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Economic Evaluations of Clinical Pharmacy Services in Ireland, 2007 - 2015

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A thesis submitted to the National University of Ireland, Cork for the degree of Doctor of Philosophy in the School of Pharmacy.

March 2016

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4 Table of Abbreviations

ACCP	American College of Clinical Pharmacy
ADE	Adverse drug events
ADR	Adverse drug reaction
AMS	Anticoagulation management service
AP	Academic pharmacist
BMI	Body mass index
CEAC	Cost-effectiveness acceptability curve
CDSS	Clinical decision support system
CHEERS	Consolidated health economic evaluation reporting standards
COPD	Chronic obstructive pulmonary disorder
CPS	Clinical pharmacy service
CUH	Cork University Hospital
DoH	Department of Health
DPS	Drugs Payment Scheme
DVT	Deep vein thrombosis
EHC	Emergency Hormonal Contraception
ESCP	European Society of Clinical Pharmacy
FEMPI	Financial Emergency Measures in the Public Interest
FIP	International Pharmaceutical Federation
GMS	General Medical Services
GP	General Practitioners
HPAI	Hospital Pharmacist Association of Ireland
HIQA	Health Information Quality Authority
HSE	Health Service Executive

HRQoL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
INR	International normalized ratio
IPU	Irish Pharmaceutical Union
IT	Information Technology
ITT	Intention to treat
LOS	Length of stay
LTI	Long term illness
MAS	Minor ailments schemes
MUR	Medication use reviews
NCPE	National Centre for Pharmacoeconomics
NICE	National Institute for Clinical Excellence
NHS	National Health Service
NOAC	New oral anticoagulant
OECD	Organisation for Economic Co-operation and Development
PCT	Primary care trust
PE	Pulmonary embolism
PGD	Patient Group Directive
PIER	Pharmacists in Industry, Education and Regulatory
PIP	Potentially inappropriate prescribing
POC	Point of care
POM	Prescription Only Medicine
PR	Primary rater
PST	Patient self-testing
PSI	Pharmaceutical Society of Ireland

QALY	Quality-adjusted life year
RCT	Randomised controlled trial
SD	Standard deviation
SPRM	Structured pharmacist review of medication
STOPP	Screening tool of older persons prescriptions
START	Screening tool to alert doctors to right treatment
TTR	Time in therapeutic range
UCC	University College Cork
UK	United Kingdom
US	United States
WTE	Whole time equivalent

5 Declaration

I declare that this thesis has not been previously submitted for a degree at this, or any other university. It is entirely my own work, apart from due acknowledgement. The library may lend or copy this thesis upon request

Signed: Date:

_____ _____

6 Acknowledgements

A friend of mine when talking about pharmacy in UCC, once wrote the following,

“I love my course and I love my class...”

Now, to give a bit of context he was writing to the Board of Examiners as part of an appeal but I think he captures the sentiments of anyone who has spent time in this institution. Since September 2006, University College Cork and the School of Pharmacy in particular, have had an incredibly positive impact on my life. So first of all, to the staff (past and present) who have helped build this school, thank you for making this a wonderful environment to learn and develop!

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7 Thesis Abstract

Introduction

The concept of this thesis was driven by stagnation within the Irish healthcare system. Multiple reports from pharmacy organisations had outlined possible future directions for the profession but progress was minimal, especially in comparison with other countries. The author's directive was to evaluate the economic impact of a series of clinical pharmacy services (CPS) in hospital and community settings.

Methods

A systematic review of economic evaluations of clinical pharmacy services in hospital patients was undertaken to gain insight into recent research in the field. Eligible studies were evaluated using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS), to establish the quality, consistency and transparency of relevant research.

A retrospective analysis of an internal hospital pharmacy interventions database was conducted. A method first described by Nesbit *et al.* was implemented to estimate the level of cost avoidance achieved.

A cost-effectiveness analysis based on data from a randomised controlled trial of a pharmacist-supervised patient self-testing (PST) of warfarin therapy is presented. Outcome measure was the incremental cost associated with six months of intervention management.

