registry data from 1994 to 2010, average survival after a diagnosis of late-stage breast cancer in the target population in Ireland was estimated at 5 years. The average QALY decrement associated with a diagnosis of late-stage breast cancer by age at diagnosis was calculated by combining utility weights during and after treatment with the average life expectancy after a diagnosis, assuming that treatment is completed in one year. A similar approach was adopted for early-stage breast cancer, using previously published utility weights for early-stage breast cancer during and after treatment from one study (0.87 and 0.96 respectively) combined with Irish data on the average life expectancy for women diagnosed with early-stage cancers within the target population (16 years).^(325;329)

Figure 4.6 shows the undiscounted total QALY loss associated with a diagnosis of early-stage and late-stage cancer by age at diagnosis and demonstrates that the weighted average QALY loss derived using these estimates is consistent with previous estimates of the average utility loss associated with a diagnosis of breast cancer (Figure 4.6).⁽³²⁴⁾ In the economic analysis the cumulative QALY decrement per diagnosis is discounted to reflect QALY losses that occur in the years after the initial diagnosis, and this discounted total average QALY loss

is again discounted in the analysis to take account of when the diagnosis is made in the modelled cohort.

FIGURE 4.6 TOTAL UNDISCOUNTED QALY LOSS PER DIAGNOSIS FOR EARLY-STAGE AND LATE-STAGE CANCERS BY AGE AT DIAGNOSIS



4.3.5 ESTIMATES OF COST

Data on the cost of case finding (screening mammography and clinical assessment) were taken from an efficiency review of the Irish breast screening programme commissioned by the Department of Health, published in 2012.⁽³³⁰⁾ Treatment data by stage at diagnosis was estimated using data from the National Cancer Registry Ireland between 2008 and 2011 on the percentage of early and late stage patients receiving radiotherapy, chemotherapy, endocrine therapy, mastectomy or breast conserving surgery.⁽³³¹⁾ Average costs for treatment in Ireland were obtained from a health technology assessment of screening for women at increased risk of breast cancer, published in 2013.⁽³³²⁾ Productivity losses were estimated using the human capital approach, by measuring the value of the economic output that is lost due to disease-related mortality as indicated by the market wage.⁽³³³⁾ Irish data on labour force participation and average earnings for women aged 50 to 85 years by year of age was obtained from the International Labour Organisation (ILO) and the Central Statistics Office (CSO).^(265;266) Discounting was used to incorporate the time value of future earnings into the overall cumulative productivity loss by age at death, which was again discounted to reflect the year in which the loss is incurred in the modelled cohort.

Table 4.5 shows mean estimates and data sources for costs and all parameters relating to the screening programme. All analyses were carried out using TreeAge Pro 2014 and all graphs were produced in Excel.^(106;107)

TABLE 4.5 CLINICAL AND COST PARAMETERS USED IN THE ECONOMIC ANALYSIS

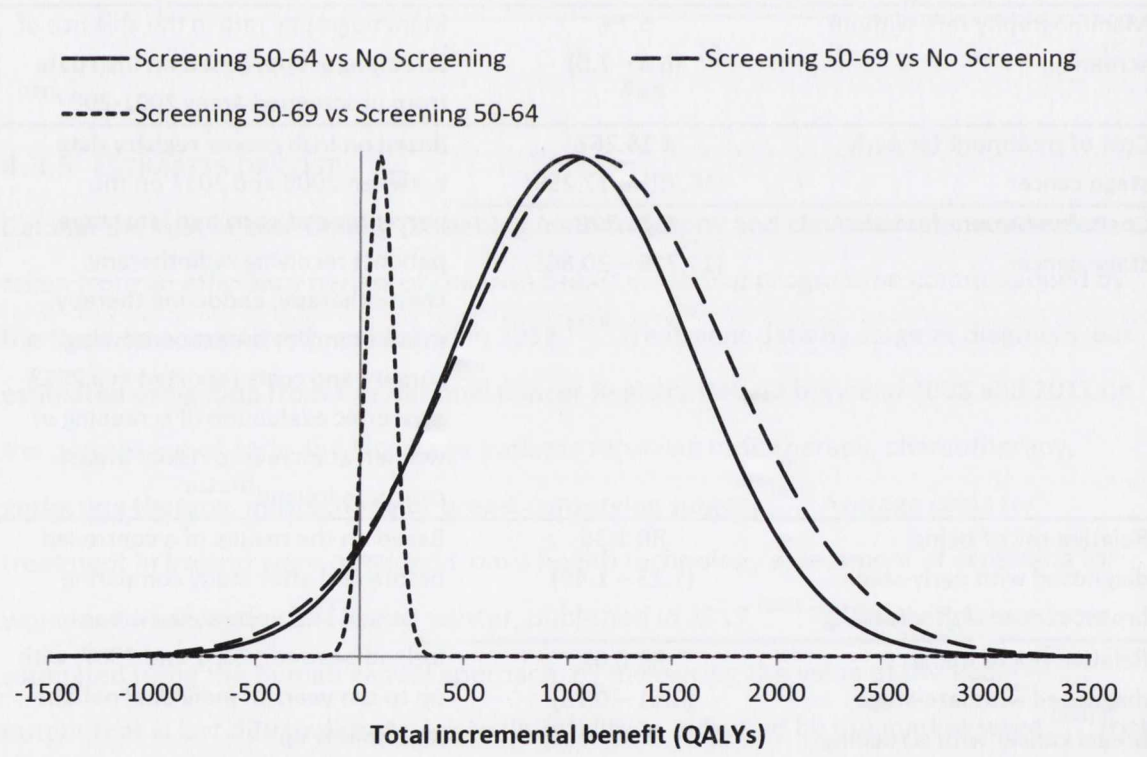
Parameter	Mean Estimate (95% CI)	Source
Cost of a screening mammogram	€ 85 (77.06 – 92.85)	Average BreastCheck costs from 2009-2011, inflated to 2014 Euro, reflecting costs in an established screening service ⁽³³⁰⁾
Cost of assessment	€ 1,235 (1071 – 1399)	
Negative assessment rate	3.7% (3.3 – 4.1)	Rate of recalls for assessment that do not result in a diagnosis, based on Breastcheck data from 2009-2013 ⁽³³⁰⁾
Uptake of screening	73.5% (69.8 – 77.3)	BreastCheck data on the average percentage uptake within the known target population 2001 to 2012 ⁽³³¹⁾
Mammography rate without screening	6.7% (6.3 – 7.0)	Mammography rate in the absence of screening group, based on Irish data from unscreened areas 2001-2007 ⁽³³¹⁾
Cost of treatment for early-stage cancer	€ 18,262 (16,795 – 17,259)	Based on Irish cancer registry data between 2008 and 2011 on the percentage of early and late stage patients receiving radiotherapy, chemotherapy, endocrine therapy, mastectomy or breast conserving surgery and costs reported in a 2013 economic evaluation of screening of women at increased risk of breast cancer in Ireland ^(331;332)
Cost of treatment for late-stage cancer	€ 21,528 (19,716 – 20,865)	
Relative risk of being diagnosed with early-stage breast cancer with screening	RR 1.36 (1.23 – 1.49)	Based on the results of a controlled before and after study comparing screened and unscreened areas in Ireland between 2001 and 2007, with up to ten years of individual patient level follow up ⁽³³¹⁾
Relative risk of being diagnosed with late-stage breast cancer with screening (three year lead time adjusted)	RR 0.62 (0.51 – 0.75)	
Relative risk of dying from breast cancer with screening	RR 0.84 (0.70 – 1.00)	
Screening interval	2 years	BreastCheck screening interval ⁽³⁰²⁾
Age at start of screening	50 years	BreastCheck start age ⁽³⁰²⁾

4.3.6 RESULTS OF THE ECONOMIC ANALYSIS

4.3.6.1 UTILITY ANALYSIS

For the 2014 cohort of women aged 50 years in Ireland (n=30,636), screening from ages 50 to 64 and 50 to 69 generates an additional 1019 QALYs and 1114 QALYs, respectively, over a 35 year time horizon, compared with no screening. The existing Irish screening programme was associated with a mean increase in utility in the screened cohort compared to no screening in 97% of simulations and in 93% of simulations an extended programme for women aged 50 to 69 years produced a mean increase in utility compared with the existing programme (Figure 4.7).

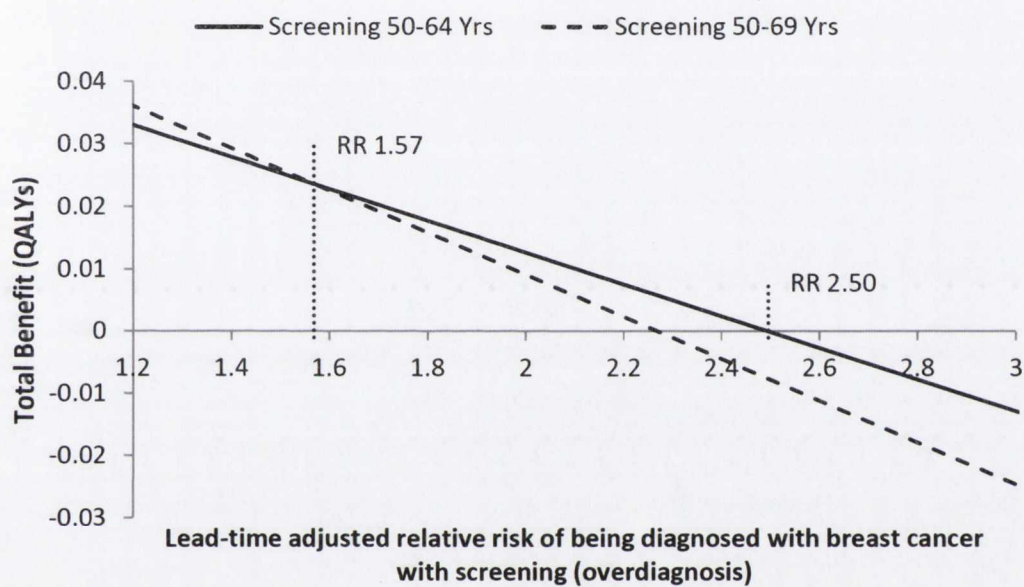
FIGURE 4.7 DISTRIBUTION OF ESTIMATES OF THE INCREMENTAL EFFECT OF SCREENING OVER THE COURSE OF 10,000 PROBABILISTIC MODEL SIMULATIONS



The results of a sensitivity analysis show that if the current rate of overdiagnosis of one in six (RR 1.19) cancers detected during screening increased to approximately one in three (RR 1.57, Figure 4.8), then extension of the screening age to 69 would result in a net utility loss

compared with continuing with the current screening programme. For the harms of the current Irish screening programme for those aged up to 64 years to exceed the benefits, three out of every five cancers detected in the screened cohort would need to be overdiagnosed (RR 2.50, Figure 4.8).

FIGURE 4.8 UNDISCOUNTED INCREMENTAL BENEFIT OF SCREENING WITH INCREASING RATES OF OVERDIAGNOSIS



4.3.6.2 PAYER PERSPECTIVE

From the perspective of the health service, the incremental cost effectiveness ratio (ICER) for the current Irish screening programme for women aged 50 to 64 years compared to no screening is approximately €49,000/QALY, with a 42% probability of being the most cost effective strategy at a willingness to pay (WTP) threshold of €45,000/QALY (see Table 4.6 and Figures 4.9 and 4.10). The ICER for the extended screening programme for women aged 50-69 years compared to the existing programme for women aged 50-64 years is approximately €162,000/QALY. Compared to a strategy of no screening, the extended screening programme is associated with an ICER of approximately €56,000/QALY.

TABLE 4.6 ICER CALCULATION (PAYER PERSPECTIVE)

Strategy	Cost (€)	Incremental Cost (€)	Effect (QALY)	Incremental Effect (QALY)	ICER (€/QALY)
No screening	988	-	12.66923	-	-
Screening 50-64	1520	532	12.67998	1.0749×10^{-2}	49,491
Screening 50-69	1621	101	12.68061	6.2517×10^{-4}	161,555

FIGURE 4.9 COST EFFECTIVENESS PLANE AND ICERS (HEALTH SERVICE PERSPECTIVE)

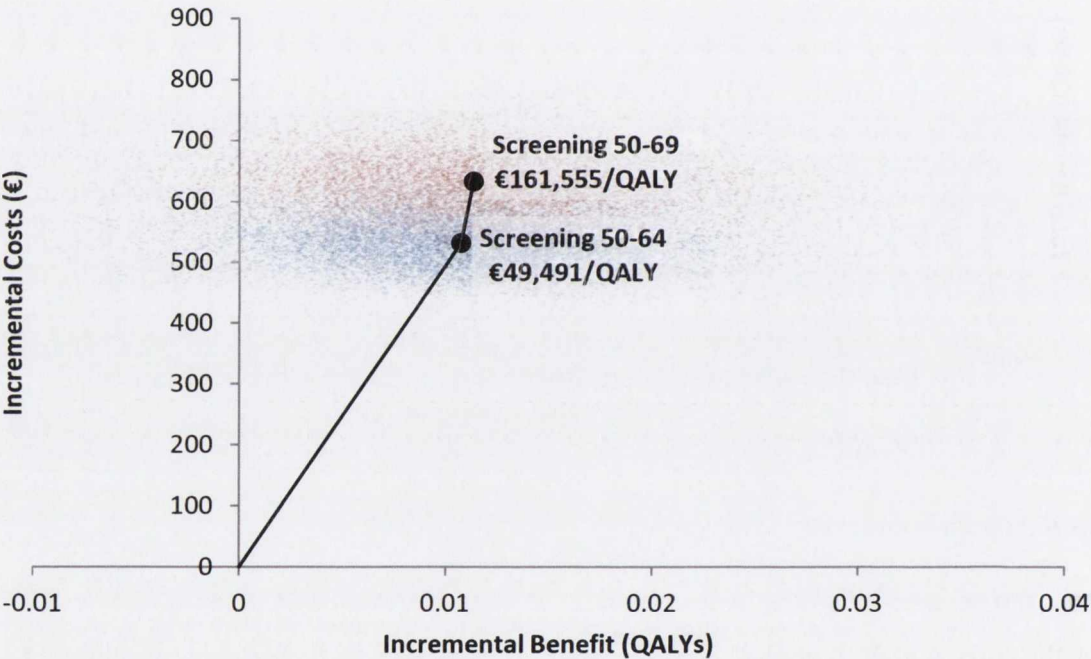
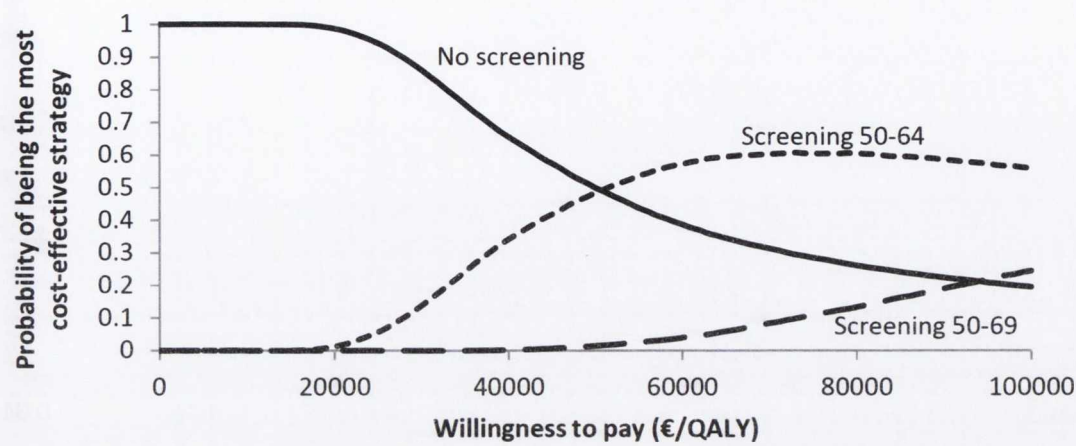


FIGURE 4.10 COST EFFECTIVENESS ACCEPTABILITY CURVE (CEAC, HEALTH SERVICE PERSPECTIVE)



4.3.6.3 SOCIETAL PERSPECTIVE

When a limited societal perspective is adopted by including productivity losses associated with premature mortality from breast cancer the ICER for the current screening programme compared to no screening is reduced to approximately €20,000/QALY, with a 71% probability of being the most cost effective strategy at a WTP threshold of €45,000/QALY (see Table 4.7 and Figures 4.11 and 4.12). The ICER for the five year extension to the age range of the screening programme compared with the existing programme is approximately €160,000/QALY. Comparing the extended programme to a strategy of no screening produces an ICER of approximately €28,000/QALY.

TABLE 4.7 ICER CALCULATION (SOCIETAL PERSPECTIVE)

Strategy	Cost (€)	Incremental Cost (€)	Effect (QALY)	Incremental Effect (QALY)	ICER* (€/QALY)
No screening	28401	-	12.6699	-	-
Screening 50-64	28621	220	12.6807	1.0760x10 ⁻²	20,464
Screening 50-69	28722	100	12.6813	6.2511x10 ⁻⁴	160,484

* Due to rounding error the ICER value calculated using the incremental cost and incremental effect values reported in this table may differ from the ICER value reported in the table. Where any such differences do occur please note that the ICER value reported in the table provides the most accurate estimate.

FIGURE 4.11 COST EFFECTIVENESS PLANE AND ICERS (SOCIETAL PERSPECTIVE)

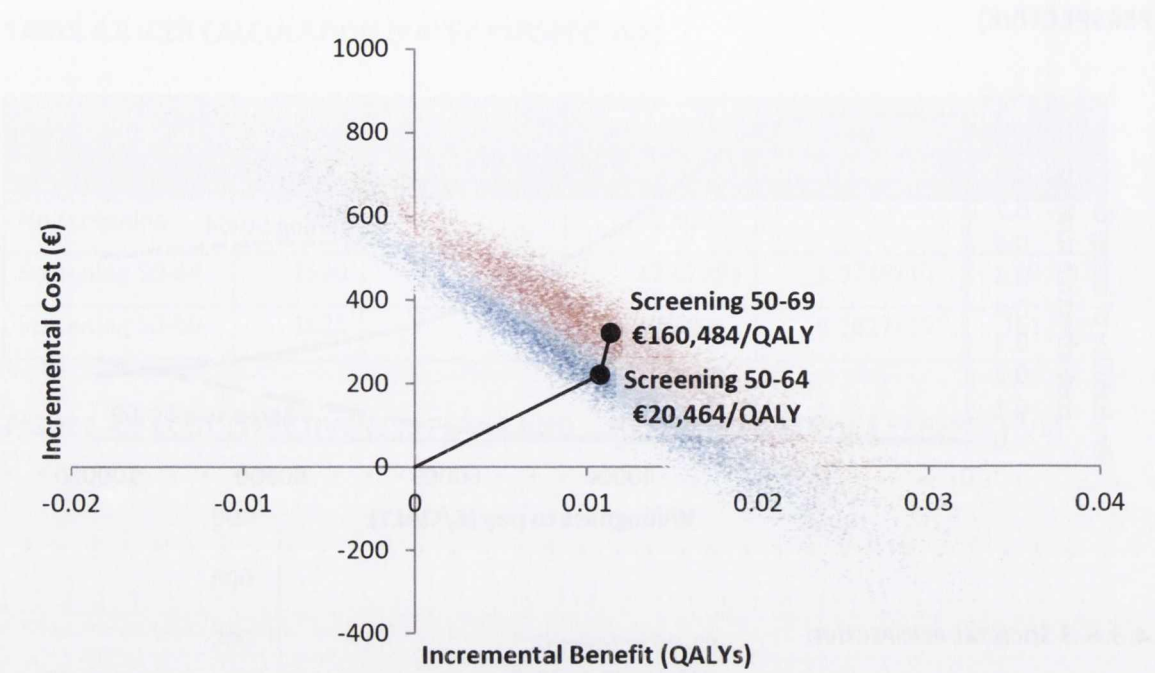
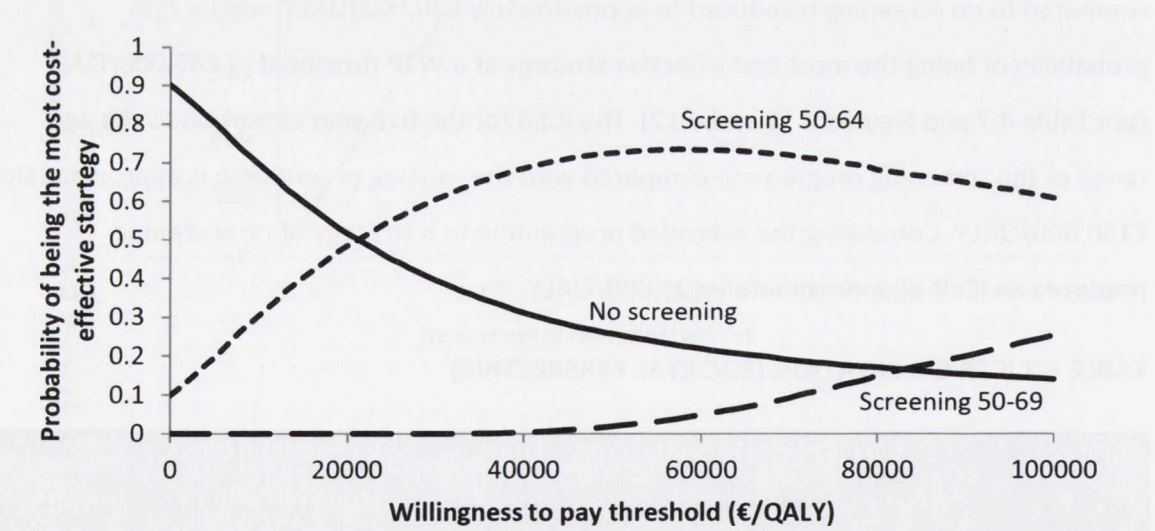