A similar cost-effectiveness analysis based on previously published RCT data was used to evaluate a novel structured pharmacist review of medication in older hospitalised patients. Cost-effectiveness analysis was presented in the form of an incremental cost-effectiveness ratio (ICER). An ICER is an additional cost per unit

effect, in the case of this study, the cost of preventing an additional non-trivial ADR in hospital.

A method described by Preaud *et al.* was adapted to estimate the clinical and economic benefit gained from vaccination of patients by a community pharmacist in Ireland in 2013/14. Sample demographic data was obtained from a national chain of community pharmacies and applied to overall national vaccination data.

Results

Systematic review identified twenty studies which were eligible for inclusion. Overall, pharmacist interventions had a positive impact on hospital budgets. Only three studies (15%) were deemed to be "good-quality" studies. No 'novel' clinical pharmacist intervention was identified during the course of this review.

Analysis of internal hospital database identified 4,257 interventions documented on 2,147 individual patients over a 12 month period. Substantial cost avoidance of €710,000 was generated over a 1 year period from the perspective of the health care provider. Mean cost avoidance of €166 per intervention was generated. The cost of providing these interventions was €82,000. Substantial net cost-benefits of €626,279 and a cost-benefit ratio of 8.64 : 1 were generated based on this evaluation of pharmacist interventions.

Results from an evaluation of a novel pharmacist-led form of warfarin management indicated indicated that on a per patient basis, PST was slightly more expensive than established anticoagulant management. On a per patient basis over a six month period, PST resulted in an incremental cost of €59.08 in comparison with routine care. Overall cost of managing a patient through pharmacist-supervised PST for a six month period

is €226.45. However, for this increase in cost a clinically significant improvement in care was provided. Patients achieved a significantly higher time in therapeutic range during the PST arm in comparison with routine care, (72 ± 19.7% vs 59 ± 13.5%). Difference in overall cost was minimal and PST was the dominant strategy in some scenarios examined during sensitivity analysis.

Structured pharmacist review of medication was determined to be dominant in comparison to usual pharmaceutical care. Even if the healthcare payer was unwilling to pay any money for the prevention of an ADR, the intervention strategy is still likely to be cost-effective (probability of being determined cost-effective = 0.707).

Implementation of pharmacist-led influenza vaccination has resulted in substantial clinical and economic benefits to the healthcare system. The majority of patients (64.9%) who availed of this service had identifiable influenza-related risk factors. Of patients with influenza-related risk factors, age ≥65 year was the most commonly cited risk factor. Pharmacist vaccination services averted a total of 848 influenza cases across all age groups during the 2013/2014 influenza season. Due to receipt of vaccination in a pharmacy setting, 444 influenza-related GP visits were prevented. In terms of more serious influenza-associated events, 11 hospitalisations and five influenza-related deaths were averted. Costs averted were approximately €305,000. These were principally wider societal-related costs associated with lost productivity.

Conclusion

Overall, clinical pharmacy services are adding value to the Irish healthcare system in both hospital and community settings, but provision of additional funding for new services would enable them to offer a great deal more.

1 - Chapter 1: Thesis Introduction

1.1 Introduction

This concept of this thesis was driven by stagnation within the Irish healthcare system. Multiple reports and pharmacy organisations had outlined possible future directions for the profession but progress was minimal, especially in comparison with other countries. The author's directive was to evaluate the economic impact of a series of clinical pharmacy services (CPS). The economic focus of this thesis had two primary stimuli. In essence, these proposed services had clinical evidence to support them but policy decisions in a modern healthcare service require economic evaluation. Furthermore, the Irish healthcare system and pharmacy services in particular had been the target of significant reductions in expenditure in the years directly preceding the commencement of this thesis. Therefore, resources are scarce and any potential services require a comprehensive economic evaluation to inform decisions surrounding their adoption.

This research focused on providing evidence for policy makers on a range of CPS which had been proposed for introduction or recently introduced as a pharmacy service at a national level. Due to the nature of the question, the research has a quantitative focus consisting of a systematic review and four separate service evaluations. Service evaluations were in both community and hospital pharmacy settings. Three of the chapters had a hospital setting for the research. A systematic review focusing on economic outcomes of pharmacist interventions on hospital inpatients acts as an introduction for chapters investigating the impact of pharmacist clinical interventions on hospital inpatients. The remaining chapters of the thesis are composed of economic evaluations of community pharmacy based services namely pharmacist-led warfarin monitoring and influenza vaccination services.

This chapter will provide some background and context to the current status of pharmacy services in Ireland. An overview of the Irish healthcare service, its current status and future issues, will also be described. In addition, the state of pharmacy services at an international level will be furnished to inform the reader of the overall state of CPS and the extent and limitations of its scope. The development of health economics and its importance in setting health policy will be discussed. Finally, this chapter will describe why we feel this research is worth undertaking and outline the aims and objectives associated with this thesis.

1.2 Background

1.2.1 Clinical Pharmacy Services

Pharmacy is currently undergoing a paradigm shift from a "*product focused to a patient focused*" profession [1]. The traditional focus of a pharmacist was ensuring the patient receives the correct medication prescribed by a physician. While this role remains an integral part of pharmacy practice, advances in global healthcare systems are such that the primary focus of modern pharmacists should be directed towards medication optimisation. It is more of a broader focus than the traditional role, a role which should benefit the patient while also being more rewarding for the professional. Whilst the concept that pharmacists should perform a role outside of preparing and dispensing medications has been promoted for over 40 years [2], transformation of the profession is far from complete.

The concept of clinical pharmacy originated in the United States (US) in the mid-20th century. Initial developments included the gradual increase in number of pharmacists employed by hospitals, the establishment of drug information centres, clinical pharmacokinetic monitoring and early methods of drug therapy management [2].

Developments in Ireland have been largely influenced by progress in the United Kingdom (UK) and US and we are still striving to compare with pharmacy systems in place in these countries.

Due to the organic development of the concept of clinical pharmacy, there is no universal definition as to what clinical pharmacy entails. Numerous pharmacy representative bodies have tried to develop an all-encompassing definition but the true meaning of the term is still debated. The American College of Clinical Pharmacy (ACCP) definition of clinical pharmacy has proposed the following unabridged definition [3],

"Clinical pharmacy is defined as that area of pharmacy concerned with the science and practice of rational medication use."

As all interventions assessed in this thesis have been carried in a European setting, the European Society of Clinical Pharmacy (ESCP) [4] definition will be employed during the course of this thesis, unless otherwise stated. This group defines clinical pharmacy as the following,

"It is a health specialty, which describes the activities and services of the clinical pharmacist to develop and promote the rational and appropriate use of medicinal products and devices.

Clinical Pharmacy includes all the services performed by pharmacists practising in hospitals, community pharmacies, nursing homes, home-based care services, clinics and any other setting where medicines are prescribed and used."

The confusion is compounded by the existence of another related concept, "*pharmaceutical care*". Pharmaceutical care as defined by Hepler and Strand is the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life [5]. Unfortunately, they have almost become rival theories when in fact they should be viewed as complementary methods of patient management. Neither definition fully articulates the potential of a pharmacist but the two interlinking concepts provide a useful starting point in the description. During the course of this thesis, the author will predominantly use the term clinical pharmacy as it is the most widely established term [6].

Bodies may differ in terms of their definition of clinical pharmacy; however objectives associated with it are shared. Exponents of clinical pharmacy attempt to combine a caring orientation with therapeutic expertise, experience and clinical judgement for the overall benefit of their patients. In addition to optimising patient therapy, clinical pharmacists should also have a public health role in the promotion of health wellness and disease prevention [3]. The term 'clinical' does not entail that the practice is confined to a hospital setting. Clinical pharmacy is equally as vital in primary care.