FIGURE 4.12 COST EFFECTIVENESS ACCEPTABILITY CURVE (CEAC, SOCIETAL PERSPECTIVE)

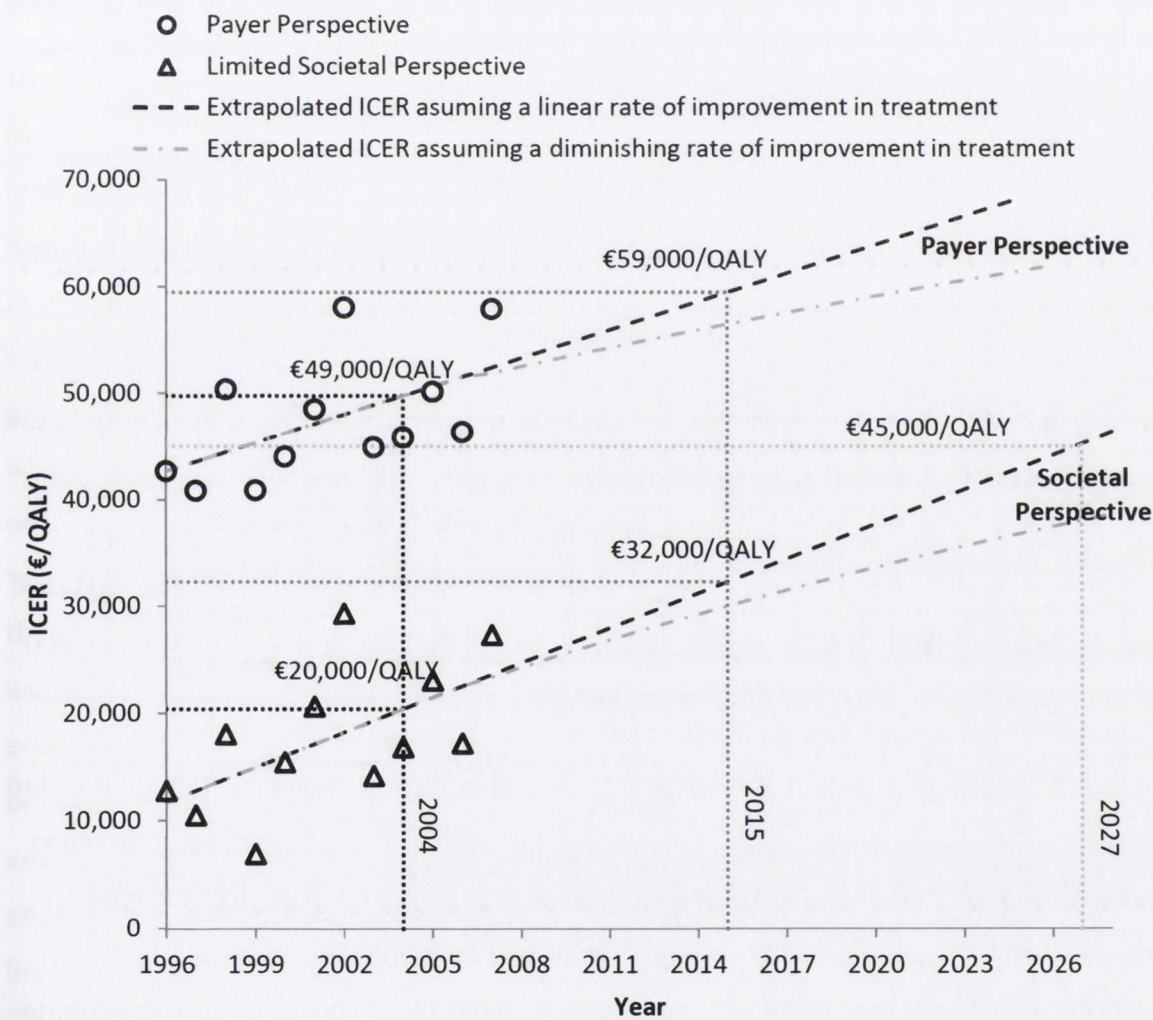


4.3.6.4 SENSITIVITY ANALYSIS

Using the baseline breast cancer mortality rate in unscreened areas between 1996 and 2007, an increasing trend over time was observed in the ICER estimate for the existing screening programme for women aged 50 to 64 years (Figure 4.13). Assuming this

background decreasing trend in breast cancer mortality continued after the introduction of screening, by 2015 the ICERs for screening (compared to no screening) using a health service and limited societal perspective are estimated to be €59,000/QALY and €32,000/QALY, respectively, with the latter expected to exceed a WTP threshold of €45,000/QALY by 2027.

FIGURE 4.13 ESTIMATED IMPACT OF DECREASING BREAST CANCER MORTALITY RATES ON MEAN ICER ESTIMATES FOR THE CURRENT SCREENING PROGRAMME FOR WOMEN AGED 50-64 YEARS COMPARED TO NO SCREENING



4.4 DISCUSSION

Comparing the undiscounted utility gains from decreased breast cancer mortality and earlier diagnosis as a result of screening with utility losses due to overdiagnosis, the Irish screening programme was found to result in a considerable net benefit compared with no screening. The estimated current rate of overdiagnosis of one in every six cancers diagnosed within the screened cohort would have to increase to one in three for the proposed extension of the screening age range to do more harm than good compared with the existing situation, where screening is offered to women aged 50 to 64 years. For the existing programme to be more harmful than no screening the majority of cancers (three out of five) detected in the screening cohort would need to be overdiagnosed.

From the perspective of the health service the current screening programme for women aged 50 to 64 years is at the upper reaches of what has historically been considered a cost-effective use of healthcare resources in Ireland, having a 42% probability of being the optimal strategy at a willingness to pay (WTP) threshold of €45,000/QALY. However, if it is assumed that the decreasing trend in breast cancer mortality that was observed prior to the introduction of screening has been maintained since 2007, then the existing programme would not be cost effective, having an ICER of approximately €59,000/QALY. From the perspective of the health service, both the average and the marginal cost of each additional QALY gained by extending the age range of screening to 69 years exceed conventional WTP thresholds (€56,000 and €162,000, respectively).

If the cost of lost productivity associated with premature breast cancer mortality, calculated using the human capital approach, is included in the analysis then the existing programme would be considered cost-effective even if the pre-screening decreasing trend in breast cancer mortality continued to the present day (ICER €32,000/QALY). If sustained improvement in the management of symptomatic breast cancer through increased disease awareness, better organisation of services and the development of more effective treatments continued to decrease breast cancer mortality at the same rate into the future, then from a societal perspective the current screening programme is unlikely to exceed a WTP threshold of €45,000/QALY within the next decade. However, even from a societal perspective the marginal cost of each additional QALY gained by extending the age range of

screening to 69 years exceeds conventional WTP thresholds (€160,000/QALY). The analysis from the societal perspective did not include costs associated with lost productivity due to work absences during treatment, out-of-pocket payments or travel costs. A 2010 report by the NCRI combined data from a range of cancers to examine the types of costs incurred by patients.⁽³³⁴⁾ However, there is a lack of reliable Irish data with which to estimate the impact of a breast cancer diagnosis on time taken off work and other cost parameters. The inclusion of these costs would likely make screening less cost effective, owing to the additional costs associated with overdiagnosed cases as a result of screening.

The results highlight the importance of changes in the mortality rate of symptomatic breast cancer on the cost-effectiveness of screening, which is to be expected given that any improvement in the management of clinically detected cancers decreases the benefit of earlier detection. However, it is unclear whether the decreasing trend that was in evidence prior to the introduction of screening was maintained afterwards due to an inability to separate the effect of screening from the effect of improved treatment. This may only be possible using long term data from comparable screened and unscreened populations, where outcomes in the screening population are separable into groups that were and were not screened. The analysis used overall outcomes within screened and unscreened groups to estimate the impact of screening at a population level given an Irish uptake rate of 74% in the screened group, rather than examining outcomes for those who did or did not accept an invitation to attend for a mammogram within the screened cohort. This may now be possible due to the recent work carried out in Ireland to link data from the breast screening programme with the Irish cancer registry.⁽³³⁵⁾ A limitation however, will be that any such analysis would be prone to selection bias and since screening was extended to the whole population in 2007 any comparison will be historical. Given the widespread adoption of breast screening, it is unlikely that contemporary populations that were never offered screening exist within any Western European country to facilitate a more up to date analysis.

A 2013 evaluation of the cost effectiveness of the UK screening programme from the perspective of the health service estimated an ICER of £20,800/QALY (approximately €25,000/QALY) compared with the estimate of €49,000/QALY for the Irish screening

programme.⁽³²⁴⁾ In contrast with the UK study, the analysis reported here estimated the utility loss associated with early and late stages breast cancer separately, on the basis that because screening changes the relative proportion of early and late stage diagnoses, not doing so would fail to capture one of the principle sources of any utility difference between screened and unscreened populations. Although the combined average utility loss associated with a diagnosis of breast cancer is the same using both approaches (Figure 4.6), this analysis finds a greater average benefit per person because it includes the utility gains associated with stage shifting, where cancers that would have been detected at an advanced stage are instead detected when the severity of treatment and associated morbidity are lower. Treatment costs were calculated based on the proportion of patients receiving each type of treatment in Ireland between 2008 and 2011, when screening was in place throughout the country. Therefore the treatment costs for early stage disease are indicative of average costs in the presence of any overdiagnosis as a result of screening, so avoiding the need to make the numerous assumptions required in the UK study to estimate the absolute cost of treating an overdiagnosed case even though it is impossible to distinguish overdiagnosed cases from non-overdiagnosed cancers.⁽³³⁶⁾ The cost of treating overdiagnosed cases is therefore higher in this study than in the UK study. However any differences should not greatly affect the results, as the authors of the UK study point out that the cost of treating an overdiagnosed case had limited impact on the cost effectiveness of screening.⁽³³⁷⁾ The biggest difference between the two analyses was that the UK study used a screening interval of three years and a relative reduction in breast cancer mortality of 20%, based on pooled RCT data from trials conducted 20 to 30 years ago, prior to advances in the management of symptomatic disease that would serve to reduce the benefit of earlier detection. Our analysis modelled the two year interval used both in Ireland and every other European country apart from the UK, and a mortality reduction of 16% estimated using contemporary data from the Irish screening programme. Running the model developed for this thesis using a three year screening interval and a 20% mortality reduction produces an ICER of €26,159/QALY, which is consistent with the results of the UK study.

4.5 CONCLUSION

The undiscounted cumulative utility generated by the Irish screening programme as a result of decreased breast cancer mortality and earlier diagnosis outweighs the utility lost due to overdiagnosis. When productivity losses due to premature breast cancer mortality are taken into account, the current screening programme for women aged 50 to 64 is likely to be cost effective. However the marginal cost per QALY gained from extending the age range to 69 years far exceeds conventional willingness to pay thresholds in Ireland. The cost effectiveness of screening will reduce over time if the decreasing trend in breast cancer mortality observed prior to the start of screening has continued after it was introduced.

5. GENERALISED COST EFFECTIVENESS ANALYSIS OF PUBLIC HEALTH INTERVENTIONS

5.1 INTRODUCTION

The preceding sections of this thesis examine three national public health interventions, comparing each of them to the current standard of care within that disease area. Prospective public access defibrillation and atrial fibrillation (AF) screening interventions are compared to routine care for out-of-hospital cardiac arrest and AF, respectively, and an expanded breast screening programme for women aged between 50 and 69 is compared to the current programme for those aged 50 to 64 years. While these analyses provide relevant information in regard to each of these three policy decisions, what is lacking, from the point of view of someone administering a national budget for public health interventions across all disease areas, is information on how they compare to each other, and whether existing interventions included in the standard of care are themselves cost effective. This would help answer some of the most important questions in relation to the overall use of public health resources, such as whether a new screening programme for AF should be prioritised over the setting up of a national AED programme, or whether resources allocated to existing programmes, such as the current breast screening programme, could be put to better use elsewhere.

This section of the thesis explores methods for carrying out this broader type of cost effectiveness analysis, using the three interventions described previously as an example. The aim of this is twofold, seeking both to find out what such analysis can reveal about the relative merits of each of the three interventions, as well as what the three interventions can tell us about the theoretical validity and empirical utility of sectoral cost effectiveness analysis within the area of public health in Ireland.

5.2 BACKGROUND

The primary aim of cost effectiveness analysis in healthcare is to improve the efficiency of health service delivery by maximising the amount of health benefit produced from the resources that society sees fit to provide for this purpose. Efficiency is therefore a measure of the value of a particular health intervention, which focuses on achieving the optimal balance of inputs and outputs, rather than just focusing on maximising health gain or minimising costs.

Efficiency can be examined from a number of different perspectives. Technical efficiency considers the inputs required for a given outcome, and is achieved when that outcome could not be produced with any reduction in inputs. For example, if the recommended dose of atorvastatin for people with type II diabetes could be reduced from, say, 40mg/day to 20mg/day and achieve the same reduction in cholesterol then that would improve the technical efficiency of that intervention. Productive efficiency is broader than technical efficiency since it considers whether alternative interventions can achieve the same or better outcomes in a different way, using a different combination of resources. For instance, if the increase in clinical effectiveness of using HPV DNA testing instead of cytology for cervical cancer screening was greater than the increase in costs, then this would represent an improvement in productive efficiency. Productive efficiency does not, however, consider reallocation of resources between different types of interventions across a range of diseases, such as whether breast screening or public access defibrillation is a better use of scarce resources. The optimal use of resources in this broader context is called allocative efficiency, which aims to achieve the right mixture of healthcare programmes to maximise the health of society.⁽³³⁸⁾

The prevailing approach to cost effectiveness analysis in healthcare primarily addresses decisions relating to technical and productive efficiency by comparing the incremental costs and benefits of a prospective new intervention with current practice.⁽³³⁹⁾ For instance in the analysis of the cost effectiveness of extending the age range of breast screening to 69 years the primary comparator is the existing programme that screens women to the age of 64. Where the new intervention is being introduced for the first time within a health system, as

with screening for atrial fibrillation, the primary comparator is no screening, where AF cases are detected incidentally during other investigations or when people present with symptoms of the disease. Limiting the analysis to direct comparators for the provision of a given intervention provides decision makers with important information on the value proposition of the new intervention compared with the existing standard of care for the production of a given health outcome, be it a reduction in AF strokes or breast cancer mortality. However, in the general case where the existing standard of care is not strongly dominated by the new intervention, there is rarely any consideration given to the fact that its introduction will require disinvestment in some other health sector or disease area funded from the same budget.⁽³⁴⁰⁾ To do this would require knowledge of which currently funded programmes would have to be curtailed in order to introduce a new intervention. However, at present the cost effectiveness of the existing standard of care is not systematically re-evaluated as part of the process of evaluating new technologies. Therefore, although an economic analysis may show that incremental changes are better than the status quo, this does not imply that they are optimal. Generalised cost effectiveness analysis may provide a means of tackling some of these wider issues by comparing both new and existing interventions with reference to a base case of doing nothing, thereby allowing for an analysis of the allocative efficiency of different sets of interventions.

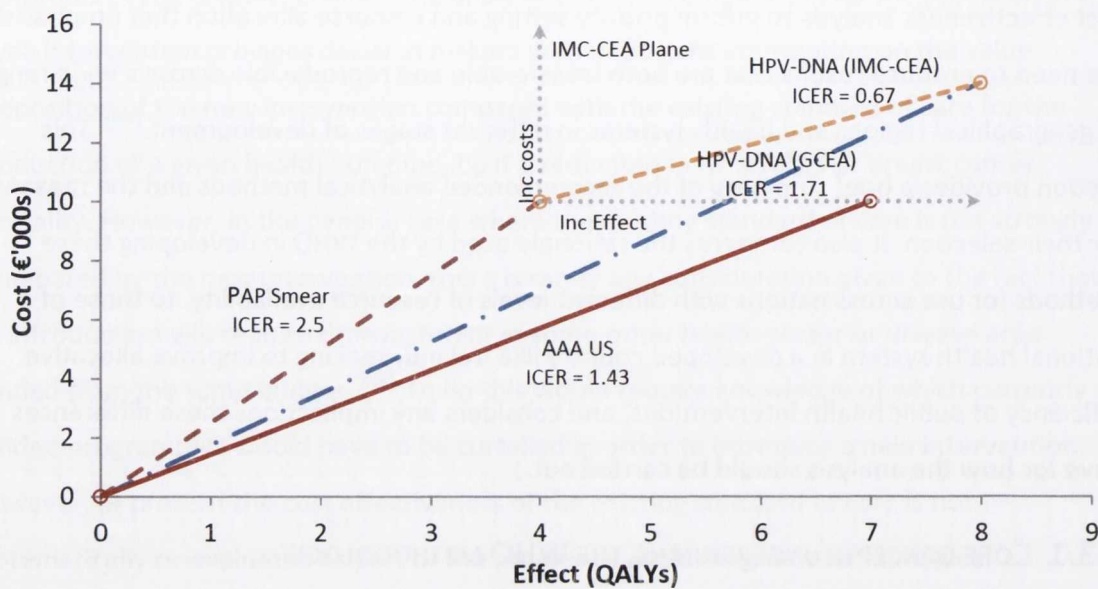
5.3 WHO APPROACH TO GENERALISED COST EFFECTIVENESS ANALYSIS

In 2003 the World Health Organisation (WHO) published a guide for conducting generalised cost effectiveness analysis to inform priority setting and resource allocation that emphasises the need to produce results that are both transferable and reproducible across a wide range of geographical regions and health systems in different stages of development.⁽³⁴⁰⁾ This section provides a brief summary of the recommended analytical methods and the reasons for their selection. It also compares the rationale used by the WHO in developing these methods for use across nations with different levels of resource availability, to those of a national health system in a developed country like Ireland, seeking to improve allocative efficiency of public health interventions, and considers any implications these differences have for how the analysis should be carried out.

5.3.1 CORE CONCEPTS UNDERPINNING THE WHO METHODOLOGY

Generalised cost effectiveness analysis (GCEA) seeks to identify what interventions would be implemented if decision makers were free to start afresh and allocate resources across all potential interventions within a particular area. In reality the ability to do this is inhibited by a number of factors, such as prior commitments to continue funding existing interventions, systemic difficulties in reallocating staff or capital resources, and political or societal resistance to the withdrawal of certain services. Conventional cost effectiveness analysis operates within these boundaries by performing what has been termed 'intervention-mix constrained' cost effectiveness analysis (IMC-CEA), which is constrained insofar as it is conducted with reference to the existing standard of care arrived at through historical decision making about the allocation of resources.⁽³⁴⁰⁾ While this approach successfully addresses narrowly defined questions of relevance in specific contexts, it fails to identify and capitalise on opportunities to increase the overall health gain at a population level by replacing existing interventions with more cost effective ones. This is presented in the hypothetical example shown in Figure 5.1, which, like all such examples in this chapter, is devised using arbitrary estimates of both costs and effects in order to illustrate the point.

FIGURE 5.1 HYPOTHETICAL EXAMPLE OF APPLICATION OF GENERALISED COST EFFECTIVENESS ANALYSIS



Here fictitious incremental cost effectiveness ratios (ICERs) are used for two methods of screening for cervical cancer (the Papanicolaou [PAP] test and HPV DNA testing) and ultrasound (US) screening for abdominal aortic aneurysms (AAA). If the PAP smear was the best available test for cervical cancer when the programme was first introduced it would have been compared to a comparator of no screening, giving an ICER of, say, €2,500/QALY. Decades later decision makers may be faced with separate proposals advocating changing from PAP to HPV DNA testing for cervical screening and calling for the introduction of a new AAA screening programme. At present, these would likely be evaluated separately compared to the current standard of care in each area, per the IMC-CEA approach. On completion of the analyses the decision maker would be informed that the marginal cost of each QALY gained by introducing HPV DNA testing and US screening for AAA are €670 and €1,430, respectively. However, when all competing alternatives are compared to the null comparator of doing nothing, per the GCEA approach, it shows that although switching from PAP to HPV DNA testing will improve the (productive) efficiency of cervical screening, this intervention is still less cost-effective than ultrasound screening for AAA (ICERs of 1,710/QALY and €1,430/QALY, respectively). If both were to be funded from the same

budget and decision makers were free to reallocate all resources then AAA screening should be given priority, something that would not be apparent from conventional IMC-CEA analysis. This is because the analysis of HPV DNA testing, which uses as its origin the existing standard of care, examines interventions on the IMC-CEA plane shown in Figure 5.1 and does not consider whether or not the PAP smear programme is itself cost effective.

5.3.1.1 THE NULL COMPARATOR

As shown in the preceding example, one of the main differences between GCEA and IMC-CEA is the use of the null comparator that represents the situation where none of the interventions being examined are implemented. Taken to its extreme, the null comparator should reflect population health outcomes and costs if no health interventions were ever introduced. This could then be used to estimate the maximum achievable outcomes if one were free to start afresh and replace the current mix of interventions in the most efficient way. However it is not realistic to think that a valid estimate of the null comparator on such a scale is possible, because of the complexity involved in disentangling the complex interaction of the effect of interventions that people have been exposed to throughout their lifetimes and estimating the counterfactual of these exposures.