1.2.2 Clinical Pharmacy Services in Ireland

Since its foundation in 2003, School of Pharmacy, University College Cork (UCC) has been prominent in the development of clinical pharmacy services from an Irish and global perspective. It has proven the valuable clinical impact that pharmacist interventions can have on a diverse range of healthcare outcomes in both community and hospital settings [7, 8]. However, despite proving the clinical benefit of additional pharmacy services, these services have not yet been implemented on a widespread basis. Transformation within a complex health system is never straightforward; but the adoption of clinical pharmacy services within the Irish healthcare system is slow. In order to facilitate the more widespread adoption of additional clinical pharmacy services, economic data is a fundamental requirement. Services such as medication use reviews (MUR) and minor ailments schemes (MAS) have been established in England, Scotland and even Northern Ireland [9, 10]. However, similar services have not been implemented in Ireland.

Previously, the development of pharmacy as a profession in Ireland was hampered by a shortage of qualified professionals [9]. The formation of two additional Schools of Pharmacy in the State in 2002 and 2003 has created a critical mass of newly qualified pharmacy graduates available to implement additional clinical pharmacy services in all sectors. Furthermore, the emergence of a number of postgraduate training courses has further enhanced the overall knowledge and capabilities of Irish pharmacists.

The landmark “Pharmacy 2020” report published in 2008 outlined the vision of the Pharmaceutical Society of Ireland (PSI) for the development of pharmacy services in Ireland [9]. The services outlined in this report are easily achievable and have been

implemented in many other settings but almost a decade later, the majority of the objectives in the report have yet to be realised.

However, it must be acknowledged from the outset that the production of this report approximately coincided with a major financial crisis in Ireland [11]. Between 2008 and 2015, public expenditure on health was reduced by 9%. These savings were achieved through reductions in pharmaceuticals and human resources, increased productivity and health system revision [11]. During this period of austerity and declining healthcare budgets, the Irish public health system was required to cope with additional demands due to a growing, ageing population with a higher burden of chronic disease [12] Therefore, any improvement in pharmacy services since the onset of the financial crash in Ireland would have been difficult to achieve.

In order to provide initial employment and a viable and progressive career path for the graduates of the three Schools of Pharmacy, it is imperative that the additional pharmacy services outlined in the "Pharmacy 2020" report are finally implemented. Furthermore, the development of pharmacy services in Ireland, can help the government achieve its stated goal of providing a healthcare system which is more focused on providing care in a community setting [13].

1.2.3 Current status of hospital pharmacy in Ireland

Despite being at the forefront of the development of clinical pharmacy services, hospital pharmacy remains fastened to a "production-based culture" rather than a "patient-based culture" [14]; this is still the situation for many hospitals in Ireland. The traditional dispensary based functions account for a large part of a pharmacist's working day. Clinical services remain very much secondary to dispensing functions. The International Pharmaceutical Federation (FIP) has developed the Basel

Statements, which outline the goals and objectives for the future development of hospital pharmacy. The primary aim of the statements is to ensure that hospital pharmacists are in a position to optimize patient outcomes through the judicious, safe, efficacious, appropriate and cost-effective use of medicines [15]. The implementation of these goals in Ireland is variable.

A study on the status of hospital pharmacy commissioned by the PSI was published in 2012 [16]. This baseline study gives an accurate reflection of the workings of hospital pharmacy in Ireland at the time when this thesis was commenced. An overview of the workforce, systems, services, potential and limitations demonstrated throughout the country is described. On the surface, Irish hospital pharmacy appears to be in a robustly healthy state. It is only when one delves deeper into the report that the problems within the system become apparent.

Pharmacist staff numbers in hospital compare favourably to most other European countries. Approximately 1.8 pharmacists are employed for every 100 hospital beds. In terms of this indicator Ireland is ahead of the majority of European countries (average 0.9 pharmacists/100 beds) [17]. However, it is still lower than US and UK staffing levels [17]. A Health Service Executive (HSE) (primary provider of health services in Ireland), recruitment embargo has placed additionally pressure on resources, due to a disproportionately high number of staff who have taken maternity leave during the embargo period [16]. This embargo was as a result of financial pressures in due to a series of austerity budgets outlined previously. Pharmacy staff employed at hospital level are highly qualified; more than 40% of the workforce has completed Masters level postgraduate qualifications. As an overall workforce, they

have significant experience; over 70% have five years or more experience in a hospital setting [16]. Pharmacists surveyed had positive views on their relationship with other members of the hospital team and feel they are appreciated by other professions.

All hospitals surveyed performed core dispensary services [16]. Most operate a centralised dispensary service, however individualised patient dispensing still occurs. Pharmacists felt that clinical pharmacy services could be improved with additional resources. While many hospitals had established medicines reconciliation and ward based interventions, they were largely confined to specific wards within a hospital rather than being a universal service [16].

Considering the knowledge accrued of the system due to their lengthy employment within a hospital setting and post-graduate qualifications of the current cohort of hospital pharmacists, if additional roles were opened up, training requirements or education would be minimal. As the vast majority of pharmacists in the Irish system have greater than five years of employment (71.3%), it would be a considerable setback if this expertise was to be lost [16]. Enhanced roles which hospital pharmacists feel they could adequately fulfil include medicines reconciliation, outpatient antimicrobial treatment, structured patient medication review and discharge, specialising in a therapeutic area and integration into a multidisciplinary team.

1.2.4 Current status of community pharmacy in Ireland

The pivotal Health Act (1970) ended the antiquated dispensary based system and was the foundation of the current primary care system in Ireland, which is principally based on General Practitioners (GPs) and community pharmacists. The General Medical

Services (GMS) scheme followed in 1972, providing vulnerable members of society with free access to primary care services. The GMS scheme is the national public (tax-funded) health insurance programme [13]. Eligibility is primarily determined on the basis of income based means testing. Most people who qualify are low-income, and due to differing means thresholds, the majority of people aged over 70 years also qualify. Altogether, approximately 40% of the Irish population qualifies for the GMS scheme. Because everyone in the state is entitled to free or subsidised hospital care, the main benefit of the GMS scheme is free primary care inclusive of GP visits and access to prescription medicines (subject to minimal co-payments). Prior to 1970, a system was in place whereby district doctors were responsible for both prescribing and dispensing medication to patients. The onset of the GMS scheme and the significant increase in new medications from the pharmaceutical industry, transformed the everyday practice of pharmacy in Ireland.

A barrier to the development of clinical pharmacy services in recent years has been the deterioration of the relationship of pharmacists and representative bodies with the state to the point where it has almost become adversarial. The community pharmacy – state network is a complex one. Although community pharmacies in Ireland are independent businesses, they in effect have a single customer, the HSE. Without a contract to provide medication under state schemes, it would be exceptionally difficult for a business to remain viable [18].

Community pharmacists derive the vast majority of their income from reimbursement for items dispensed under state run drug schemes, €345 million in 2011 [19]. Therefore, the HSE has a transcendent influence on the operation of community

pharmacy in Ireland. A series of unilateral reductions in reimbursement fees and medicine prices has threatened the continued viability of the community pharmacy sector in Ireland. Reductions to pharmacy income can be summarised as follows:

Table

Date	Reason for reduction	Influence on pharmacy income
July 2009	Financial Emergency Measures in the Public Interest (FEMPI)	8.8% due to a reduction in professional fees to healthcare professionals.
February 2010	Framework agreement between the Irish Pharmacuetical Healthcare Association (IPHA) and the DOH and HSE on the supply, terms, conditions and prices of medicines	4.3%, reduction in cost price of medications
October 2010	Association of Pharmaceutical Manufacturers of Ireland (APMI) agreement	6.2% reduction in cost price of generic medications
June 2011	FEMPI 2011	1.3%, reduction in retail/wholesale mark ups and reduction in patient

		care fees for items dispensed under High Tech schemes.
June 2013	FEMPI 2013	2.4%, removal of mark-up on Drugs Payment Scheme (DPS) and Long-Term Illness (LTI) schemes.