The WHO guidelines handle this through the use of partial null comparators, which represent the counterfactual for a limited group or subset of interventions within a particular disease area that either interact with each other or are mutually exclusive. For instance in a GCEA analysis of cervical cancer screening the null comparator could include mutually exclusive options like screening using PAP smears, liquid based cytology or HPV DNA testing, as well as related interventions such as HPV vaccination in young girls, that will have an effect on subsequent screening outcomes. Interventions that are unrelated to cervical cancer, such as those for cardiovascular disease, can be excluded from the determination of the partial null comparator. By examining the area as a whole GCEA overlaps with traditional IMC-CEA analysis to an extent (e.g. in comparing the incremental effect of extending the current screening intervals) but is also provides a way of looking at the cost-effectiveness of different combinations of new and existing interventions (e.g. vaccinating girls under 15 and screening from age 25 versus vaccination and no or less

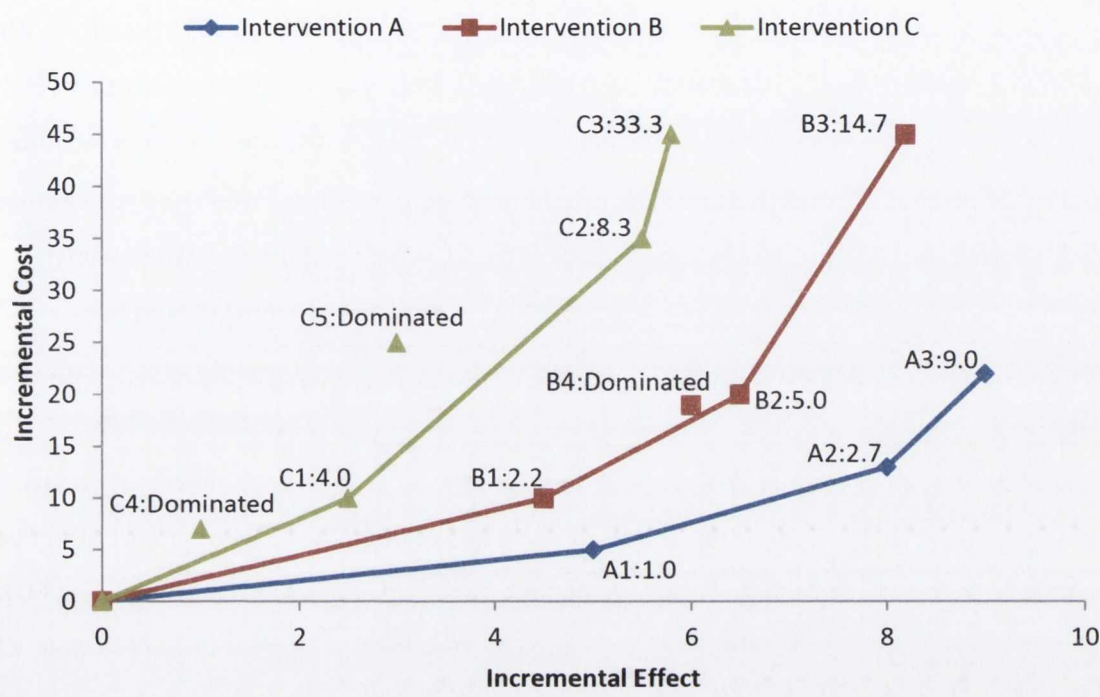
intensive screening) in order to provide policy relevant information that can be used to improve overall health outcomes.

When evaluating the null comparator it is also important to distinguish between an intervention never having been in place and an intervention being brought to an immediate halt. In some cases it may not be possible to determine the epidemiological profile of a population that never had a given intervention due to limitations in the available data, and it is necessary to instead estimate what the change would be in the current epidemiological profile if a given intervention was withdrawn. For some types of interventions this change may take a number of years to occur. The WHO guidelines recommend that all intervention are evaluated at full implementation over ten years, with all health effects that result from that ten year period of implementation being included, even if they happen much later on.⁽³⁴⁰⁾

5.3.1.2 PRESENTING THE RESULTS OF GCEA

The results of GCEA cannot be presented in the same format as traditional IMC-CEA because non-dominated strategies for different interventions may not all lie on a single frontier. Instead, a league table approach is advocated for the initial presentation of results, which lists ICERs for each intervention compared to the next best alternative. These ICERs are taken from separate analyses of mutually exclusive comparators and any weakly dominated strategies are excluded. This is illustrated in Figure 5.2.

FIGURE 5.2 EXAMPLE OF GCEA COMPARISON OF THREE DIFFERENT TYPES OF MUTAULLY EXCLUSIVE INTERVENTIONS



Here all strategies are compared to the null comparator and the incremental costs of mutually exclusive comparators are compared to the next best alternative. The league table for each of these interventions is shown in Table 5.1, which once again was created using arbitrary estimates of both costs and effects in order to illustrate the point.

TABLE 5.1 LEAGUE TABLE OF ICERS FOR ALL STRATEGIES COMPARED TO NEXT BEST OPTION

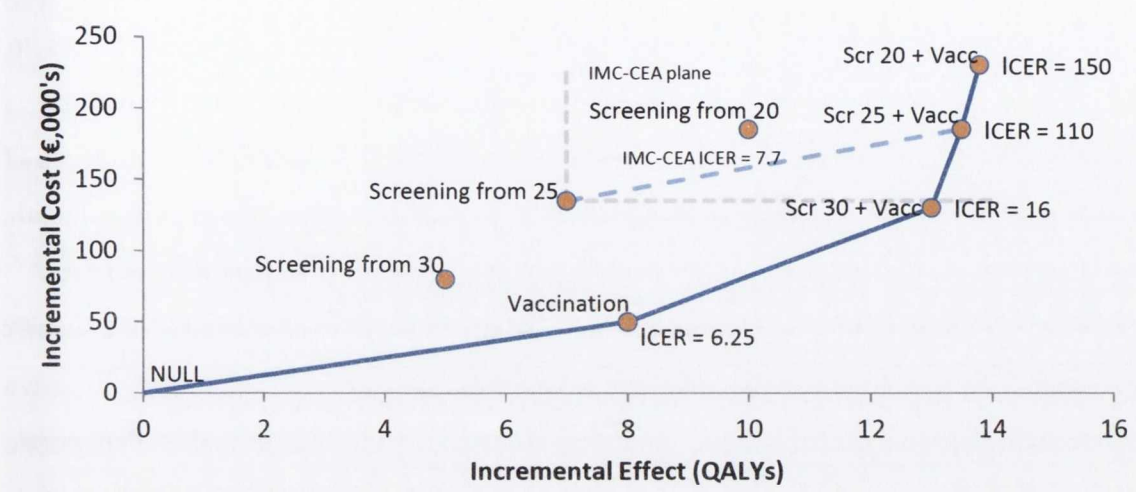
Strategy	ICER
A1	1.0
B1	2.2
A1→A2	2.7
C1	4.0
B1→B2	5.0
C1→C2	8.3
A2→A3	9.0
B2→B3	14.7
C2→C3	33.3

This provides decision makers with valuable information about the allocative efficiency of different intervention mixes as well as the expansion path for mutually exclusive strategies for a particular type of intervention. To illustrate how the results would be used in practice consider a situation where intervention C4, which could be smoking cessation using nicotine patches, is currently in place. An IMC-CEA would show that moving from C4 (nicotine patches) to C1 (say, e-cigarettes) would have an ICER of 2. However, the fact that nicotine patches do not appear on the GCEA ICER league table would indicate that this intervention itself is inefficient. The most cost effective option is A1, which could be bowel screening using FOBT. Therefore the funding used to provide C4 (nicotine patches) should be reallocated to FOBT screening (A1), as it will produce the greatest benefit for the resources consumed. The next most cost-effective option is B1, which could be selective BCG vaccination in high risk groups. If both FOBT screening and selective BCG vaccination are already in place, then if additional resources became available the next most cost effective strategy would be to replace A1 (FOBT screening) with A2 (say, bowel screening using FIT). Only once this was funded would the use of e-cigarettes for smoking cessation (strategy C1) be the most cost-effective use of additional resources. If sufficient resources were available to fund additional interventions after this then replacing B1 (selective BCG vaccination) with B2 (say, universal BCG vaccination) should be prioritised before replacing C1 (e-cigarettes) with C2 (say, sustained-release bupropion hydrochloride).

This example illustrates how GCEA can help identify current inefficiencies in the mix of interventions provided and show the most efficient way of expanding mutually exclusive strategies for a given type of intervention. It can be used to examine interventions that interact with each other on costs or benefits or both. Since the costs and benefits of two interventions that interact to a significant degree are unlikely to be additive, this requires that each mutually exclusive combination of interventions be compared to the null comparator separately. For instance a hypothetical GCEA of cervical cancer interventions that included HPV vaccination and three separate screening strategies is shown in Figure 5.3.



FIGURE 5.3 HYPOTHETICAL EXAMPLE OF GCEA ANALYSIS OF INTERVENTIONS WITH COST-EFFECTIVENESS INTERACTIONS



In this hypothetical example vaccination and screening interact on benefits but not on costs, with the incremental benefits of earlier screening being lower when the population has been immunised against persistent HPV infection. In a country that had already implemented cervical screening for women aged 25 years and over (like Ireland), an assessment of the incremental benefit of adding vaccination using the traditional IMC-CEA approach would yield an ICER of €7,700/QALY. However a GCEA analysis would show that if it were possible to reallocate all resources, the existing situation of having a screening programme for women aged 25 and over on its own is unlikely to be cost-effective. Rather the expansion pathway, which would depend on the available resources, would show that both vaccination only (ICER of €6,250/QALY) and vaccination plus screening from age 30 (ICER €16,000/QALY) are both more cost effective than vaccination plus screening from age 25, which has a far higher ICER than that obtained when the origin is taken as the current (inefficient) mix of interventions (€110,000/QALY).

5.3.1.3 INTERPRETING AND USING THE RESULTS OF CGEA

The value of generalised CEA is that it allows policymakers to identify inefficiencies in the current mix of interventions that are funded and shows what could be achieved if all resources could be reallocated. As this is not the case in most situations the results need to

be interpreted cautiously. The WHO guidelines recommend against comparing the ICERs obtained from GCEA to a willingness to pay (WTP) threshold on the basis that many of the assumptions required for the identification of such a threshold do not apply in health, such as the requirement for perfect information on the consequences of consumption choices. In the absence of this information such thresholds are generally more indicative of historical resource allocation decisions within a particular health system than any notional estimate of the benefits that society is willing to forego in order to gain one year of life in perfect health. This is a general problem when using a threshold that is based on an individual or societal valuation of a QALY, given the inherent difficulty in estimating this value outside of a specific context.⁽³⁾ For a GCEA analysis that does not necessarily reflect the existing mix of interventions within a health system, comparing ICERs to any given threshold is even more problematic. As an alternative, the WHO guidelines recommended that GCEA results are instead used to broadly categorise interventions into those that are very cost effective, moderately cost effective and not cost effective. However, there is a lack of detail on how such distinctions are to be made and the concept of categorisation, wherein groups of interventions are regarded as equal in all respects, runs counter to the incremental nature of cost effectiveness analysis. These compromises are considered acceptable on the basis that the goal of GCEA is not to have hard and fast rules for decision making, but rather to facilitate gradual streamlining of health service provision by highlighting where the biggest improvements may be made. It is also compatible with GCEA's role as an adjunct to, rather than a replacement for, IMC-CEA. Once potential inefficiencies are identified, IMC-CEA is still required to find the best way of achieving the most efficient mix of interventions from the starting point of the prevailing situation, taking into account the contextual constraints and practical challenges of reallocating resources across different interventions. This can be quite a complex task if these interventions are carried out using different types of technology or involve different types of health professionals.⁽³⁴⁰⁾

The view espoused by the WHO is, therefore, that the role of GCEA should be to provide general information on the relative cost effectiveness of a range of available interventions to inform wider debates on resource allocation priorities, rather than as a tool for making specific decisions with a known budget constraint or other ethical or political limitations.⁽³⁴⁰⁾

The latter, it is feared, will result in cost effectiveness analysis becoming more esoteric and less generalisable, with the result that it will contribute less to the public dialogue on the direction and shape of national health policy. Increasing contextualization also increases the complexity of the analysis and reduces the transferability of findings, which places a greater burden on health services and may preclude poorer nations from using GCEA to increase allocative efficiency.

5.3.1.4 EVIDENCE FOR ALLOCATIVE INEFFICIENCIES IN HEALTH CARE

The potential contribution of GCEA to improving the delivery of healthcare depends on the extent to which the set of currently implemented interventions deviates from the most allocatively efficient mix. The WHO guidelines identified three previous attempts to conduct sectoral CEA in order to produce a league table of cost effective interventions, two of which were carried out within the USA and one conducted at a global level.⁽³⁴¹⁻³⁴³⁾ None of these studies specifically used the GCEA approach, but they did find evidence of allocative inefficiency and a very diverse range of ICERs for technologies that were already in place. One of the main findings in the global analysis carried out by the World Bank was that “many of the interventions currently undertaken are very expensive ways of improving health, while many of the low cost ways of improving health are not fully funded. This implies there is considerable room to improve allocative efficiency, even if technical efficiency is also low.”^(340;343)

5.3.1.5 DISTRIBUTIVE ISSUES

A comprehensive social welfare function that could rank health interventions in terms of their overall effect on the welfare of the population would need to include distributional effects and equity preferences in the analysis of economic efficiency. This would involve identifying who bears the costs, who receives the benefits and what increase in production is associated with that benefit.⁽³⁴⁰⁾ The principle of diminishing marginal utility implies that the utility loss associated with having to contribute €100 for the provision of a health intervention would be far greater for a poor person than a rich person. Equally it means gains in health that allow people to produce more, say by being able to go back to work, are more valuable to those with fewer resources. However, because of differences in

productivity, the total increase in non-health related consumption opportunities as a result of a given gain in health are likely to decline the poorer people are. Including this type of information would require knowledge of marginal effects on health and non-health consumption for each recipient of the intervention. The issue of dealing with distributive issues like this is not confined to GCEA, and difficulties with incorporating this type of information satisfactorily and the complexity it adds to the analysis have meant that it is not generally done in conventional cost effectiveness analyses, which instead make an assumption of distributive neutrality that assigns the same value to every QALY gained, regardless of who receives it.⁽³⁴⁴⁾

Incorporating societal preferences for the distribution of health benefits could potentially be done by applying different weightings to outcomes in different groups within society in which health gains were deemed to be more or less valuable.^(345;346) As an example, it has previously been suggested that society would support positive weights being applied to health gains in children or in parents of young children, and negative weights in people whose unhealthy lifestyle contributed to the need for treatment.^(347;348) However there is considerable uncertainty about what weights should be used and a lack of consensus about whom they should be applied to. In the absence of any such weighting system, the use of QALYs tends to favour interventions in young populations with longer life expectancies, who have the potential for greater QALY gains as a result of successful treatment.

The WHO guidelines acknowledge the importance of distributive issues in cost effectiveness analysis of healthcare, but come to the conclusion that the additional complexity involved in attempting to incorporate these into a GCEA analysis would considerably increase the time and resources needed to carry out any analysis, decrease the transferability of results and make it much harder to communicate the findings to decision makers and the public. Therefore empirical methods of including distributive effect in GCEA are omitted in an effort to make the results as generalisable as possible, so that they can be used to inform the wider debate about resource allocation within health systems.⁽³⁴⁰⁾

5.3.2 APPLICATION OF GENERALISED CEA WITHIN THE IRISH HEALTH SYSTEM

The primary objective of the WHO guide to generalised cost effectiveness analysis is to provide a framework for identifying opportunities to improve allocative efficiency, which is a goal relevant to all health systems. However, they also seek to deal with issues of transferability across different regions and resource constraints in developing countries, which are not necessarily obstacles to the use of generalised cost effectiveness in Ireland. Therefore, when considering the potential role of GCEA within the Irish health system it is necessary to examine the degree of overlap between the objectives of the WHO guidelines and those of a single national health system, and consider the impact this has on how GCEA can be used to improve health outcomes.

5.3.2.1 *THE PROBLEM OF REALLOCATION OF RESOURCES*

One of the main limitations of applying the results of GCEA is an inability to freely disinvest in existing interventions and transfer that funding into other interventions. This may be because the withdrawal of an existing service may provoke strong resistance from affected patient groups, or because the resources associated with one type of intervention cannot easily be transferred to another, especially if the interventions differ in the type of healthcare personnel involved or if significant capital investment has been made in specialised equipment that cannot be used elsewhere. Another related obstacle may be the absence of a centralised budget controlled by a single decision maker. If the interventions included in a GCEA are funded through different healthcare budgets controlled by multiple decision makers with individual responsibility for their own area, the optimal mix of interventions identified in the overall analysis may not represent the best outcomes within certain sectors. For instance a GCEA may find that from a national perspective disinvestment in liver transplant and increased funding for primary care interventions to reduce alcohol consumption would increase allocative efficiency. However, from the point of view of someone in charge of secondary care services for people with liver disease, removing curative services in favour of preventative interventions would result in a decrease in health outcomes for the patient population they are responsible for.

These issues are unlikely to ever be fully resolved in the context of the overall health system, so the ultimate goal of using GCEA to bring about the optimal mix of interventions for the entire health system is unrealistic. However, there are certain sectors in which the requirements for GCEA are met to a greater extent than others. From an economic perspective, public health interventions are often those that would be underprovided by the private sector due to an underlying market failure attributable, at least in part, to the market's inability to provide public goods or handle externalities. Funding models that rely on the self-interest of individuals to pay for diagnostic or preventative treatments, whether directly or through insurance schemes, are unlikely to provide efficient and sustainable public health programmes. Rather, these generally have to be initiated and funded by the state, taking a societal view of the costs and consequences. This distinction is acknowledged by the Department of Health in the planned reform of the Irish health system outlined in the white paper on the introduction of universal health insurance.⁽¹⁰⁾ This describes how the structure and funding of the Irish health system will move from the current mix of public and private provision to a system of universal health insurance, where all citizens will be required to purchase private health insurance from competing private health insurers, who will then pay for services for their members from not-for-profit hospital trusts. As the report states, "the population-based focus of health and wellbeing services means that they do not necessarily align well with the decentralised, individualised focus of an insurance-based health system. This is particularly the case when moving towards a multi-payer model. As such, the Government proposes that health and wellbeing services would be excluded from the standard UHI package and financed via a separate Health and Wellbeing Fund."⁽¹⁰⁾ This fund will be used to provide screening and immunisation programmes and other public health interventions. Given these circumstances, public health is arguably the area where GCEA has the best opportunity to make a positive impact in Ireland. This is one of the few areas in health that will have a single decision maker who is capable of taking an overall societal perspective and centrally coordinated service provision that allows for direct control over the degree of investment and disinvestment in particular programmes across different disease areas. It will also have a known, relatively fixed budget with which to fund the basket of services deemed to be in the best interest of society.

5.3.2.2 SUSTAINABILITY, GENERALISABILITY AND METHODOLOGICAL HETEROGENEITY

A major obstacle to the use of GCEA identified by the developers of the WHO guidelines was the expertise, time and money required to conduct cost effectiveness analysis, all of which may be in short supply in developing countries in particular.⁽³⁴⁰⁾ With this in mind, recommendations throughout the report focus on minimising the complexity of the analysis and maximising the generalisability of the results. It also highlights the problem of the effect of differences in how cost effectiveness methods have developed in different countries, which have resulted in the use of different perspectives, discount rates and cost calculations. In an effort to overcome some of these limitations the WHO-CHOICE project provided estimates of unit costs and epidemiological profiles for 14 subregions in the world.⁽³⁴⁹⁾

One of the advantages of conducting GCEA within a single country like Ireland, which already has a developed health economics infrastructure, is that many of the problems of sustainability, generalisability and methodological heterogeneity are avoided. The expertise and resources required to conduct IMC-CEA are already in place, and national guidelines have been developed to standardise the reporting of cost data, use of discount rates, and other methodological issues.⁽¹⁰⁵⁾ This provides a consistent framework upon which to develop and integrate the use of GCEA in addition to IMC-CEA to improve the efficiency of health services delivery in Ireland. The sheer ambition of the WHO guidelines in attempting to develop a GCEA framework that could be used internationally is both admirable and worthwhile. From a global perspective improving allocative efficiency by identifying opportunities to replace relatively expensive ways of improving health with more efficient ones represents perhaps the best opportunity to significantly improve outcomes in the short term. Considering the vast array of health systems in different stages of development, it seems very likely that many such opportunities exist. However, while providing what is conceptually a good framework, the pragmatic challenges that exist in relation to this broad approach to GCEA may well be the rock that the WHO-CHOICE approach has foundered upon.

Included among these practical challenges is the fact that, within specific countries, both the implementability and credibility of GCEA is improved by using established methodologies

and contextualised data.^(350;351) Failure to do this, by using different methods and regional data from a number of different countries, can undermine confidence in the results. Decision makers are also more likely to support the use of GCEA where there is a high probability of being able to implement the changes it recommends, rather than facing a situation where immediate disinvestment in particular interventions is not a realistic option. This issue overlaps to some extent with the resource reallocation issues outlined in the preceding section, but also encompasses wider issues about the feasibility of change in respect of preventative interventions. It is likely that there would be considerable difficulty in trying to bring about improvements in allocative efficiency that involved a calculated decision to reduce health outcomes within an identifiable patient group, in order to redirect resources towards a subpopulation that is not readily visible. As well as generating strong public and political resistance, there may also be legal or ethical impediments to such a move. The difficulty in giving adequate weight to the opportunity cost within an unknown, silent, cohort as a result of investing in interventions for a known, vocal, patient population are not limited to GCEA specifically, but are likely to be a recurring feature of any attempt to improve allocative efficiency.