Competition between pharmacies has also increased. In 2001 the number of pharmacies in Ireland was approximately 1200 [18]. By December 2014, this number had increased to 1848 [20]. Ireland has the fourth highest number of pharmacies per head of capita amongst Organisation for Economic Co-operation and Development (OECD) countries [21]. Average net profit is reported at 6% in 2012 [22], making the viability of a number of businesses questionable especially if new services are not implemented. Regardless, consolidation within the pharmacy sector is probably inevitable, but remaining pharmacies should be stronger, better staffed and better able to implement additional clinical pharmacy services.

Pharmacists have a desire to broaden the range of services provided but are realistic regarding what can be achieved. At present, enhanced services in an Irish setting are very much provided on an ad-hoc basis and generally only to private patients who are able to afford to pay for the cost of services. Considering in 2014, 39% of the

population were considered eligible for a medical card under the GMS [23]; this considerably reduces the number of patients who can avail of these services. Furthermore, medical card patients have a higher proportion of older and more vulnerable patients and would have most to gain from the provision of additional services [24].

Similar to the discussion on hospital pharmacy, the PSI commissioned a report on the status of community pharmacy in Ireland at the outset of this thesis [25]. The majority (76%) of community pharmacists would like to see enhanced services in a community setting. Services which pharmacists favoured included; health promotion programmes, screening, diagnostic and monitoring services, blood sugar / cholesterol testing and international normalized ratio (INR) monitoring [25]. Some pharmacists did not want to facilitate these services and were of the opinion that core pharmacy services (dispensing and counselling) are the staple work of a community pharmacist and should retain priority focus. However, a consensus was visible based on pharmacists interviewed as part of the PSI report indicating that two key services would be worthwhile pursuing; namely medicine use reviews and a minor ailment scheme [25].

There is no clear vision for the future of pharmacy in Ireland. Under-appreciation and underutilisation is a common theme for both community and hospital pharmacists. Despite some advances in the provision of clinical pharmacy services over the past few years, the perception remains that these have been isolated events and there is no overall plan for how pharmacy should be developed and where it should fit within the delivery of healthcare services to patients [25].

One of the few clinical pharmacy services which received support from the state, the influenza vaccination scheme, was implemented around the same time as the HSE significantly reduced fees they paid to GPs for administering flu vaccinations [26]. The timing of this event provides further evidence to claims that pharmacists are seen by the HSE as a means of cutting costs rather than provide solutions. The impact of this service is investigated in Chapter 6.

Another example of an additional pharmacy service implemented in Ireland, was the switching of emergency hormonal contraception (EHC) from a prescription only medicine (POM) to one which is available from a pharmacy (P medicine). POM medication is only provided on receipt of a prescription written by a registered medical doctor, whereas P medications can be provided under the supervision of a pharmacist. Instead of the initial implementation being in the form of collaboration between pharmacist representatives and the HSE / Department of Health (DoH), it was forced through as a patient group directive (PGD) by an individual pharmacy group [27]. This PGD was subsequently replicated by additional pharmacies. While the service has proved to be a success, it has received no support from state bodies and is only available to private patients, which subsequently limits the availability of the service to patients [28].

POM to P switching is an area of community pharmacy which has seen limited development, but overall has not reached its full potential. Since the publication of the "Pharmacy 2020" report, a number of substances have been reclassified from POM to P but they have largely been medications which had adequate alternatives already available [29]. It has largely been a missed opportunity; suitable medications for the

treatment of self-limiting conditions such as conjunctivitis, minor urinary tract infections and minor skin infections have remained under POM classification. The potential of developing a new category of medication, “pharmacy prescribed” or a minor ailment scheme has been ignored. Potential medications which could be included in this scheme include simvastatin and oral contraceptives. These medicines have been prescribed under similar schemes in other jurisdictions [30, 31]. Based on a recent postal survey of Irish GPs, this is likely to be met with strong resistance [32].