This thesis proposes a more targeted use of GCEA than the WHO approach, limited to the set of public health interventions that are initiated at the behest of the state to improve population health outcomes. While Irish national guidelines recommend that cost effectiveness analysis should primarily be carried out from the perspective of the health service, GCEA should adopt a societal perspective that includes all costs and benefits regardless of who they fall on, and the resources used should be valued as the opportunity cost to society of not being able to allocate them to the next best use, which wouldn't necessarily have to be in the production of health.^(105;340) The use of this broader perspective is particularly appropriate in GCEA, which seeks to identify what the overall mix of interventions should be if we were free to start again and recreate the health service. As such it represents an attempt to quantify the desirability of different states of affairs from an ex-ante position of not knowing whether or not one will stand to benefit or lose out from any particular decision, while recognising that resource allocation in health will displace other worthwhile activities. As Gold et al. put it, "the societal perspective does not

represent the situation from the viewpoint of particular agents in society, but it is the only perspective that never counts as a gain what is really someone else's loss".⁽⁴⁾ For pragmatic reasons it may be necessary to limit the costs and benefits that are included from the societal perspective due to the unavailability of data or to limit the complexity of the analysis. Any decisions to do so must be made following careful consideration of the potential effect of these omissions on the results of the analysis.

The WHO guidelines use disability adjusted life years (DALYs) as the primary outcome measure in GCEA and recommend that others do so too for the purposes of comparability.⁽³⁴⁰⁾ However they recognise that quality adjusted life years (QALYs) provide an alternative time-based measure of health that combines changes in the duration of life with changes in health related quality of life. In this GCEA analysis QALY outcomes are preferred, in order to ensure compatibility with the existing IMC-CEA methodology, which is an important concern given that GCEA and IMC-CEA are complementary activities with a high degree of overlap. Estimating the potential impact of using QALYs rather than DALYs requires consideration of the fundamental differences between the two outcome measures. One of the main ways in which they deviate from each other is in how utility weights for different diseases are calculated. DALYs tend to use a consistent set of weights developed by a panel of experts that are applied equally across all settings, while QALY weights are generally obtained from particular populations or groups of patients, and are therefore more context specific.⁽³⁵²⁾ Although the use of standard weights has benefits in terms of transferability of results, this approach has been criticised for failing to take account of social, cultural and environmental factors that can greatly affect the quality of life of people with a given disease or disability.⁽³⁵³⁾ Unlike the WHO approach, use of GCEA in the manner proposed in this thesis does not involve international comparisons, so the use of QALY outcomes is preferable. The other major contributor to differences in results obtained from QALY and DALY calculations is the use of age weights in the latter that attributes less value to years of life lived at younger and older ages than those lived in between.⁽³⁵²⁾ Although recommended in the WHO GCEA guidelines, it is something that has proved controversial and is not routinely done as part of QALY calculations for IMC-CEA in Ireland or

elsewhere.^(105;340) Therefore to ensure consistency in the methodological approach, the use of QALY outcomes is more appropriate for country-specific GCEA.

5.3.2.3 *DEFINING THE NULL COMPARATOR*

The null comparator is typically defined in relation to a set of interventions for a given disease area. Previous examples of this in the past have included malaria, HIV and breast cancer.⁽³⁵⁴⁻³⁵⁶⁾ Rather than focusing on a specific disease, GCEA is applied within the area of public health, which can encompass a broad range of different illnesses. One of the effects of this is to reduce, but not eliminate, the amount of interaction between different strategies, thereby simplifying the analysis. For instance, in a GCEA of malaria treatment there will almost certainly be a high level of interaction when combining strategies, since all interventions seek to affect the same outcome. However for a GCEA of public health programmes aimed at different diseases within the same population, such as screening for breast or colorectal cancer, the degree of interaction on costs or benefits is likely to be lower. There may still be instances where interaction occurs between non-mutually exclusive interventions, such as the previously described case of HPV vaccination and cervical cancer screening, or smoking cessation interventions and lung cancer screening. Attempting to deal with such interaction introduces further uncertainty in to the analysis. In general the combined effect of related interventions is unlikely to be additive, so multiplicative models are often used to estimate the effect of these interventions together, or for back-adjusting to arrive at the counterfactual when both interventions are currently in place.⁽³⁴⁰⁾ However this may require a number of untested assumptions to be made, which poses a threat to external validity. Therefore limiting the use of GCEA to public health interventions, where the level of interaction is far lower, decreases the amount of certainty about the cost effectiveness of different mixes of interventions.

As described earlier (Section 5.3.1.1), when estimating the null comparator it is sometimes difficult to ascertain the likely effect of an existing intervention never having been implemented, so it may be necessary to instead estimate the effect of that intervention being stopped forthwith. For certain types of interventions, the effects of the withdrawn programme may be present in the epidemiological profile of the population for some time

after they are halted. This is particularly true for the type of preventative interventions that are common in public health. One way of minimising the impact of this in the cost effectiveness analysis is to use longitudinal cohort models rather than cross sectional population models. By taking a cohort of previously untreated people and following them over time, the estimated incremental benefits and costs compared to a comparable treated cohort can be obtained without the need to account for the lingering effects of a withdrawn intervention within the overall population. To illustrate this take the example of estimating the counterfactual of breast screening for women aged 50 to 64 years. If this was stopped immediately then the impact of screening on breast cancer incidence would still be observable in the screening population for some years to come, and a cross sectional population model of all women over 50 years would have to take this into account. However, if instead the analysis compares costs and outcomes by simulating a longitudinal cohort of women aged 50 who have never been screened and a similar cohort who did go on to be screened over a given time horizon, then the need to account for the impact of stopping screening on those within the population who are older than the modeled cohort is avoided. Depending on the needs of the decision maker, it may still be useful to estimate the residual impact of withdrawn interventions within the overall population if a specific course of action is being considered. This can be done using a population model within the IMC-CEA framework, but is not necessary for GCEA to achieve its objective of identifying the optimal mix of interventions if all resources could be reallocated.

5.3.2.4 PROPOSED ROLE OF GCEA WITHIN THE IRISH HEALTH SYSTEM

GCEA has the potential to address one of the main shortcomings of conventional cost effectiveness analysis by identifying opportunities to improve allocative efficiency in health service delivery. The broad based approach outlined in the WHO guidelines focuses on generalisability and the application of GCEA within specific disease areas. This thesis describes a GCEA approach that is tailored to the needs of a health system in a developed country that already uses CEA information to guide decision making about the introduction of new treatments. It also identifies public health as an appropriate area within which to introduce GCEA, due to the greater degree of centralised control over which interventions are provided and to what extent. Tailoring the approach to a single country allows for fewer

compromises to have to be made in terms of the complexity and level of contextualisation of the analysis, which increases the relevance and applicability of the results within the health system in which they are intended to be used.

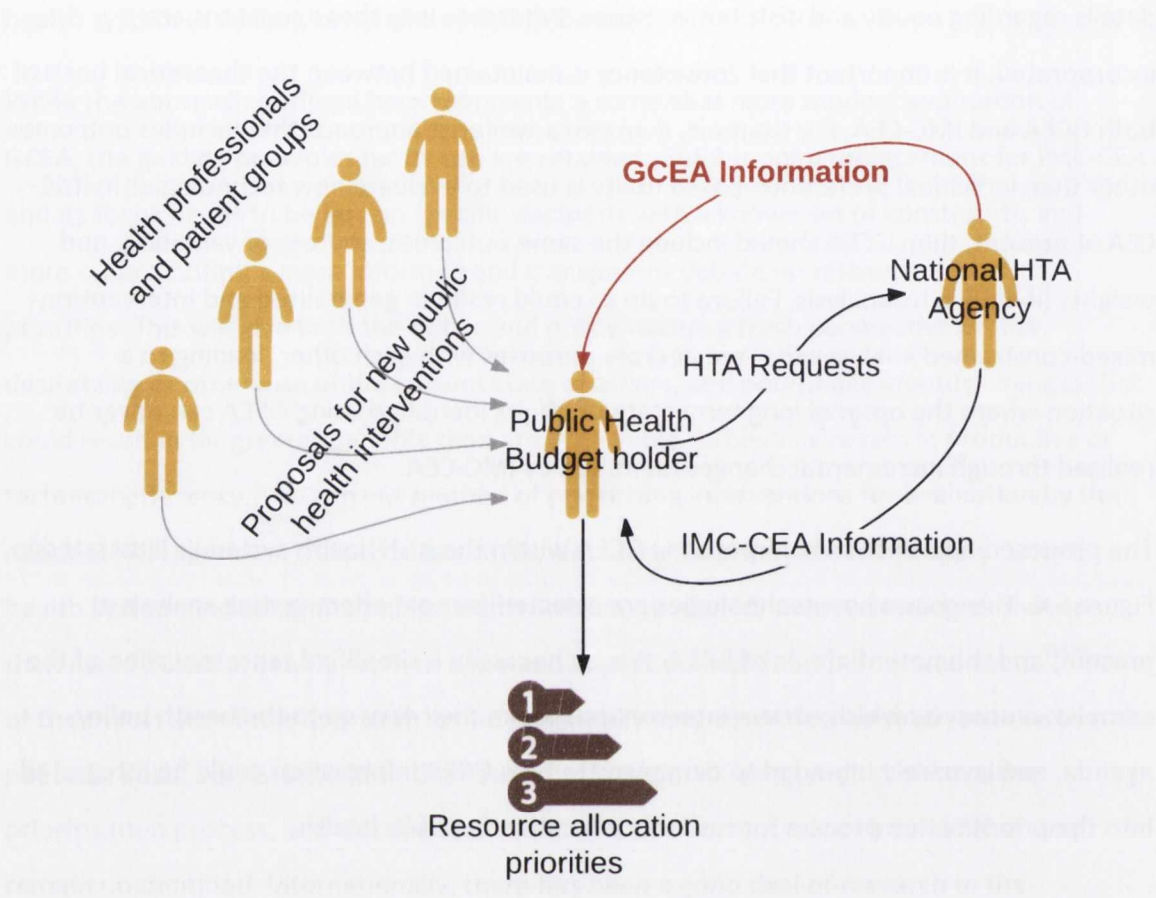
While the approach outlined here represents a somewhat more modest application of GCEA, the guiding principles for its use are retained. GCEA is not a replacement for IMC-CEA and its focus needs to be less on specific decisions with a known set of constraints, and more on promoting a more informed and transparent debate on resource allocation priorities. This will give both the public and policymakers a fresh perspective on the desirability or otherwise of the current state of affairs, and potentially identify changes that could result in far greater benefits than are achievable through increases in productive or technical efficiency. The current method of prioritising interventions for evaluation by the national HTA agency in Ireland relies on key decision makers within the publicly funded health system, including the public health division, to identify new technologies that are then rated based primarily on their expected impact on health outcomes and costs.⁽³⁵⁷⁾ One of the main risks of this approach is that potentially very cost effective interventions that do not have vocal advocates within the health profession risk being excluded from the prioritisation process, and existing inefficiencies in the current mix of intervention may remain unidentified. Internationally, there has been a good deal of research in the development of methods to identify opportunities for disinvestment, but it remains an intractable problem.^(358;359) The most common approach thus far is to try to identify obsolete technologies which have been directly superseded by newer innovations or interventions that have received negative recommendations in clinical guidelines.⁽³⁶⁰⁾ GCEA provides greater scope to identify inefficient interventions that haven't necessarily been rendered obsolete, by focusing on groups of interventions in a particular area rather than specific technologies. This is one of the key findings of a recent study aimed at finding ways to advance the emerging field of disinvestment, which highlighted the difficulties in trying to assess the appropriate role of technologies in isolation from the broader pathway of care that includes other related technologies.⁽³⁵⁹⁾

The primary benefit of the type of country-specific GCEA described in this thesis is therefore that it addresses many of the pragmatic challenges in improving allocative efficiency,

without undermining the validity of the conceptual framework outlined in the WHO guidelines. However, there remains a good deal of ambiguity in relation to some of the finer details regarding equity and distributive issues. Whatever way these concerns are incorporated, it is important that consistency is maintained between the theoretical basis of both GCEA and IMC-CEA. For example, if an extra-welfarist approach that includes outcomes other than individual preference-based utility is used to evaluate new technologies in IMC-CEA at present, then GCEA should include the same outcomes, sources of valuation, and weights (if any) in its analysis. Failure to do so could result in generalised and intervention-mixed-constrained analyses that are at cross purposes with each other, leading to a situation where the optimal long term state of affairs identified using GCEA can never be realised through incremental changes identified by IMC-CEA.

The proposed approach to incorporating GCEA within the Irish health system is illustrated in Figure 5.4. This shows how technologies are selected for cost effectiveness analysis at present, and the potential role of GCEA. It is by necessity a simplified representation of the complex process by which certain interventions make their way on to the health policy agenda, and is merely intended to demonstrate how GCEA information could be integrated into the prioritisation process for resource allocation in public health.

FIGURE 5.4 ROLE OF GCEA IN INFORMING THE DEBATE ON RESOURCE ALLOCATION IN PUBLIC HEALTH



At present, proposals for new public health interventions originate from a wide range of sources, including patient advocacy groups, health service managers at regional and national level, and clinicians working in specific sectors of the health system. Support for these proposals can be increased through public awareness campaigns, political lobbying or as a result of high profile incidents that highlight the need for improving services within a particular area. Once a proposal is being given serious consideration by the budget holder, a cost-effectiveness analysis may be requested if it is felt that there is a need for additional information on the relationship between costs and benefits. The type of analysis carried out at this point is generally an IMC-CEA, which compares the proposed intervention to the current standard of care to find out if introducing it would result in an improvement in technical or productive efficiency. This information is then used along with other important factors to decide on resource allocation priorities.

What is lacking in this current process is a mechanism for systematically identifying opportunities for improving allocative efficiency. While there may be a certain level of awareness that particular interventions are probably of relatively low value, unless there is evidence of harms or an international consensus that a given intervention no longer represents best practice, it is unlikely that disinvestment would be actively considered without a sectoral cost effectiveness analysis showing the potential increase in health outcomes achievable if resources could be reallocated. GCEA would therefore allow a national HTA agency to close the loop in regard to the contribution of cost effectiveness analysis to resource allocation, by contributing valuable information at both ends of the process, helping to identify the most desirable state of affairs (GCEA) as well as the optimal path to achieving it (IMC-CEA). This would be an incremental process, with a more complete picture being built up over time as additional interventions were added. The work required to do this would undoubtedly require further resources, but given the high level of overlap between IMC-CEA and GCEA there are likely to be opportunities to leverage one off the other in order to minimise the additional workload. It is also important that everyone involved is aware of the required time frame and understands that use of GCEA is not a quick fix. If IMC-CEA is the engine that drives efficiency improvements in the health system, then GCEA acts as a rudder, ensuring that all our efforts are ultimately directed towards the long term goal of achieving the mix of interventions that optimises health outcomes within the population served.

5.4 GENERALISED CEA OF PUBLIC HEALTH INTERVENTIONS IN IRELAND

5.4.1 INTRODUCTION

As outlined in the previous sections, the principal advantage of GCEA is that it shows what could be achieved if one were free to start over and reallocate all resources anew. The ability to do this is almost always curtailed in practice, but there are some areas of the health system, such as public health, that are more amenable to disinvestment and reinvestment of resources than others. However, methodological issues relating to the use of GCEA within a single sector that treats a broad range of diseases, rather than for a related set of interventions for a particular disease area, has not been examined previously. The objective of this section is to conduct a proof of concept analysis to examine if and how this information can contribute to a more informed debate on resource allocation priorities, using the three public health interventions evaluated as part of this thesis, all of which are either already implemented or under active consideration by decision makers in Ireland.

5.4.2 METHODS

5.4.2.1 INTERVENTIONS

Details of how each of the cost effectiveness analyses were carried out were reported previously (see Chapters 2 – 4). There were two mutually exclusive comparators within breast cancer screening, which were the existing programme for women aged 50 to 64 and the expanded programme for women aged 50 to 69. In the evaluation of atrial fibrillation (AF) screening a sensitivity analysis was carried out that included 30 potential strategies based on different combinations of start ages and screening intervals. Only strategies that involve annual or biennial screening are included in the generalised CEA. This was done to limit the amount of comparators for this intervention to those that were considered the most realistic options in terms of implementation. In the context of an opportunistic screening programme involving one minute pulse palpation during a routine GP consultation, there is a danger that extended screening intervals may lead to reduced coverage due to difficulties in keeping track of patients. Longer intervals may also pose challenges for the sustainability of the programme, by making it harder for regular opportunistic pulse palpation in the target population to become ingrained in standard GP

practice. Systematic screening programmes that manage attendance through individual invitations using a register of eligible people can exercise greater control over maintaining coverage in programmes with longer screening intervals. In the generalised CEA of public access defibrillation (PAD) all comparators included in the original analysis, from the comprehensive programme outlined in the draft legislation to a scaled back scheme targeting building types with the highest incidence of cardiac arrest, are retained.

5.4.2.2 PERSPECTIVE AND OUTCOMES

The appropriate perspective for GCEA is that of society.⁽³⁴⁰⁾ Therefore all results included in this analysis are derived using a societal perspective. However, due to a lack of perfect data about the full health and non-health costs of an intervention, it is necessary in most cases to approximate the societal perspective by including the most important costs and omitting those that are unlikely to significantly affect the results, either because they are small or because they are likely to be common to the different options. As a result there are differences in the costs that were included in each of the three interventions. The PAD and AF screening analyses included all direct costs as well as the cost of care provided by family members and productivity losses, while the breast cancer analysis was the most limited as it only included productivity losses. Benefits in all three analyses were expressed in QALYs.

5.4.2.3 PARTIAL NULL COMPARATORS

The three different types of intervention selected for this proof of concept analysis were chosen on the basis of their relevance to public health decision making and the fact that the level of interaction between them on either costs or benefits was minimal, thereby simplifying the analysis. Since both PAD and AF screening would represent new departures within their disease area, routine care was the null comparator for both of these. Breast screening was first introduced in approximately half the target population in Ireland in 2000 but it was not until 2008 that screening was extended to the other half. Therefore the null comparator, which represents the breast cancer incidence and mortality rate if mammography screened had never been introduced, was estimated using data to 2007 from the half of the country that was not offered screening until 2008.

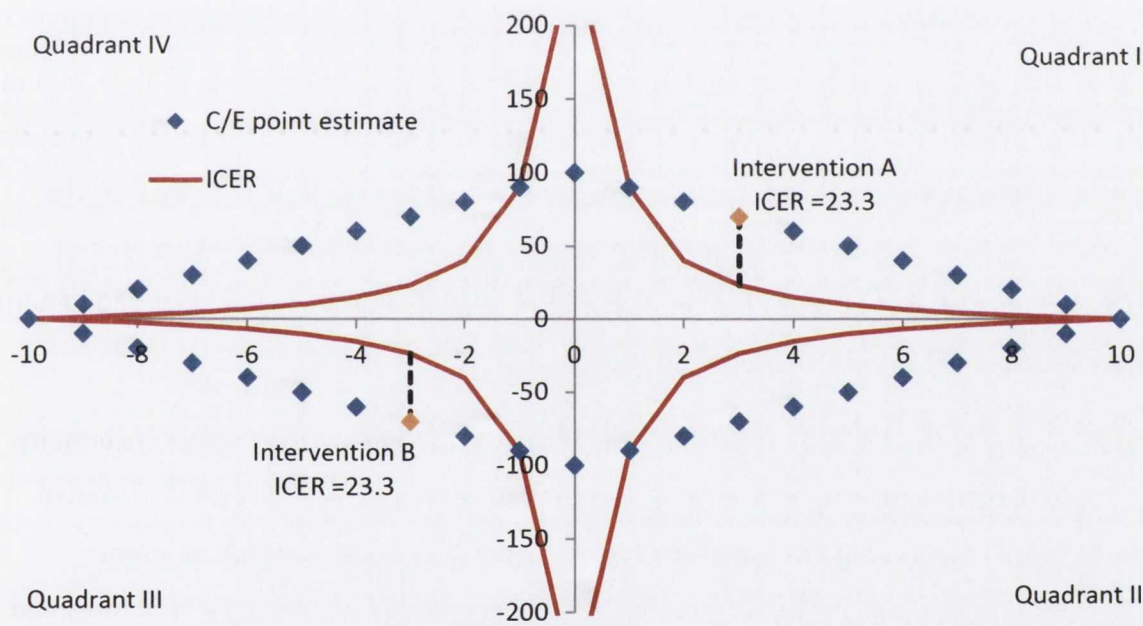
The level of interaction between these three interventions is assumed to be minimal. Since only one of them is currently in place, any potential interaction would not affect estimation of the null comparator. If interaction did occur it would be necessary to account for this in estimating the combined effect of two or more interventions being provided simultaneously. However, although both cardiac arrest and atrial fibrillation are diseases characterised by an abnormal heart rhythm, there is a lack of evidence to suggest a causal relationship. Some studies have reported that the risk of sudden cardiac death (SCD) is higher in those with a diagnosis of atrial fibrillation, but the evidence is taken from a diverse range of groups with different co-morbidities and treatment regimens, which leaves them particularly susceptible to confounding.⁽³⁶¹⁻³⁶³⁾ It has previously been suggested that the relationship between AF and SCD might be explained by a third variable, heart failure, but the evidence for a relationship between SCD and AF in patients with heart failure is inconsistent.^(362;364-367) If the risk of cardiac arrest was increased in patients with AF, perhaps as a result of AF induced ventricular tachycardia, or proarrhythmias precipitated by AF treatment, then this risk is likely to be greater for those with severe symptomatic AF, rather than the asymptomatic or minimally symptomatic cases that would be detected through screening. This means that the effect of AF screening on cardiac arrest incidence is likely to be negligible. There is also no reason to believe that the introduction of AF screening or public access defibrillation will have any effect of breast cancer incidence or outcomes.

5.4.2.4 DEALING WITH UNCERTAINTY

Cost-effectiveness acceptability curves (CEACs) for each of the three individual cost effectiveness analyses were reported previously (see sections 2.3.6.3, 3.3.7.3 and 4.3.6.3), which provides a means of communicating the level of uncertainty in relation to a particular intervention being the most cost effective option at a given willingness to pay (WTP) threshold. When examining a mix of interventions in a generalised CEA, it would be more informative to be able to show how widely the ICER estimates for each interventions are spread around the mean and the level of overlap between different estimates presented in the league table of ICERs. However, the statistical challenges associated with generating confidence intervals for an ICER are well documented, and primarily relate to the fact that since an ICER is a ratio of differences there is a chance that the incremental effect could be

zero, so the parameter does not necessarily have a finite mean or variance.⁽³⁶⁸⁾ There is also ambiguity in relation to the comparison of ICERs in different quadrants because two interventions with different costs and effects can have the same ICER. Figure 5.5 was drawn in order to illustrate this, and shows that as incremental effectiveness approaches zero, the ICER is asymptotic to the Y-axis, and a discontinuity occurs when the estimate of effect crosses the origin. It also illustrates how interventions in opposite quadrants can have the same ICER value, despite being two very different propositions from the point of view of policymaking.

FIGURE 5.5 STATISTICAL PROPERTIES OF THE ICER



The WHO guidelines recommend using a stochastic league table that provides an estimate of the probability of each intervention being included in the optimal mix of interventions for a given budget.⁽³⁴⁰⁾ This method requires an estimate of the overall budget impact of providing each intervention, something which is not easily calculable from longitudinal cohort models. A cross sectional population model that included people of all ages who would be offered the intervention would provide a more readily available estimate of the total amount of funding required to implement a given programme. However as outlined earlier, longitudinal cohort models have advantages in terms of minimising the effects of discontinuing existing interventions in the null comparator. Even if a population model was

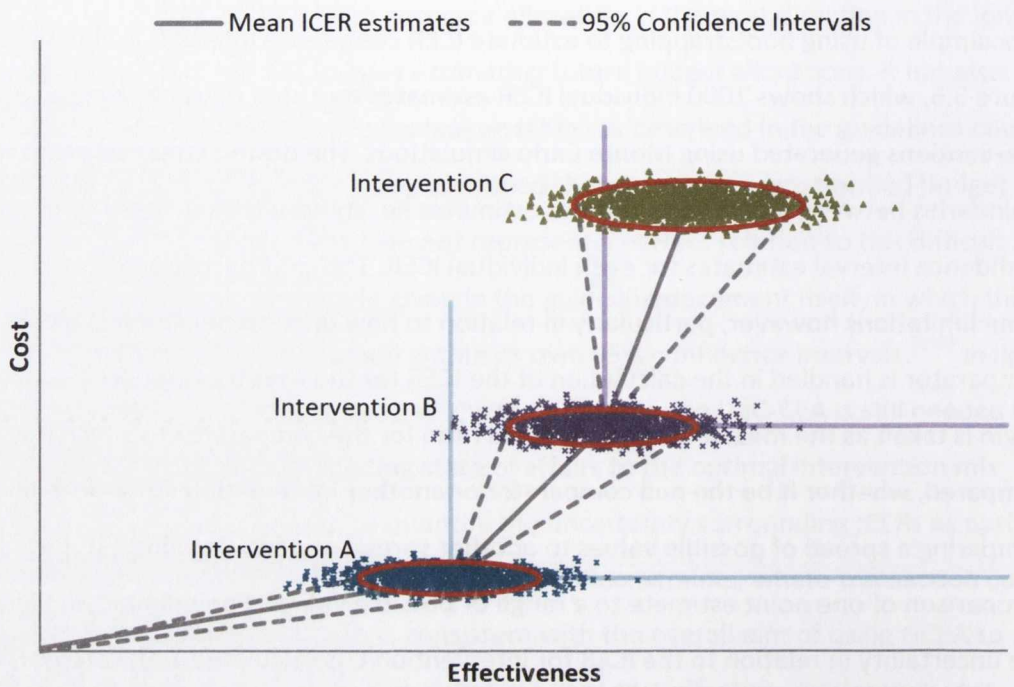
used in a generalised CEA, it would not include transaction costs and, by taking a societal perspective, would include costs that fall outside the health budget. Furthermore, given that GCEA is concerned with guiding health resource allocation in the right direction in the long term, there is also likely to be difficulties estimating future budget allocations. It has also been suggested that the use of stochastic league tables as described in the guidelines could result in optimal intervention mixes being identified that exceed any prespecified budget limit.⁽³⁶⁹⁾ That stochastic league tables do not represent a perfect solution to this difficult problem is apparent from the example given in the guideline document itself, in which the mean value of one ICER is not contained within its own 95% confidence intervals.⁽³⁴⁰⁾ In light of these challenges, and in consideration of the fact that since an IMC-CEA is still needed to find the best way to get from the existing state of affairs to the optimal intervention mix identified by GCEA, it is more useful to quantify the uncertainty surrounding ICERs as part of a context-specific IMC-CEA analysis with a known set of constraints, where transaction costs can also be factored in. This approach is consistent with the overall aim of using GCEA to broadly categorise interventions into those that are very cost effective, moderately cost effective and not cost effective, rather than attempting to surpass conventional IMC-CEA in how precisely the individual estimate is defined.

That being said, there is potential benefit in being able to estimate the relative uncertainty in the ICER estimates produced by GCEA without reference to a WTP threshold or known budget constraint, as this could aid long term prioritisation decisions when different interventions have similar ICER estimates. The requirement to avoid using a WTP threshold excludes approaches based on acceptability curves and net monetary benefits (NMB). Two approaches that do not require this information are the Fieller theorem method and nonparametric bootstrapping.⁽³⁷⁰⁾ These methods produce interpretable confidence intervals when both incremental costs and effects lie in quadrant I of the CEA plane (see Figure 5.5).^(368;370;371) Problems arise when the denominator (the difference in effect) is close enough to zero for the confidence interval to cross the Y-axis, which is often the case when comparing similar interventions. When this happens the confidence intervals are unbounded on one side because as the incremental effect approaches zero the ICER becomes arbitrarily large. In cases where the spread of ICER estimates encompasses the

origin it is impossible to construct lines containing 95% of observations, so the confidence intervals are unbounded on both sides.⁽³⁷²⁾

An example of using bootstrapping to estimate ICER confidence intervals is illustrated in Figure 5.6, which shows 1000 individual ICER estimates for three mutually exclusive interventions generated using Monte Carlo simulations. The dotted lines represent the boundaries between which 95% of these estimates lie, and can thus be used to obtain 95% confidence interval estimates for each individual ICER. This approach is associated with some limitations however, particularly in relation to how uncertainty about the base comparator is handled in the calculation of the ICER for the next best option. Usually the origin is taken as the mean cost effectiveness ratio for the comparator to which it is being compared, whether it be the null comparator or another intervention. Therefore instead of comparing a spread of possible values to another spread of possible values, it is a comparison of one point estimate to a range of possible values. For example, in Figure 5.6, the uncertainty in relation to the ICER for intervention C is calculated with reference to the mean ICER estimate for intervention B.

**FIGURE 5.6 NONPARAMETRIC BOOTSTRAPPING METHOD FOR ESTIMATING ICER
CONFIDENCE INTERVALS**



Communicating the results of this type of analysis is problematic, as interpretation of ICER ranges that cross the Y-axis is difficult, and in practice there is usually much more overlap than is shown in the example given above. Therefore it is probably unrealistic to expect decision makers who are not experts in cost effectiveness analysis to understand and use these results. Rather, what would likely be of more benefit is a way of graphically illustrating the relative uncertainty of successive interventions in the GCEA league table, even if this did not correspond with the absolute range of values that could be expected.

A proposed approach to achieving this is explored in this thesis, which is based on the assumption that the costs and benefits of all strategies that are mutually exclusive variants of the same intervention are directly correlated. This assumption would imply, for instance, that relatively high sampled values from cost distributions in the PAD analysis that resulted in a high ICER estimate for, say PAD15, would also result in high ICER estimates for each of the other PAD comparators. This may not always be the case, of course, depending on the costs and effects involved, but for closely related (mutually exclusive) interventions, it is

reasonable to assume that in general higher sampled treatment costs or higher sampled effect size estimates will make all similar interventions in a given disease area more costly or more effective. In the analysis for this thesis, normal distributions for the total costs and total benefits of each comparator are estimated based on 10,000 iterations of each decision-analysis model (AF screening, PAD and breast screening). A GCEA model is constructed that includes all interventions with mean ICER estimates in quadrant I, where total costs and effects for included interventions are defined as directly correlated multinormal distributions. Costs and effects are only correlated with other costs and effects within sets of mutually exclusive interventions for the same disease and no correlation is assumed to exist between costs and effects within interventions. The model calculates the mean and standard deviation of a single payoff (ratio of incremental costs to benefits [ICER]) based on 10,000 sampled values from the distributions of the costs and effects for all comparators. This approach reduces the probability of the difference in sampled costs and effects being less than or equal to zero, leading to more well-behaved, interpretable confidence intervals. Although these intervals are not indicative of the full range of uncertainty, they can provide a measure of the relative uncertainty between the ICERs of non-mutually exclusive interventions that is centered on the mean ICER estimate calculated using the fully probabilistic model. Whether this approach is likely to provide decision makers with more easily interpretable information on the relative uncertainty in regard to interventions in different disease areas that have comparable mean ICERs is explored.

5.4.3 RESULTS

The generalised cost effectiveness plane showing the total costs and effects within the modelled cohort for three sets of mutually exclusive public health interventions is shown in Figure 5.7.

FIGURE 5.7 GENERALISED COST EFFECTIVENESS ANALYSIS PLANE

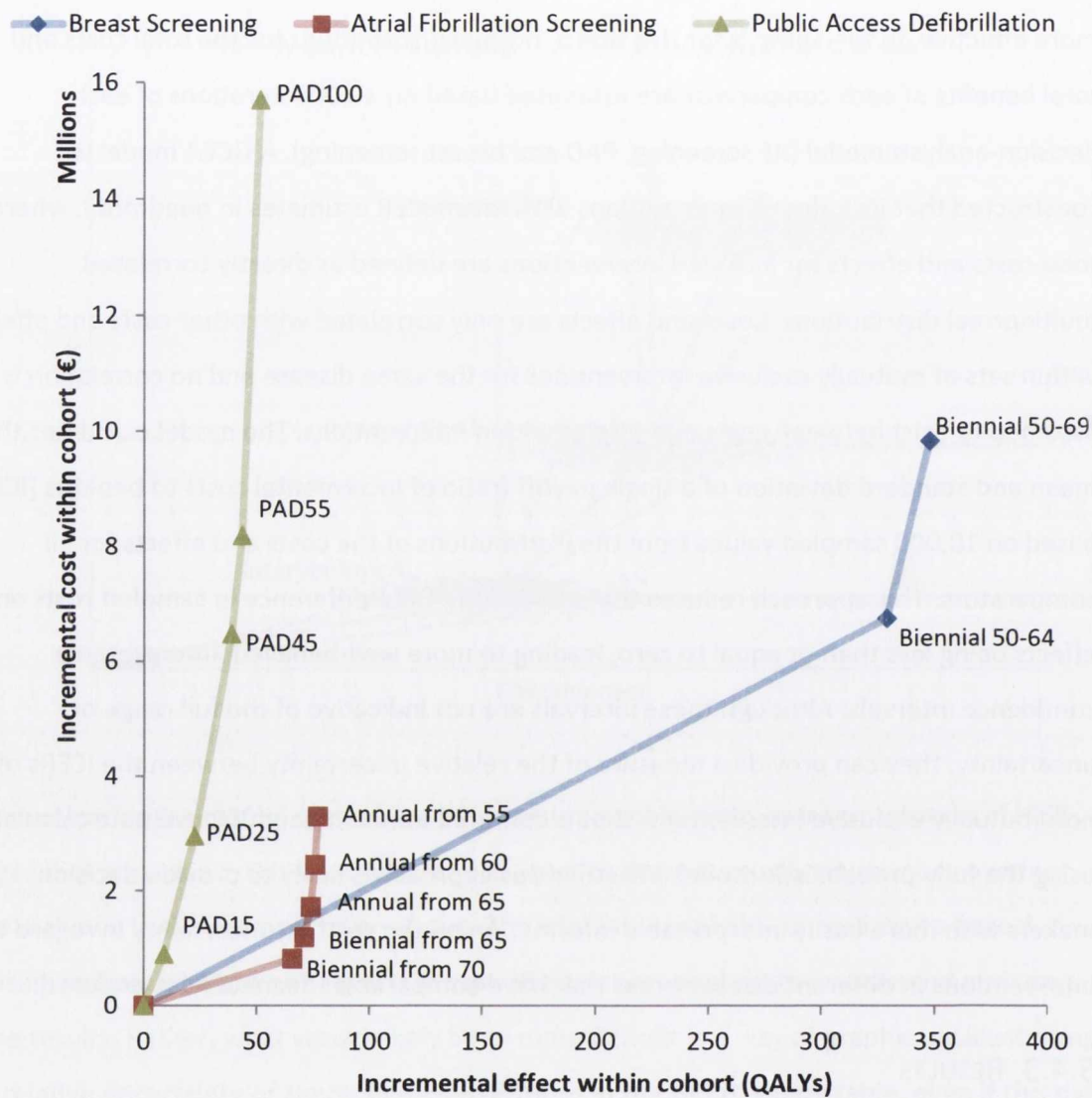


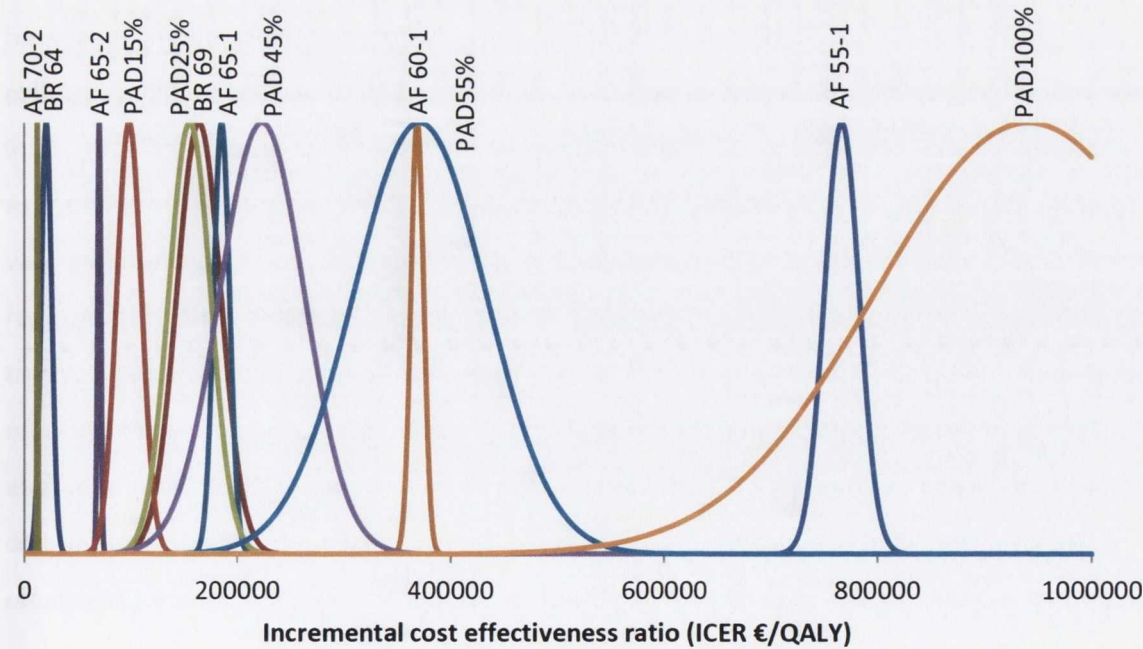
Table 5.2 shows the resultant league table of ICERs in ascending order, which can be used to examine the allocative efficiency of the current mix of interventions as well as showing the optimal expansion path for mutually exclusive interventions.

TABLE 5.2 GENERALISED COST EFFECTIVENESS ANALYSIS LEAGUE TABLE

Intervention	ICER (€/QALY)
Biennial AF screening from 70 yrs	12,158
Breast screening 50-64 yrs	20,464
Biennial AF screening from 65 yrs	70,144
PAD 15%	95,640
PAD 25%	151,243
Breast screening 50-69 yrs	160,484
Annual AF screening from 65 yrs	183,525
PAD 45%	214,108
Annual AF screening from 60 yrs	372,524
PAD 55%	373,545
Annual AF screening from 55 yrs	792,619
PAD 100%	928,450

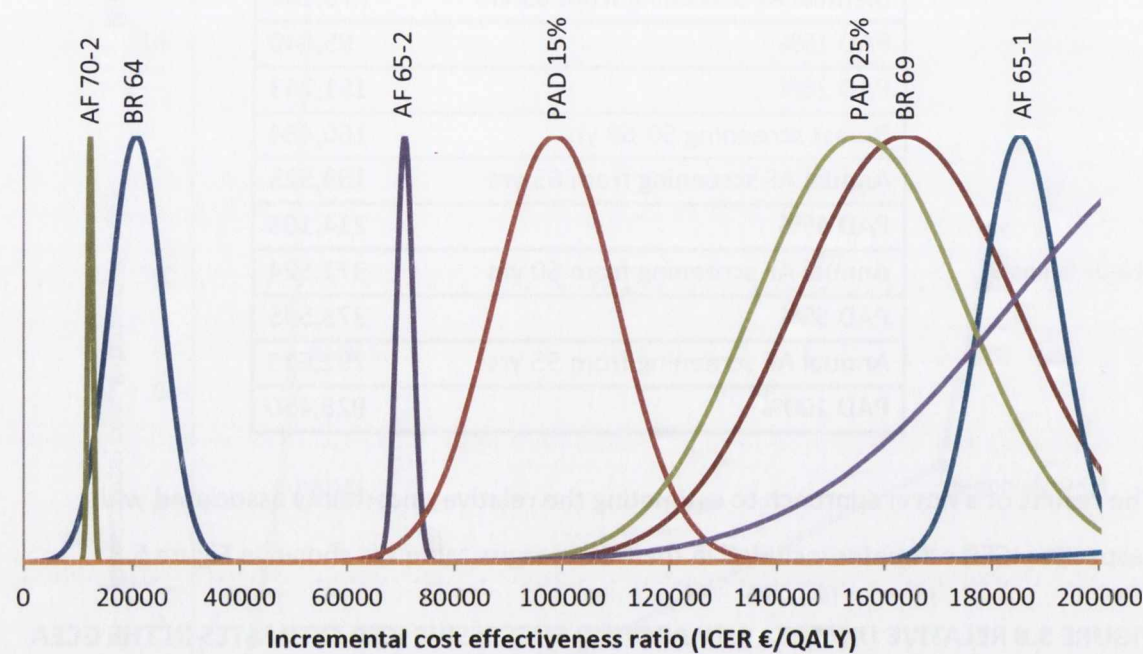
The results of a novel approach to estimating the relative uncertainty associated with respective ICER estimates included in the GCEA league table are shown in Figure 5.8.

FIGURE 5.8 RELATIVE UNCERTAINTY AROUND SUCCESSIVE ICER ESTIMATES IN THE GCEA [RANGE 0 TO 1,000,000]



As many of the included interventions are clustered at the left of Figure 5.8, the relative uncertainty over the range 0 to €200,000/QALY is shown separately for clarity (Figure 5.9).

FIGURE 5.9 RELATIVE UNCERTAINTY AROUND SUCCESSIVE ICER ESTIMATES IN THE GCEA [RANGE 0 TO 200,000]



The results of the GCEA analysis indicate that relatively low intensity AF screening (every two years from age 70) and breast screening in women aged 50 to 64 years could generally be considered very cost effective. Since breast screening is already in place in Ireland, screening for AF should be prioritised. If further resources are available after these two interventions have been funded then lowering the age range of AF screening should be considered before implementation of the most scaled back public access defibrillation programme (PAD15%). However, PAD15% is likely to represent a better use of resources than the planned extension of the age range of breast screening to 69 years. Given the similarity between the mean ICER estimate and relative uncertainty of the extension of the age range for breast screening and the extension of the PAD scheme to include retail stores and public administration buildings (PAD25%), other factors are likely to influence which of these would be considered a higher priority.

5.5 DISCUSSION

This analysis demonstrates that it is feasible to carry out generalised cost effectiveness analysis of competing interventions for different disease areas within the field of public health. The information generated allows health service policymakers to consider the allocative efficiency of the current mix of interventions and identify potential opportunities to increase health gain by replacing relatively expensive ways of generating health outcomes with more efficient alternatives. Though this proof of concept analysis was limited to three different sets of interventions, it provides information that is relevant to resource allocation decisions that are currently on the Irish public health agenda. It shows that while the existing breast screening programme is likely to cost-effective from a societal perspective, the cost of each additional QALY gained by increasing the upper age range from 64 to 69 is relatively high compared to competing alternatives and suggests that from a cost effectiveness point of view, it would be worthwhile for decision makers to consider prioritising AF screening ahead of the extension of breast screening.

The only currently implemented intervention included in the analysis (breast screening from 50 to 64 years) was found to be cost effective, so in this case achieving the optimal mix of interventions does not require that any existing programmes are withdrawn. This avoids having to deal with the logistical and political complexity associated with disinvestment in programmes identified as being of lesser value. However, it is likely that as more interventions are added to the analysis, existing inefficiencies would be identified. For example, a recently published study estimated that the current programme of universal BCG vaccination of all infants in Ireland to prevent tuberculosis is associated with an ICER in the region of €600,000/QALY compared with no vaccination.⁽³⁷³⁾ As discussed earlier, freedom to reallocate resources between programmes is a key requirement for improving allocative efficiency and despite the fact that it may be a more realistic prospect in public health than elsewhere, significant challenges remain. A major step forward in this regard would be the centralisation of population health interventions outlined in the government's white paper on universal health insurance, which would all be financed through a single health and wellbeing fund.⁽¹⁰⁾ At the moment the degree of control over which interventions are provided and at what level is limited as they are spread across different areas of the health

system. For example, breast screening is provided through the National Cancer Screening Service and the National Clinical Programme for Stroke is taking the lead on developing a national AF screening programme. While both of these are a part of the Health Services Executive, coordinating decision making across different areas with separate priorities and budgets is challenging. The PAD intervention evaluated in this analysis was intended to be based in legislation, which would mean that any subsequent plans to amend or withdraw the intervention would first have to go through the legislative process. While it would be possible to coordinate decision making across all of these areas, the changes proposed as part of the move to universal health insurance are expected to make this a far more achievable goal. The existence of a single, known, budget from which all public health interventions are funded would also provide a means of estimating how many interventions on the GCEA league table it is possible to fund, subject to additional contextualised IMC-CEA and budget impact analysis identifying the most technically efficient way to proceed.

The relative uncertainty in the estimates of successive ICERs in the GCEA league table is communicated using a novel approach that makes the assumption that overall costs within the same disease area are normally distributed and correlated across mutually exclusive interventions, as are effects. No assumptions are made about the relationship between costs and effects within interventions. This approach retains a stable mean ICER estimate but greatly narrows the spread of bootstrapped ICER estimates obtained from Monte Carlo simulation, making them less likely to include a discontinuity at the point when the interval crosses the Y-axis on the cost effectiveness plane. While the results do not therefore reflect the full level of variability associated with each ICER estimate, they do help convey the relative uncertainty of successive strategies, and are more easily interpretable. When considering the potential utility of this approach one must distinguish between hypothesis testing and parameter estimation. It has been argued that there is very limited scope for hypothesis testing to support statistical inference in cost effectiveness studies, due to the distributional problems of ICERs and an inability to define a willingness to pay threshold.⁽³⁷⁴⁾ What is more useful in the context of GCEA is to provide a means of comparing the relative uncertainty surrounding different interventions with comparable mean ICERs. Having some estimate of how much or how little overlap exists between strategies provides valuable

information when considering the practical implications of the cost effectiveness results. For example, Figure 5.8 shows that the relative uncertainty for PAD interventions is greater than that of AF screening interventions and that for all interventions the level of uncertainty in the ICER increases for successive strategies along the frontier. Similarly, Figure 5.9 shows that although the mean ICER for PAD25% is lower than that for an extended breast screening programme (BR 69), the level of overlap in their intervals means that for the purposes of prioritisation they could generally be considered equivalent. For the purposes of this exploratory analysis it is assumed that this approach can only be used for interventions that lie in quadrant I, which are those with higher costs and benefits. This is more likely to be the case in GCEA than IMC-CEA, because all strategies are evaluated with reference to the null comparator of doing nothing at all, and dominated strategies are not included in the GCEA league table. Exceptional cases where interventions are less costly and less effective than doing nothing may exist, in which case they should be handled separately rather than being included in the analysis of quadrant I interventions. While much more work remains to be done to examine if this approach provides a consistent framework for calculating the relative uncertainty of successive ICER estimates, it has clear advantages in terms of communicating the results in a way that is accessible to decision makers.

Other areas that require further work include the addition of more public health interventions to the model, in order to build up a more complete picture of what the most efficient mix of interventions would be. However, the more interventions that are included the more chance there is of having significant interaction on costs or effects and this increases both the level of complexity and uncertainty in the analysis. Public health interventions designed to treat communicable diseases may require the use of transmission models of infectivity and pose particular challenges for the estimation of the null comparator. Mechanisms must also be developed by which GCEA results can feed into long term policymaking, and strategies to facilitate disinvestment decisions are also needed. While it is undoubtedly a good thing to know which existing interventions are likely to be of relatively low value, the benefit of this knowledge is not realised until these are replaced with more cost effective interventions.

The three examples used in this proof of concept analysis also serve to illustrate some of the challenges in establishing reliable effect estimates that can be applied in a cost effectiveness analysis, even when significant levels of interaction are absent. In the case of the economic evaluation of public access defibrillation the aim of the systematic review was both to identify which comparators to include, as well as estimating individual parameter values for the model. While it successfully achieved the former aim, the latter was not so straightforward. This is because although one RCT involving static AED placement was identified, differences in the study setting limited the transferability of the results. The study only included densely populated urban areas, whereas the PAD legislation would apply to the whole of Ireland, which is a predominantly rural country. Secondly, the deployment rule used in the study (based on OHCA incidence) differed from that used in the prospective Irish programme (based on building type). In order to overcome these difficulties it was necessary to find an alternative method of estimating the impact of a national PAD programme in Ireland, which involved calculating the expected increase in people receiving bystander defibrillation prior to the arrival of an ambulance and applying survival outcomes for existing bystander defibrillation cases to these. Although this approach has lower external validity than direct transposition of RCT results, it has greater applicability since it is designed to simulate the programme as it would actually be rolled out in Ireland. This issue is highlighted in even sharper focus in the analysis of a national screening programme for atrial fibrillation. In this case RCT data was available from a comparable population (over 65's in the UK) using the exact same intervention (opportunistic screening in primary care). However, there were some important obstacles that prevented the overall odds ratio for the effect of screening being directly applied in the economic model. The first was that the study only examined once-off screening, whereas the analysis of a prospective Irish programme had to take into account multiple years of successive screening rounds. There were also some other peculiarities that limit the transferability of the results, including the fact that the baseline AF prevalence was 14% higher in the control group than the screened group (7.7% versus 6.9%). This differences in baseline prevalence is explainable in two ways; either AF was actually more common in the control group than the screened group (in which case randomisation failed), or routine practice in the control group was simply better at detecting AF than routine practice in the screened group. Either of these present

problems for the transferability of the results as each would tend to overestimate the effect of screening (since there are more cases to find in the screening group). To overcome this the effect of screening was estimated using RCT data on the diagnostic accuracy of pulse palpation followed by ECG in this group, which is a valid outcome for estimating the effect on AF detection that is not affected by changes in disease prevalence. Finally, in the third analysis (breast screening) the considerable controversy and lack of consensus regarding the clinical outcomes associated with population based screening programmes meant that evidence synthesis would fail to arrive at a reliable estimate of the impact of screening in Ireland, so an original clinical effectiveness study, based on primary data, was required. What this experience shows is that although there are detailed and widely accepted processes regarding how to conduct evidence synthesis, they do not always guarantee that one will inevitably arrive at an effect estimate that will neatly slot into the economic model. Rather, it is important to identify original ways of generating usable data, bearing in mind any limitations that might exist and the implications these may have for the policy decision being examined.

The WHO GCEA guidelines were published in 2003 and more than a decade later this approach has yet to gain a strong foothold in mainstream cost effectiveness analysis. The guideline authors report that many of the challenges were centered around the difficulties estimating the null comparator, amid claims that it may prove impossible to reliably characterise the counterfactual of a set of related interventions for a given disease outcome.⁽³⁷⁵⁾ However, the estimation of the likely impact of withdrawing an intervention is not conceptually different from estimating the potential impact of adding a new intervention, so any limitations that exist apply equally to both. It is also apparent that a great deal of contemporary cost effectiveness analysis in developed countries is designed to support reimbursement decisions for new technologies rather than focusing on opportunities to divest health systems of existing interventions that are not cost effective, which may also explain why GCEA has received relatively little attention in the wider literature despite its potential to improve allocative efficiency.

5.6 CONCLUSION

The feasibility of conducting GCEA within the area of public health is demonstrated in the analysis, albeit with the proviso that much work remains to be done in terms of quantifying the relative uncertainty of GCEA ICER estimates in a way that is relevant and communicable to decision makers, and also in adequately dealing with the potential for interaction between the costs or effects of different interventions. GCEA is particularly suited to informing decision making about the overall mix of population health interventions that should be provided by the state because these interventions and the area of public health avoid a lot of the drawbacks that have been highlighted previously, and the assumptions underpinning cost effectiveness analysis will met to a greater extent in this area than any other under planned changes to the structure of the Irish health system. This will include the existence of a single decision maker who can take an overall societal view, direct funding of these interventions from a single, relatively fixed budget, and greater freedom to invest and disinvest in preventative programmes than there is for programmes for an identifiable cohort of people with a given disease. In addition, limiting the setting to a single health system that already has an established health economic evaluation infrastructure avoids a lot of the barriers associated with the time and resources needed to carry out this work (which is already being done in Ireland per the traditional intervention-mix-constrained approach) and the need to contextualise the data for different countries.

The combination of these characteristics makes the ultimate goal of conducting GCEA that includes the entire basket of public health interventions more achievable. This would provide decision makers with valuable information that they currently lack, which is a high level view of what the optimal state of affairs would be given the best available evidence, and therefore what they should be striving towards even if they are not completely free to reallocate all resources in the short term.

6. CONCLUSIONS, POLICY IMPLICATIONS AND FUTURE WORK

This section summarises the main findings of the thesis and discusses any policy implications or opportunities for further research. Where applicable it also lists any peer reviewed publications associated with the research.

6.1 PUBLIC ACCESS DEFIBRILLATION

MAIN FINDINGS

The national public access defibrillation programme outlined in the Public Health (Availability of Defibrillators) Bill 2013 is unlikely to be a cost effective use of resources, with an incremental cost effectiveness ratio (ICER) of over €900,000/QALY compared to the next best option, and an ICER of over €300,000/QALY compared to the current standard of care. While the cost effectiveness of an Irish PAD programme is improved by targeting the deployment of defibrillators to building types with the highest incidence of cardiac arrest, even the most scaled back comparator evaluated in the analysis would not be considered cost effective at a willingness to pay (WTP) threshold of €45,000/QALY.

Targeted deployment, in conjunction with measures that lead to an increase of at least 40% in the probability that an AED would be used if a cardiac arrest occurred nearby, is likely to be cost effective. However, while it is generally assumed that an EMS-linked AED register, greater disease awareness and the presence of trained staff members would increase the chances that someone would apply a defibrillator before the arrival of EMS, there is currently no evidence to show how much of an increase could reasonably be expected.

POLICY IMPLICATIONS

Interventions based on the premise that AEDs should be considered the same as fire extinguishers and placed in all public buildings are very unlikely to be a cost effective use of resources. Rather it is preferable to concentrate on targeting AED deployment as much as possible and prioritising measures to increase utilisation. One of the reasons why the proposed legislation is unlikely to be cost effective is that many of the highest incidence locations, such as airports and train stations, already have AEDs installed. Efforts to improve utilisation, such as the development of an EMS-linked AED register, would help improve the

effectiveness of the existing network of AEDs. These measures should be implemented and evaluated first, in order to inform any future expansion of the programme.

FUTURE RESEARCH

While some studies have reported increases in the overall number of OHCA patients receiving bystander AED intervention after implementation of a PAD programme, no data is available on the increase, if any, in the probability that an individual device will be used in the event of an OHCA. It is likely that the data required to carry out this analysis is already available in areas that have implemented PAD programmes, but because this outcome is primarily of significance when modelling the expected impact of a prospective programme (as opposed to evaluating the effect of an actual programme), it is not routinely reported. The analysis would also benefit from additional years of national data on the number and location of OHCA events in Ireland, in order to produce more precise estimates of the number of OHCA events that are likely to occur in the vicinity of a public AED annually. This data will be available over the coming years from the Irish OHCA register.

PUBLICATIONS

- Moran PS, Teljeur C, Masterson S, O'Neill M, Harrington P, Ryan M. Cost-effectiveness of a national public access defibrillation programme. *Resuscitation*. 2015; 91 pp.48-55.

6.2 ATRIAL FIBRILLATION SCREENING

MAIN FINDINGS

A national opportunistic AF screening programme involving annual pulse palpation of all those aged 65 years or over attending a GP consultation for any reason, followed by ECG confirmation of an irregular pulse, is likely to be cost effective in Ireland, with an ICER of approximately €23,000/QALY compared to no screening. Sensitivity analysis found that raising the start age of screening and increasing the screening interval improved the cost effectiveness of the intervention. Estimates of the effectiveness of screening for AF detection came from one RCT that examined once-off screening in all those over 65 years. Therefore in this thesis a conservative approach was adopted for the estimation of the effectiveness of annual screening, by assuming that incident cases that were not detected during the first screen remained undetected in subsequent screening rounds.

No studies were identified that evaluated the effect of screening on stroke outcomes or mortality. In this thesis it was assumed that those with asymptomatic or mildly symptomatic AF (who would be most likely to be diagnosed through screening) had a comparable stroke risk profile as those with symptomatically diagnosed AF. A sensitivity analysis found that if the risk of stroke in screen detected cases was more than 14% lower than in clinically detected cases then screening would not be considered cost effective at a WTP threshold of €45,000/QALY.

POLICY IMPLICATIONS

The results of the cost effectiveness analysis support a recommendation contained in the national cardiovascular strategy 2010-2019, which called for a national AF screening programme to be implemented for all those aged 65 and older. However, though screening is likely to be good value for money, it would be associated with a significant increase in spending in the primary care sector, particularly in relation to the drugs budget from which any increase in oral anticoagulation medication use would be funded. The issue of the affordability of screening would therefore need to be considered by decision makers in the context of existing budget constraints within the health service, which include the lack of

provision for increased expenditure in the primary care drugs budget in the HSE Service Plan 2016.⁽³⁷⁶⁾

FUTURE RESEARCH

There are a number of potentially relevant ongoing studies that are due to report in the coming years whose findings may affect the results of this analysis. These include one RCT of AF screening using intermittent ECG recordings, which is due to report both the effect of screening on AF detection, as well as stroke outcomes in screening versus unscreened groups, in 2019. An RCT examining the effect of opportunistic screening by pulse palpation on AF detection in a Spanish primary care setting is due to report in 2016. As these results become available, it may be possible to refine the estimates for certain parameters used in the economic model, subject to an appraisal of the applicability and methodological quality of the studies.

PUBLICATIONS

- Moran PS, Flattery MJ, Teljeur C, Ryan M, Smith SM. Effectiveness of systematic screening for the detection of atrial fibrillation. *Cochrane Database of Systematic Reviews*. 2013

6.3 BREAST CANCER SCREENING

MAIN FINDINGS

The phased introduction of the Irish breast screening programme for women aged 50 to 64 years created a natural experiment, where half of the target population in Ireland was screened for a period of seven years while no screening was offered to the other half. The results of a controlled before and after study showed that the current breast screening programme for women aged 50 to 64 was associated with a 16% reduction in breast cancer mortality and an overdiagnosis rate of 19% during active screening. While the overdiagnosis estimate is broadly consistent with data from the original screening RCTs carried out over two decades ago, the mortality reduction is less than the pooled RCT estimate of 20%. A utility analysis comparing the overall benefits and harms of screening in terms of quality adjusted life years (QALYs) found that despite the level of overdiagnosis, screening was associated with a significant net benefit within the screened population.

An economic evaluation found that while the existing programme is likely to be cost effective from a societal perspective, the cost per additional QALY gained by the proposed extension of the upper age limit to 69 years exceeded conventional willingness to pay thresholds. An important consideration in the evaluation of breast screening is the decreasing background trend in breast mortality as a result of improved treatment, which decreases the benefits of earlier detection. If it is assumed that the decreasing trend in breast cancer mortality that was observed prior to the introduction of screening has been maintained since 2007, then the existing programme would not be cost effective from the perspective of the health service.

POLICY IMPLICATIONS

Ireland is currently the only Western European country that does not screen women until the age of 69 years. Therefore extending the age range would appear to be a reasonable measure that would bring Ireland in line with international practice. However, the results of a cost effectiveness analysis shows that the incremental effect of this is low compared with the incremental costs, with an ICER of over €160,000/QALY compared with the current

programme. Therefore, from the point of view of efficient resource allocation, it is likely that there are other public health interventions that represent better value for money.

FUTURE RESEARCH

It is unlikely that any new RCTs of mammography will be conducted anywhere in the coming years that could estimate the relative benefits of screening in the context of modern treatments for symptomatic cancers and improvements that have occurred in disease awareness and the organisation of services since the original mammography trials were performed.^(377;378) Therefore, the best evidence for contemporary screening programmes will continue to come from observational studies in countries that introduced screening in such a way as to create a concurrent unscreened group with which to compare breast cancer incidence and mortality. Further years of data from Irish women in the screened and unscreened groups may allow differences in incidence-based mortality to be more accurately defined. In addition, data linking cancer diagnoses to screening status is due to become available in Ireland in the near future, which would allow for an analysis of breast cancer outcomes for those who accepted an offer to attend screening.

6.4 GENERALISED COST EFFECTIVENESS ANALYSIS OF PUBLIC HEALTH INTERVENTIONS

MAIN FINDINGS

Generalised cost effectiveness analysis (GCEA) can be used in conjunction with standard (or intervention mix constrained [IMC]) cost effectiveness analysis to improve the allocative efficiency of the mix of public health interventions provided by the state, by systematically identifying opportunities for disinvestment in existing programmes that are of relatively low value. It also provides a means of prioritising different types of interventions across a range of disease areas, and shows the optimal expansion path for mutually exclusive interventions for any given budget.

Although there are some pragmatic and methodological challenges in adapting GCEA for use within a single health system that already has established processes for conducting cost effectiveness analysis to evaluate new interventions, this thesis demonstrates that these can be overcome while retaining the theoretical framework outlined in the WHO guidelines.⁽³⁴⁰⁾ Use of GCEA within the area of public health in Ireland, as opposed to its more traditional use within a particular disease area, has a number of advantages. These include centralised decision making, a known, relatively fixed budget, and greater freedom to reallocate resources than in other areas of the health service. However, while the strength of GCEA lies in its ability to show what the optimal state of affairs could be if one were not constrained by past policy decisions, in reality there may be significant transfer costs and organisational challenges associated with moving resources from one type of intervention to another. Therefore, intervention mix constrained cost effectiveness (IMC-CEA) analysis is still required to identify the best way of achieving the desired outcome given the existing situation.

POLICY IMPLICATIONS

Consideration should be given to broadening the use of cost effectiveness analysis to routinely re-evaluate existing programmes, rather than focusing exclusively on an assessment of the incremental costs and benefits of new interventions compared to the current standard of care. There is likely to be substantial benefits to acquiring this information, especially when considering the potential scale of accumulated inefficiencies in

the present system as a result of past decisions made without the benefit of the latest available evidence.

FUTURE RESEARCH

Areas for further research include the addition of other public health interventions in the analysis to build up a more complete picture about the relative cost effectiveness of competing interventions. Work also need to be carried out to evaluate the relative uncertainty of GCEA results in a way that is relevant and communicable to decision makers, as well as dealing with any interaction that may exist between the costs or effects of different public health interventions. As this was a proof of concept analysis it did not extend to tackling the problems associated with disinvesting in existing programmes. Further research is needed to examine any potential issues that are unique to disinvestment decisions, to assess the feasibility of limiting or stopping particular types of public health programmes.

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APPENDICES

APP 1.1 CONTRIBUTIONS TO EACH SECTION OF THE ANALYSIS

1. Public Access Defibrillation (PAD)

Review of clinical effectiveness

Patrick Moran designed the search strategy, conducted the search, reviewed all citations for inclusion and performed the data extraction, quality appraisal, evidence synthesis and reporting of the results. Dr Conor Teljeur independently reviewed relevant citations, appraised study quality and extracted data from included studies, in order reduce errors by cross checking results, per international best practice.

Review of cost effectiveness

Patrick Moran designed and conducted the search, reviewed all citations for inclusion and performed the data extraction, quality appraisal, evidence synthesis and reporting of the results. Dr Conor Teljeur independently reviewed relevant citations, appraised study quality and extracted data from included studies, in order reduce errors by cross checking results, per international best practice.

Cost effectiveness analysis

Patrick Moran designed, developed and implemented an original decision analysis model with which to compare the costs and benefits of different public access defibrillation (PAD) configurations, and carried out all of the analysis, interpretation and reporting of results. The majority of parameters used in the analysis were obtained by Patrick Moran from primary data sources or the scientific literature. Estimation of some parameters required access to restricted data sources or specialist expertise, these included;

- I. The number of designated places in each PAD comparator and the number of cardiac arrests occurring within 200m of designated places was estimated using geospatial analysis techniques to cross reference the locations of cardiac arrests with the locations of designated places in each PAD configuration. This was carried out jointly by the Out of Hospital Cardiac

Arrest Register (OHCAR), the HSE Health Intelligence unit and the HIQA HTA directorate.

- II. Data on average life expectancy and health-related quality of life (HRQoL) post-discharge for cardiac arrest survivors was estimated from a 2014 review of the available literature carried out by HIQA.
- III. A micro-costing exercise was carried out to estimate the costs associated with patients who survived to hospital admission but died before being admitted to a ward. This was done using data from Mr Derek Barton, Consultant in Emergency Medicine, St. Vincent's Hospital, Dublin, on the staff time and resources required for these patients, combined with average staff and equipments costs obtained from the HSE and published literature.

2. Screening for Atrial Fibrillation

Review of clinical effectiveness

Patrick Moran designed the search strategy, reviewed all citations for inclusion and performed the data extraction, quality appraisal, evidence synthesis and reporting of the results. Dr Conor Teljeur independently reviewed relevant citations, appraised study quality and extracted data from included studies, in order reduce errors by cross checking results, per international best practice. The search of Medline, Embase and the Cochrane Register of Controlled Trials was conducted by the Trial Search Coordinator for the Cochrane Heart Group.

Review of cost effectiveness

Patrick Moran designed and conducted the search, reviewed all citations for inclusion and performed the data extraction, quality appraisal, evidence synthesis and reporting of the results. Dr Patricia Harrington independently reviewed relevant citations, appraised study quality and extracted data from included studies, in order reduce errors by cross checking results, per international best practice.

Cost effectiveness analysis

Patrick Moran designed, developed and implemented an original decision analysis model with which to compare the costs and benefits of screening for atrial fibrillation, and carried out all of the analysis, interpretation and reporting of results. All parameters used in the analysis were obtained by Patrick Moran from primary

data sources or the scientific literature, with the exception of the 2015 PCRS data on the standard of care for a subset of the AF patients identified in the TILDA study, which was supplied by Prof Kathleen Bennett, Royal College of Surgeons in Ireland.

3. Breast Cancer Screening

Clinical effectiveness study

Patrick Moran conceived and designed the study, obtained the raw data from the National Cancer Registry Ireland, and carried out all of the analysis, interpretation and reporting of the results. Prof Kathleen Bennett, Royal College of Surgeons in Ireland, reviewed the statistical analysis plan and provided feedback on the suitability of the methods used.

Cost effectiveness analysis

Patrick Moran designed, developed and implemented an original decision analysis model with which to compare the costs and benefits of breast screening in two age cohorts, and carried out all of the analysis, interpretation and reporting of results. All parameters used in the analysis were obtained by Patrick Moran from primary data sources or the scientific literature.

4. Generalised Cost Effectiveness Analysis

Patrick Moran conceived the study, devised all of the adaptations to the existing theoretical framework described in the thesis, carried out all of the analysis, interpretation and reporting of the results and formulated the proposals for how generalised cost effectiveness analysis could serve as a useful adjunct to conventional cost effectiveness analysis within individual health system in developed countries.

APP 2.1 PAD SEARCH STRATEGY AND RESULTS

Pubmed		Search strings	Results
24/10/2013			
Searches	#1	(((((defibrillat*[Title/Abstract]) OR arrest[Title/Abstract]) OR ohca[Title/Abstract]) OR out of hospital[Title/Abstract]) OR cardiac arrest, out of hospital[MeSH Terms]))	102388
	#2	(((((community[Title/Abstract]) OR access[Title/Abstract]) OR public[Title/Abstract]) OR communal[Title/Abstract]) OR witness*[Title/Abstract]) OR bystander[Title/Abstract]) OR responder[Title/Abstract])	666596
	#3	#1 AND #2	4374
	#4	#3 AND Filters: Clinical Trial; Randomized Controlled Trial; Review; Systematic Reviews; Meta-Analysis; Guideline; Practice Guideline; English	995

Embase		Search strings	Results
24/10/2013			
Searches	#1	defibrillat*:ab,ti OR arrest:ab,ti OR ohca:ab,ti OR (out* NEAR/3 hospital):ab,ti OR 'out of hospital cardiac arrest'/exp	148594
	#2	community:ab,ti OR access:ab,ti OR public:ab,ti OR witness*:ab,ti OR bystander:ab,ti OR responder:ab,ti OR communal:ab,ti	796401
	#3	#1 AND #2	9731
	#4	#3 AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [public health]/lim AND [humans]/lim AND [english]/lim AND [abstracts]/lim	2486

Scopus		Search strings	Results
24/10/2013			
Searches	#1	TITLE-ABS-KEY-AUTH(public access defibrillation) AND (LIMIT-TO(DOCTYPE, "ar") OR LIMIT-TO(DOCTYPE, "re")) AND (LIMIT-TO(LANGUAGE, "English"))	216

Cochrane Library		Search strings	Results
24/10/2013			
Searches	#1	"public access defibrillation":ti,ab,kw (Word variations have been searched)	22
	#2	community:ti,ab or access:ti,ab or public:ti,ab or witness*:ti,ab or bystander:ti,ab or communal:ti,ab or responder:ti,ab	29754
	#3	defibrillat*:ti,ab or arrest:ti,ab or ohca:ti,ab or "out of hospital":ti,ab or "out-of-hospital":ti,ab	3135
	#4	MeSH descriptor: [Out-of-Hospital Cardiac Arrest] explode all trees	35
	#5	#3 or #4	3138
	#6	#2 and #5	350
	#7	#1 or #6	350
Cochrane reviews			6
Other reviews (DARE)			5
Trials			319
HTAs			2
Others (excluded)			18

ClinicalTrials.gov		Search strings	Results
07/11/2013			
Searches	#1	defibrillator OR defibrillate OR defibrillation	572

ISRCTN		Search strings	Results
07/11/2013			
Searches	#1	defibrillator OR defibrillate OR defibrillation	16

APP 2.2 DATA EXTRACTION TABLE FOR REVIEW OF PAD COST-EFFECTIVENESS LITERATURE

Study	Intervention	Analysis Details	Clinical Outcomes	Costs	Results
Nichol 2005⁽⁸⁴⁾ and 2009⁽⁸⁵⁾	CEA based on the PAD trial (CPR only versus CPR+AED)	Country: USA & Canada Discount rate: 3% Perspective: Societal Time Horizon: Lifetime Costs: 2005 USD	PAD trial results showing twice as many survivors in intervention group compared with control group	Actual cost of equipment, training and hospital treatment were taken from the PAD trial	Defibrillation by volunteers was associated with an incremental cost of \$46,700 (€44,900) per QALY
Folke 2009⁽⁸⁶⁾	Public access defibrillation scheme in Copenhagen, Denmark	Country: Denmark Discount rate: 0% Perspective: Health service Time Horizon: Lifetime Costs: 2008 USD	25% survival where AED were used versus 14% where not used, this outcome data was from the literature	Treatment costs taken from previous studies. Equipment and maintenance costs derived from local data	Incremental cost per QALY calculated for different AED placement strategies; \$33,100 (€28,900) for ERC guidelines*; \$51,100 (€44,500) for AHA guidelines**; \$79,400 for existing placement and \$135,900 (€118,500) for unguided total coverage of city
Walker 2003⁽⁸⁷⁾	Deployment of AEDs in all major airports, railway and bus stations in Scotland	Country: Scotland Discount rate: 6% for costs; 1.5% for benefits Perspective: Health service Time Horizon: Lifetime Costs: 2001 GBP	Applied survival data from out-of-hospital cardiac arrests attended in less than 3 minutes to all cases in an area with an AED	Direct costs to the health service, including AED purchase and maintenance, training and marginal treatment costs.	Total direct costs to the ambulance service of deploying 31 AEDs in 17 sites was £18,325 per year. QALY gain was 0.44, giving a cost per QALY gained of £41,146 (€62,300)

Cram 2003 B⁽⁸⁸⁾	AEDs in selected public locations such as airports, sports venues, hotels and restaurants. Sites assumed to have a 20% annual probability of an out-of-hospital cardiac arrest	Country: USA Discount rate: 3% Perspective: Societal Time Horizon: Lifetime Costs: 2002 USD	Clinical outcomes data and risk of out-of-hospital cardiac arrest events obtained from the literature	Costs from a societal perspective obtained from the literature and contact with suppliers and training providers	Outcomes were reported per site; mean annual cost was \$3,400 and QALY gain was 0.114, giving an annual cost of \$30,000 per QALY gained (€31,300)
Sund 2012⁽⁸⁹⁾	Dual dispatch of ambulance and fire services in Stockholm	Country: Sweden Discount rate: 4% Perspective: Societal Time Horizon: 10 years Costs: 2007 EUR	Clinical outcomes from SALSA trial	Equipment and treatment costs were taken from the SALSA project	16 additional lives saved and cost per life saved of €60,000
Nichol 2003⁽⁹⁰⁾	Public access defibrillation by lay responders in casinos in the US	Country: USA Discount rate: 3% Perspective: Societal Time Horizon: Lifetime Costs: 2003 USD	Relative benefit of public access defibrillation was calculated as a function of response time, based on the probability of VF rhythm and subsequent survival to discharge (from Valenzuela 2000) All survivors had ICD implantation	Equipment costs were obtained from suppliers. Training costs were based on instructor wages. Hospital and treatment costs were based on available literature.	Public access defibrillation provided by non-traditional responders in a casino setting had an incremental cost of \$56,700 (€57,900) per additional QALY. If responder wages while being trained were included this rose to over \$100,000 per QALY

Groenveld 2005 ⁽⁹¹⁾	Training unselected laypersons in CPR/defibrillation and deploying AEDs in their own home	Country: USA Discount rate: 3% Perspective: Societal Time Horizon: Lifetime Costs: 2004 USD	Survival with bystander defibrillation was twice that of bystander CPR only (from PAD trial), and four times that of no bystander CPR (assumed based on conflicting literature)	Equipment and training costs obtained from a survey of suppliers. Opportunity cost of training was set at 1/3 average US hourly wage. Literature used to cost treatment.	Cost per trainee was \$62 and each trainee yielded 2.7 quality-adjusted hours of survival, giving a cost per QALY of \$202,400. Home AED deployment increased the cost per QALY to \$2,489,700 (€2.5M).
Berger 2004 ⁽⁹²⁾	AED deployment in public high schools in the USA	Country: USA Discount rate: 3% Perspective: Societal Time Horizon: Lifetime Costs: 1999 USD	Survival to hospital admission, no description of how probability of survival was estimated	Only direct costs of equipment, training and treatment were included. Cost of personnel time, training resources were omitted	If the intervention saves 5 people over 5 years it was calculated to have an ICER of \$108,344 (€122,100) per life year gained. If it saved 10 people over 5 years the resulting ICER would be \$55,897 (€63,000)
Cram 2003 A ⁽⁹³⁾	AED deployment on commercial aircraft	Country: USA Discount rate: 3% Perspective: Societal Time Horizon: Lifetime Costs: 2003 USD	Outcome data was obtained from the literature and a small utility benefit for passive benefits (sense of security) was added	Equipment and treatment costs were taken from the literature, no training costs were included	Aircraft AED deployment increased survival to discharge from 2.1% to 16.7%, cost of AED deployment \$5million, cost per QALY gained was \$34,000

Forrer 2002 ⁽⁹⁴⁾	Police AED programme in four suburban communities in the US	Country: USA Discount rate: 0% Perspective: Police and health service Time Horizon: 7 years Costs: 1999 USD	Survival benefit was estimated based on the decreased time to first shock as a result of the intervention	Costs from the community perspective, with data taken from the 7 year cohort study	Time from call to first shock reduced by 1.8 minutes, with a resulting estimated survival benefit of 0.24 lives saved per year, giving a cost per year of life saved of \$16,060 (£19,200)
Groeneveld 2001 ⁽⁹⁵⁾	AED deployment on US commercial aircraft	Country: USA Discount rate: 3% Perspective: Societal Time Horizon: Lifetime Costs: 2001 USD	Outcome data from 36 cases of out-of-hospital cardiac arrest from American Airlines, base case estimated using data from studies with emergency medical services transport times >20 minutes	Airline costs taken from FAA and air transportation association. Medical costs from literature. Training costs calculated as employee opportunity cost.	Deploying AEDs on all commercial aircraft would save 33 additional lives annually, with an ICER of \$94,700 (£100,500). Only deploying AEDs on large commercial aircraft would save an additional 7 lives per annum with an ICER of \$35,300 (£37,400)
Foutz 2000 ⁽⁹⁶⁾	Placing AEDs in long-term care facilities (LTCF) in Cincinnati, Ohio, USA	Country: USA Discount rate: 5% Perspective: Health service Time Horizon: 4 years Costs: 1999 USD	Registry data showed 20% of out-of-hospital cardiac arrests in LTCFs were VF. Assumed that intervention would result in a survival to discharge rate of 25% of VF out-of-hospital cardiac arrests	Equipment and training costs incurred by LTCF over four years	5 additional lives saved (survival rate increased from 1.25% to 4.4%) at a cost of \$439,185, giving a cost per life saved of \$87,837 (£99,000)

Jermyn 2000⁽⁹⁷⁾	Firefighter first responder programme in an urban and rural community in Australia.	Country: Canada Discount rate: 5% Perspective: Health & fire service Horizon: 6 years Costs: 1999 USD	Authors assume an incremental survival benefit of 6% for those in VF	Cost of equipment, maintenance and instructor training included. Training costs for providers excluded.	Cost per life saved was AUS\$6,776 in urban areas and AUS\$49,274 in rural areas.
Nichol 1998⁽⁹⁸⁾	Public access defibrillation involving lay responders or police	Country: USA Discount rate: 3% Perspective: Societal Time Horizon: Lifetime Costs: 1996 USD	Outcome data taken from available literature at the time. Relative survival benefit of public access defibrillation assumed to be 1.5 (from White 1996)	Cost of AED assumed to be \$2,500, with annual training and maintenance of 10%. Treatment costs were not included as they were equal in both comparators. Future costs were also not included.	Public access defibrillation was associated with a median incremental survival of 0.7% and a median cost per additional QALY of \$44,000 (£32,600). In an urban emergency medical services system with on overall survival rate of 8%, a police AED programme was associated with a median cost of \$27,200 per additional QALY

AHA – American Heart Association; CEA – Cost-effectiveness analysis; CPR – Cardiopulmonary resuscitation; ERC – European Resuscitation Council; ICER – Incremental cost-effectiveness ratio; ICD – Implantable cardioverter defibrillator; LTCF – Long-term care facility; OHCA – Out-of-hospital cardiac arrest; PAD – Public access defibrillation; QALY – Quality-adjusted life year; VF – Ventricular fibrillation. * European Resuscitation Council (ERC) guidelines recommend placement of AED in locations with an incidence of one cardiac arrest every two years.⁽⁹⁹⁾ ** American Heart Association (AHA) guidelines recommend placement of AED in locations with an incidence of one cardiac arrest every five years.⁽¹⁰⁰⁾

APP 2.3 APPRAISAL OF STUDY QUALITY FOR INCLUDED PAD COST-EFFECTIVENESS ANALYSIS STUDIES

	Nichol 2009 ⁽⁸⁵⁾	Folke 2009 ⁽⁸⁶⁾	Walker 2003 ⁽⁸⁷⁾	Cram 2003 B ⁽⁸⁸⁾	Sund 2012 ⁽⁸⁹⁾	Nichol 2003 ⁽⁹⁰⁾	Groeneveld 2005 ⁽⁹¹⁾	Berger 2004 ⁽⁹²⁾	Cram 2003 A ⁽⁹³⁾	Forrer 2002 ⁽⁹⁴⁾	Groeneveld 2001 ⁽⁹⁵⁾	Foutz 2000 ⁽⁹⁶⁾	Jermyn 2000 ⁽⁹⁷⁾	Nichol 1998 ⁽⁹⁸⁾
Relevance														
Population	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes
Intervention	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	No	No	No
Outcomes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	No	Yes
Context	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No
Credibility														
Validation	Yes	No	No	No	No	No	No	No	No	Yes	No	No	No	No
Design	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes
Data	No	No	No	No	No	No	No	No	No	No	No	No	No	No
Analysis	Yes	No	Yes	Yes	No	Yes	No	No	Yes	No	Yes	No	No	Yes
Reporting	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes
Interpretation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Conflict of interest	No	No	No	No	No	?	?	?	No	?	?	?	?	?

For full details of the criteria used to assess relevance and credibility see: Questionnaire to assess the relevance and credibility of modelling studies for informing healthcare decision making: An ISPOR-AMCP-NPC good practice task for report⁽¹⁰¹⁾

APP 2.4 PAD ECONOMIC MODEL PARAMETERS

Parameter	Mean (95% CI)	Source
Probability of surviving to the emergency department (ED) if first treated by Emergency Medical Services (EMS)	62% (59 – 66)	Estimates of survival to emergency department, hospital admission, hospital discharge and Cerebral
Probability of surviving to the ED if first treated by bystander cardiopulmonary resuscitation (CPR)	53% (48 – 57)	Performance Category (CPC) score at discharge are based on two years of national Irish data ⁽¹¹³⁾
Probability of surviving to the ED if first treated by bystander defibrillation	46% (39 – 54)	(2012/2013) from the OHCAR register.
Probability of surviving to hospital admission, having survived to ED, if first treated by EMS	25% (20 – 31)	
Probability of surviving to hospital admission, having survived to ED, if first treated by bystander CPR	28% (23 – 33)	
Probability of surviving to hospital admission, having survived to ED, if first treated by bystander defibrillation	51% (35 – 67)	
Probability of surviving to hospital discharge, having survived to admission, if first treated by EMS	33% (20 – 47)	
Probability of surviving to hospital discharge, having survived to admission, if first treated by bystander CPR	37% (28 – 46)	
Probability of surviving to hospital discharge, having survived to admission, if first treated by bystander defibrillation	53% (36-70)	

Probability of having a Cerebral Performance Category (CPC) score of 1,2 or 3 at discharge if first treated by EMS*	CPC1: 85% (75 – 93)	
	CPC2: 13% (6 – 22)	
	CPC3: 2% (0 – 7)	
	CPC1: 80% (70 – 88)	
Probability of having a CPC score of 1,2 or 3 at discharge if first treated by bystander CPR*	CPC2: 12% (6 – 21)	
	CPC3: 8% (3 – 15)	
	CPC1: 86% (72 – 95)	
	CPC2: 14% (4 – 27)	
	CPC3: 1% (0 – 5)	
Annual survival with CPC1*	92% (90 – 94)	Data on average life expectancy and health-related
Annual survival with CPC2*	92% (90 – 94)	quality of life (HRQoL) post-discharge for cardiac
Annual survival with CPC3*	79% (77 – 82)	arrest survivors was estimated from a 2014 review of
Quality of life score for average patient prior to out-of-hospital cardiac arrest (OHCA)	0.78 (0.77 – 0.79)	the available literature carried out by the Health Information and Quality Authority. ⁽¹¹²⁾
Quality of life score for patients with a CPC score of 1 at discharge*	0.93 (0.87 – 0.97)	

Quality of life score for patients with a CPC score of 2 at discharge*	0.75 (0.66 – 0.83)	
Average quality of life score for patients with a CPC score of 3 at discharge*	0.40 (0.31 – 0.50)	
Proportion of people who have received CPR training within the last two years in Ireland	16% (14 – 19)	Taken from a 2009 national survey of cardiopulmonary resuscitation training in Ireland ⁽³⁷⁹⁾
Total CPR trained population at baseline	755,184 (652,371 – 862,030)	
Average number of public OHCA events occurring within 200 metres of an AED in the base case	145 (121 – 168)	Calculated by cross referencing the location of out-of-hospital cardiac arrest events (from OHCAR ⁽¹¹³⁾) with the location of AEDs in each public access defibrillation programme configuration (using Geodirectory data ⁽¹⁰⁸⁾) to estimate the annual number of public and residential out-of-hospital cardiac arrests likely to occur within 200m of an AED.
Average number of residential OHCA events occurring within 200 metres of an AED in the base case	320 (280 – 360)	The number of AEDs required for each comparator and the number of public and residential out-of-hospital cardiac arrest within 200m of an AED are defined as a multinormal distribution in order for them to be correlated when sampled during a Monte Carlo simulation. The geospatial analysis used to derive these estimates was carried out by
Average number of public OHCA events occurring within 200 metres of an AED in PAD15%**	165 (139 – 191)	
Average number of residential OHCA events occurring within 200 metres of an AED in PAD15%**	386 (345 – 428)	
Average number of public OHCA occurring within 200 metres of an AED in PAD20%**	165 (140 – 191)	
Average number of residential OHCA events occurring within 200 metres of an AED in PAD20%**	396 (354 – 436)	
Average number of public OHCA events occurring within 200 metres of an AED in PAD25%**	190 (162 – 217)	

Average number of residential OHCA events occurring within 200 metres of an AED in PAD25%**	495 (450 – 540)	researchers in OHCAR, the HSE Health Intelligence Unit and the Health Information and Quality Authority. ⁽¹¹²⁾
Average number of public OHCA events occurring within 200 metres of an AED in PAD45%**	221 (191 – 250)	
Average number of residential OHCA events occurring within 200 metres of an AED in PAD45%**	622 (572 – 673)	
Average number of public OHCA events occurring within 200 metres of an AED in PAD55%**	230 (201 – 261)	
Average number of residential OHCA events occurring within 200 metres of an AED in PAD55%**	659 (605 – 711)	
Average number of public OHCA events occurring within 200 metres of an AED in the PAD programme outlined in draft legislation	246 (215 – 277)	
Average number of residential OHCA events occurring within 200 metres of an AED in the PAD programme as outlined in draft legislation	718 (664 – 772)	
Total number of additional AEDs required for the PAD15% comparator**	1,878 (1,605 – 2,161)	
Total number of additional AEDs required for the PAD20% comparator**	3,145 (2,709 – 3,574)	
Total number of additional AEDs required for the PAD25% comparator**	6,779 (6,064 – 7,489)	

Total number of additional AEDs required for the PAD45% comparator**	15,340 (13,879 – 16,805)	
Total number of additional AEDs required for the PAD55% comparator**	19,596 (17,760 – 21,386)	
Total number of additional AEDs required for the PAD programme outlined in the legislation	38,395 (34,885 – 41,847)	
Probability of an OHCA patient receiving bystander defibrillation in base case	7.40%	Calculated during each replication of the model using data on the probability of cardiac arrests occurring within 200m of an AED under each modelled comparator, estimated by combining GeoDirectory ⁽¹⁰⁸⁾ data on the locations of designated places with two years of national data on the locations of cardiac arrests from the OHCAR register, along with OHCAR data on the probability of an defibrillator being used by a member of the public prior to the arrival of the emergency medical services when an arrest occurs in the vicinity of an existing AED. ^(112;113)
Probability of an OHCA patient receiving bystander CPR in base case	48.60%	
Probability of an OHCA patient receiving EMS care first in base case	44.00%	
Probability of an OHCA patient receiving bystander defibrillation in PAD15%**	8.70%	
Probability of an OHCA patient receiving bystander CPR in PAD15%**	47.60%	
Probability of an OHCA patient receiving EMS care first in PAD15%**	43.70%	
Probability of an OHCA patient receiving bystander defibrillation in PAD20%**	8.80%	
Probability of an OHCA patient receiving bystander CPR in PAD20%**	47.70%	
Probability of an OHCA patient receiving EMS care first in PAD20%**	43.60%	
Probability of an OHCA patient receiving bystander defibrillation in PAD25%**	10.50%	
Probability of an OHCA patient receiving bystander CPR in PAD25%**	46.50%	

Probability of an OHCA patient receiving EMS care first in PAD25%**	43.00%
Probability of an OHCA patient receiving bystander defibrillation in PAD45%**	12.80%
Probability of an OHCA receiving bystander CPR in PAD45%**	45.50%
Probability of an OHCA receiving EMS care first in PAD45%**	41.70%
Probability of an OHCA patient receiving bystander defibrillation in PAD55%**	13.40%
Probability of an OHCA patient receiving bystander CPR in PAD55%**	45.50%
Probability of an OHCA patient receiving EMS care first in PAD55%**	41.10%
Probability of an OHCA patient receiving bystander defibrillation in the PAD programme outlined in draft legislation	14.50%
Probability of an OHCA patient receiving bystander CPR in the PAD programme outlined in draft legislation	47.20%
Probability of an OHCA patient receiving EMS care first in the PAD programme outlined in draft legislation	38.30%
Unit cost of AED	€1,189 (973 – 1,447)
Unit cost of AED pads	€46 (38 – 57)
Unit cost of AED battery	€165 (136 – 201)
Unit cost of AED signage	€12 (10 – 15)

Calculated using data on equipment and training costs obtained from suppliers in Ireland (see Appendix 2.5) and expert opinion.^(116,117)

Unit cost of wall mounted AED storage cabinet	€134 (111 – 164)	
Lifespan of AED	8 years (6 – 10)	
Lifespan of pads	2 years (1.5 – 2.5)	
Lifespan of battery	5 years (4 – 6)	
Cost of instructor per trainee for initial training	€80 (66 – 96)	
Cost of instructor per trainee for refresher training	€50 (41 – 61)	
Duration of initial training	5 hours (4.5 – 5.5)	
Duration of refresher training	3 hours (2.6 – 3.4)	
Retraining interval	2 years (1.2 – 3.3)	
Number of trainees per AED	2 (1 - 3)	Assumption
Cost of one hour of staff time	€25 (23 – 28)	CSO average hourly labour costs ⁽¹²³⁾
Annual cost of running a national AED register	€69,259 (56,786 – 83,872)	Based on staff costs of one full time equivalent at midpoint of clerical officer grade salary scale and an average of €43,000 annual running costs for hardware, software, licensing, hosting and support, based on expert feedback and data from the Danish public access defibrillation programme. ^(112;380)
Average cost of care for patients who survive to the ED	€679 (451 – 988)	Micro-costing of resource use and staff time carried out in conjunction with Irish expert in emergency medicine. ⁽¹¹⁸⁾

Average cost of care for patients who survive to hospital admission but die in hospital	€17,911 (15,290 – 20,868)	HIPE DRG data ⁽¹¹⁹⁾
Average cost of medical care for patients who survive to hospital discharge	€22,835 (18,287 – 28,150)	
Average annual cost of medical care for patients with a CPC score of 1 at discharge*	€3,964 (3,242 – 4,786)	Average annual treatment costs for OHCA survivors with CPC score of 1 and 2 is a weighted average of the costs of the estimated proportion who receive an implantable cardioverter defibrillator (15%) and long-term treatment for coronary heart disease (85%). Costs estimated include the cost of medication, GP visits and hospital care, based on study data, inflated and converted to 2013 € per national HTA guidelines. ^(105;112;120)
Average annual cost of medical care for patients with a CPC score of 2 at discharge*	€3,964 (3,223 – 4,802)	
Average annual cost of medical care for patients with a CPC score of 3 at discharge*	€14,421 (8,220 – 23,772)	Average annual treatment costs for survivors of out-of-hospital cardiac arrest with CPC score of 3 is calculated based on the long-term treatment for coronary heart disease (inflated and converted to 2013 € per national HTA guidelines) plus the annual full time carers allowance. ^(105;120;122)

Average productivity loss associated with OHCA mortality and morbidity		€12,006 (10,236 – 14,021)	Productivity was calculated using the human capital approach based on CSO data on employment and earnings by age and gender, weighted according to the demographics of the out-of-hospital cardiac arrest population in Ireland ^(113;123)
Discount rate on future costs and benefits		5%	Per Guidelines for the Economic Evaluation of Health Technologies in Ireland ⁽¹⁰⁵⁾
VAT		23%	Standard Value Added Tax (VAT) rate in Ireland ⁽¹²⁵⁾

ED – Emergency Department; CPR – Cardiopulmonary resuscitation; AED – Automatic External Defibrillator; OHCA – Out of hospital cardiac arrest; PAD – Public access defibrillation; EMS – Emergency medical services; VAT – Value added tax

* CPC – Cerebral Performance Category (CPC 1: Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychological deficit; CPC 2: Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment; CPC 3: Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis)⁽³⁸¹⁾

** PAD15%, PAD20%, PAD25%, PAD45%, PAD55% - These abbreviations denote the PAD programmes that were modelled in the cost effective analysis, which differed in regard to the building types required to make AEDs publicly available. See Table 2.5 for the complete list of building types included in each comparator, along with the total number of AEDs in each (including existing AEDs). The naming scheme reflects the number of AEDs in each comparator as a percentage of the total number under full implementation of the proposed legislation (e.g. PAD15% includes approximately 15% of the total number of AEDs that would be in place in Ireland if the legislation was introduced in full).

APP 2.5 AED SUPPLIERS AND TRAINING PROVIDERS IN IRELAND

Companies supplying AEDs in Ireland include:

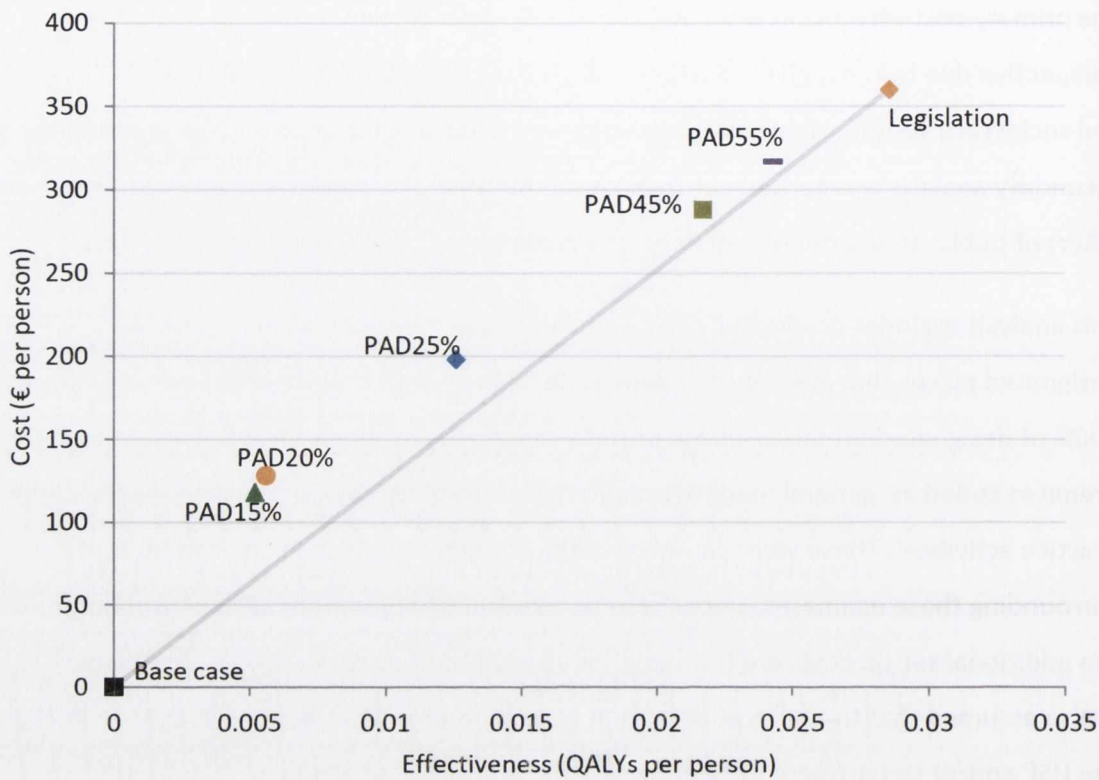
Safety Ireland	<u>www.defib.ie</u>
Eiremed	<u>www.eiremed.ie</u>
Heart Safety Solutions	<u>www.hearts.ie</u>
Fleming Medical	<u>www.flemingmedical.ie</u>
Pulse Medical	<u>www.pulsemedical.ie</u>
Flashpoint Systems	<u>www.flashpointsystems.ie</u>
Hibernian Healthcare	<u>www.hibernianhealth.ie</u>
SkillShop	<u>www.skillshop.ie</u>
AIT Medical Supplies	<u>www.aitmedicalsupplies.ie</u>
Medstore Medical	<u>www.medstore.ie</u>
Mabtech	<u>www.medicalequipment.ie</u>
MedGuard	<u>www.medguard.ie</u>
Emergency Service Supplies 999	<u>www.ess999.ie</u>

APP 2.6 PAD COST-EFFECTIVENESS ANALYSIS FROM THE PERSPECTIVE OF THE HEALTH SERVICE

The primary cost-effectiveness analysis for this thesis is carried out taking a societal perspective due to the high proportion of costs that fall outside the publicly-funded health and social care system. However, to examine the impact of the choice of perspective a secondary analysis was carried out to estimate the cost-effectiveness (incremental cost per QALY) of public access defibrillation programmes taking a narrower payer perspective.

This analysis excludes productivity costs and any equipment and training costs for designated places that are not run by the HSE. It is assumed that the HSE is responsible for 100% of designated premises whose primary function is coded as ‘hospital activities’, 10% of premises coded as ‘general medical practice activities’ and 5% of premises coded as ‘dental practice activities’. These were varied by $\pm 20\%$ to reflect the high level of uncertainty surrounding these estimates. Since these types of buildings are included in all comparators, the additional set-up costs are the same for all programmes when taking this perspective. It is also assumed that the full cost of setting up and running a national AED register will fall on the HSE and/or Department of Health. All other parameters relating to clinical outcomes and costs are retained as per the primary analysis and all costs and benefits are discounted at 5%. The relative position of each of the comparators on the cost-effectiveness plane is shown in Figure App2.6.1.

FIGURE APP2.6.1 COST-EFFECTIVENESS PLANE (QALY OUTCOMES)



Incremental cost-effectiveness ratios for each comparison, excluding any dominated strategies, is shown in Table App2.6.1.

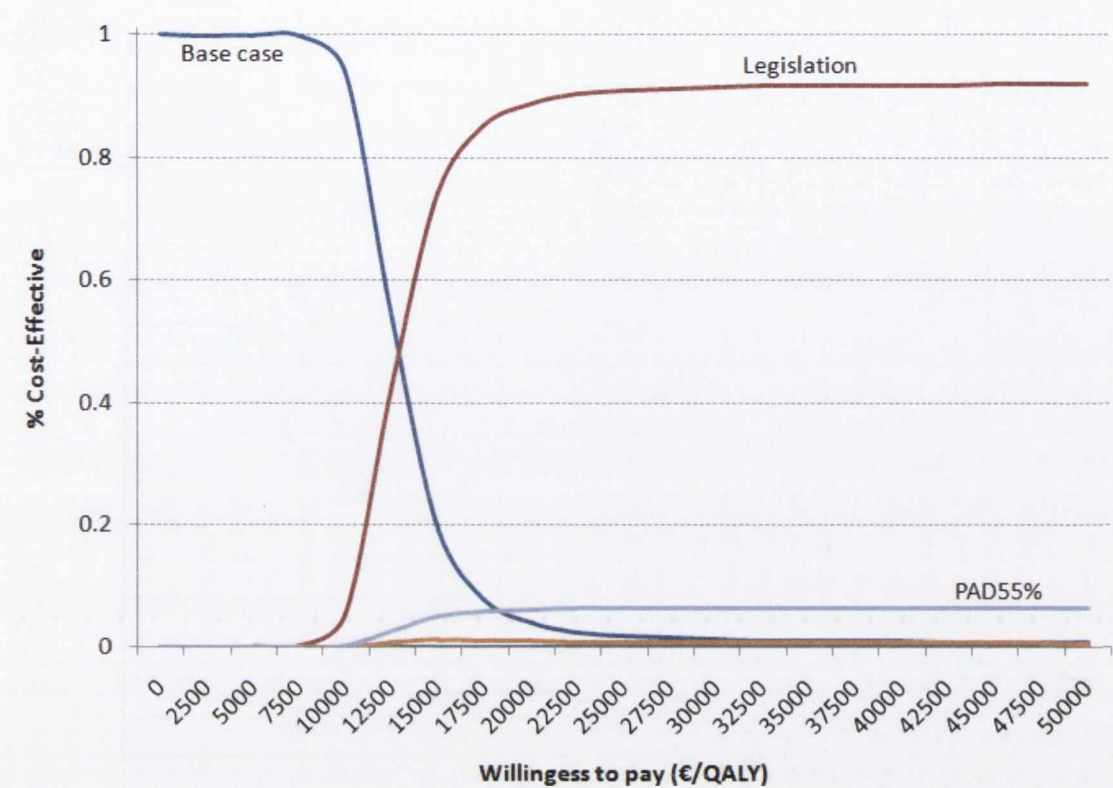
TABLE APP2.6.1 INCREMENTAL COST-EFFECTIVENESS RATIOS (QALY OUTCOMES)

Strategy	Cost (€)	Incremental Cost (€)	Effectiveness (QALY)	Incremental Effectiveness (QALY)	ICER* (€/QALY)
Base case	5,192		0.30026		
Legislation	5,552	360	0.32893	2.8673×10^{-2}	12,574

* Due to rounding error the ICER value calculated using the incremental cost and incremental effect values reported in this table may differ from the ICER value reported in the table. Where any such differences do occur please note that the ICER value reported in the table provides the most accurate estimate.

The cost-effectiveness acceptability curve taking the perspective of the public health service is shown in Figure App2.6.2.

FIGURE APP2.6.2 COST-EFFECTIVENESS ACCEPTABILITY CURVE (QALY OUTCOMES)



When the analysis is restricted to only take account of costs that are incurred by the health service, the proposed legislation weakly dominates all other public access defibrillation configurations, with a 89% chance of being cost-effective at a willingness to pay threshold of €20,000/QALY.

APP 3.1 AF SEARCH STRINGS AND RESULTS

Medline (OVID) – Date of search: May 2014
1 Mass Screening/ (72995)
2 screen*.tw. (363165)
3 Diagnosis/ (16201)
4 "Diagnostic Techniques and Procedures"/ (1840)
5 diagnos*.tw. (1357269)
6 identif*.tw. (1481939)
7 test*.tw. (1765452)
8 prevalence.tw. (294233)
9 incidence*.tw. (429563)
10 ((systemat* or opportunist* or target* or population or mass) adj2 assess*).tw. (6956)
11 Electrocardiography/ (154517)
12 Electrocardiography, Ambulatory/ (8229)
13 electrocardiogram*.tw. (29533)
14 electrocardiograph*.tw. (33936)
15 ecg.tw. (40730)
16 ekg.tw. (2117)
17 holter.tw. (7374)
18 event monitor*.tw. (603)
19 or/1-18 (4696543)
20 Atrial Fibrillation/ (28648)
21 atrial fibrillation*.tw. (29152)
22 auricular fibrillation*.tw. (740)
23 atrium fibrillation*.tw. (7)
24 af.tw. (15627)
25 a-fib.tw. (29)
26 Atrial Flutter/ (4663)
27 atrial flutter*.tw. (3879)
28 auricular flutter*.tw. (213)
29 or/20-28 (46988)
30 Pulse/ (15989)
31 (pulse adj3 test).tw. (633)
32 (pulse adj3 tests).tw. (94)
33 19 or 30 or 31 or 32 (4707679)
34 29 and 33 (22662)
35 randomized controlled trial.pt. (321630)
36 controlled clinical trial.pt. (83679)
37 randomized.ab. (226659)
38 placebo.ab. (129223)
39 clinical trials as topic.sh. (158452)

40 randomly.ab. (163835)
41 trial.ti. (97314)
42 35 or 36 or 37 or 38 or 39 or 40 or 41 (746444)
43 exp animals/ not humans.sh. (3683920)
44 42 not 43 (688202)
45 34 and 44 (2438)

APP 3.2 SUMMARY OF EXCLUDED AF SCREENING STUDIES

Study	Reason for exclusion
ACTRN12612000406808 ⁽¹⁷⁴⁾	Ineligible study design - no control group. This is an ongoing non-randomised registered trial where community pharmacists will screen members of the general public for atrial fibrillation using a combination of a manual pulse check and a handheld single-lead ECG (using the AliveCor Heart Monitor for iPhone). This will be a once off screening of approximately 5-10 minutes duration. Following screening, the pharmacist will contact the participant's GP via letter, stating the provisional diagnosis. A cardiologist will review all of the single-lead ECG recordings to ensure the pharmacists interpretation is correct. The GP will be further contacted by the research team if the diagnosis is other than reported by the pharmacist. The screening trial will be conducted over a 6-month period.
Baxter 1998 ⁽¹⁴⁶⁾	Ineligible study design - this was a pilot study of self screening for AF in an older population (age range 55-75 years). No controls were used and irregular pulse readings were not confirmed using ECG. Communication with corresponding author indicated that the study had not been continued further following this publication.
Claes 2012 ⁽¹⁷³⁾	Ineligible study design - no control group. This report describes a study where "patients over 40 years were invited through different channels (TV, radio, journals, web site, posters, leaflets) for a free screening in 69 hospitals allocated over Belgium during one week. After filling in a question on their personal history of AF, they had to fill in a questionnaire about their CHAD2-score. Afterwards a one channel ECG was taken using a versatile Heart Scan Device (Omron HCG-801-E©) by a trained nurse or a physician. If the ECG was positive for AF the patient was referred to their physician for follow-up." No control group receiving routine care was included to examine the effect of the intervention compared with no screening. 10,758 people over 40 years participated, resulting in 167 new diagnoses of AF. When calculated on the basis of those who responded to the media campaign the detection rate for new cases of AF is approximately 1.56%. It is not possible to calculate the rate

	of detection based on the total number of people who received an invitation.
DeRuijter 2008 ⁽¹⁷⁰⁾	Ineligible study design - this was a prospective cohort study to evaluate whether routinely performed ECGs in older people from the general population have added value for cardiovascular risk management beyond the information that is already available from their medical records.
Ho 2004 ⁽¹⁶⁵⁾	Ineligible study design - no controls. In this study "500 subjects were drawn by two-stage random sampling from 5,002 subjects aged 70 years and over living at home. Subjects were screened for atrial fibrillation and left ventricular systolic dysfunction using electrocardiography and echocardiography." This was a prevalence study with no data on the effect of screening compared with routine care.
Hoefman 2005 ⁽¹⁶⁸⁾	Ineligible population - participants in this study were consecutive patients presenting with unexplained symptoms suggestive of arrhythmia.
Johnson 2010 ⁽¹⁷¹⁾	Ineligible study design - no controls. This conference abstract describes a study that employed a strategy of random screening in a public venue (an inner city public market) to determine stroke risk. However no controls were used and results were not compared to multiple time points pre and post-intervention. No diagnoses of AF were made.
Maeda 2004 ⁽¹⁶⁷⁾	Ineligible study design - this was an economic evaluation which modelled the clinical outcomes and costs associated with a screening programme in Japan.
Marek 2011 ⁽¹⁷²⁾	Ineligible study design - this a retrospective cohort study of large-scale electrocardiographic screening of young adults.
Morgan 2002 ⁽¹⁶⁶⁾	Ineligible study design - no controls. This was a randomised trial comparing two different screening strategies. Patients were randomised either to nurse led screening or to prompted opportunistic case finding. Irregular pulses found during opportunistic screening did not need to be confirmed by ECG. The study was carried out over a 6-month period. Uptake in the systematic screening arm was 73%, compared to 29% (for pulse palpation alone) in the opportunistic arm. The detection rate of new cases of AF in the systematic arm was 0.8%, compared with 0.4% in the opportunistic arm.
Munschauer 1999 ⁽¹⁶³⁾	Ineligible study design - this study was designed to determine whether individuals taken from the general

	community could be taught to find and classify the pulse of another as very irregular, implying AF, or regular, implying normal sinus rhythm (NSR). No data on the effectiveness of a screening programme compared to routine practice were reported.
Somerville 2000 ⁽¹⁶⁴⁾	Ineligible study design - this study compared different methods of identifying cases in general practice using patients over 65 recruited from a general practice. 56% of invitees accepted an invitation for testing (86/154) but no data were reported on the rate of detection of new cases. The study was not designed to investigate the effect of screening compared with routine practice.
Sudlow 1998 ⁽¹⁴⁷⁾	Ineligible study design - no controls. This study compares three methods of diagnosing AF in a sample of 1235 over 65's invited from 9 general practices in the UK. The three methods of screening used were 1) checking for a digoxin prescription 2) pulse palpation and 3) limb lead ECG. Response rate was 74% (916/1235). No data on rate of new diagnoses were reported.
Wheeldon 1998 ⁽¹⁴⁸⁾	Ineligible study design - all patients over 65 years of age from a single primary care practice with 4 GPs were invited to attend for a 12-lead ECG to detect AF. An uptake rate of 85% was achieved (1207/1422). The overall detection rate of new cases of AF was approximately 0.4%.
Wright 2007 ⁽¹⁶⁹⁾	Ineligible study design - no controls. This study randomised primary care centres to either implementing AF or TIA guidelines. The type of AF testing that was associated with the AF guidelines was unclear but effects on the rate of diagnosis of new cases of AF was reported. However there was no control arm receiving routine care.