A novel area which pharmacists could use their skills for the greater benefit of the population is connected health. Connected health is a step away from directly providing care to a ‘passive’ patient. Instead it facilitates the patient, in a form of self-management collaborative care, generally through telemedicine [33]. It helps the patient take ownership of their condition; instead of only addressing it when it needs attention i.e. GP or hospital visit. Connected healthcare is a multidisciplinary approach to healthcare provision. Despite community pharmacists being in an ideal position to act as a facilitator for empowered patient management, policy on connected healthcare has failed to integrate pharmacists into future plans. Public support for pharmacist involvement in connected health programmes is strong [34]. It is still a nascent area of care which requires substantial development. Infrastructure deficits within the healthcare system may counter long-term savings [33]. However, it is an area which deserves consideration as a means of relieving pressures on acute care facilities. Chapter 4, investigates an example of connected healthcare, pharmacist expanded role in managing patient oral anticoagulation.

1.3 Pharmacy and the Irish healthcare system

Pharmacists are the third largest group of healthcare professionals [34]. However, pharmacists as a profession are traditionally poor to lobby or network at higher levels of power. Groups such as the Irish Pharmaceutical Union (IPU), Hospital Pharmacists Association of Ireland (HPAI) and Pharmacists in Industry, Education and Regulatory (PIER) have started to realise this and are beginning to advocate for the role of pharmacists. However, the small and fragmented nature of pharmacy representative groups pales into insignificance when compared with powerful medical and nursing lobby groups.

There is currently no Chief Pharmacist assigned to the Department of Health in Ireland [35]. This is a major problem, which has been unresolved for a number of years. The Chief Pharmacist would have direct access to the Minister for Health and would help influence the future progression of our profession. While academic evidence is an important part in overall service redesign, advocates interacting with high level decision makers are important to make sure all parties are made aware of all available evidence.

Successive governments have all released documents describing their vision for a better healthcare system. The potential impact of pharmacy has generally been ignored in previous strategies:

> ***1994 - Shaping a healthier future.*** *Astrategy for effective healthcare in the 1990's. Brief mention of plans for pharmacy during the government's lifetime, including plans for a new Pharmacy Act . Unfortunately, none of these plans were implemented during the course of the document's implementation. It was 2007 before a revised Pharmacy Act was produced [36].*

2001 – Quality and Fairness. *A Health System for You. No mention of pharmacy. The steering group involved in this programme had multiple representatives from medical and nursing professions, but no pharmacist input [37].*

2007 – Transformation Programme. *This was a policy document representing a commitment to advance primary, community and continuing care in order to relieve pressure on the hospital system. Again pharmacies are omitted from any consideration in the entire document [38].*

2013 – Healthy Ireland*. Anational health strategy devised by the Fine-Gael Labour coalition government (at time of writing February 2016). Despite a change in the make-up of the government, only a brief mention of pharmacy was included in the document. No details were given on what role they would have in a strategy which was very much primary care orientated and offered a perfect platform to outline the plans for the pharmacy over the coming years [39].*

These reports represent the health strategies of all administrations over the past 20 years, not one has considered the positive contribution that pharmacy could make to Ireland's on-going health resource issues.

The evidence over the past decade has indicated that the only way in which pharmacy is viewed by state bodies is an area where costs can be cut, rather than a profession which can offer viable solutions to problems within our healthcare system.

Realistically, since the onset of the financial crisis, the HSE has had limited scope to invest in further services. Drastic cutbacks to its budget have been implemented over

a prolonged period of time. A 17% reduction in overall healthcare spending was implemented between 2010 and 2012 [40]. Many of them were passed on to the pharmacy sector. Numerous Ministers for Health have referred to the development of pharmacy services but as already stated it lacks a strategic approach.

The HSE has never published a strategy or publication outlining the intended direction of pharmacy. A potential reason for this may be the high level of expenditure associated with on pharmaceuticals in the community (€1.92 billion - 2014) [23]. Therefore, focus at a national level was on reduction of this expenditure rather than addition of new services. However, only €379 million of this funding goes to community pharmacies [23].

A policy of publishing pharmacy strategies and following up on implementation has long been established in the UK and Northern Ireland.[41-43]. Furthermore in the UK, individual trusts within the National Health Service (NHS) have published prospective strategic documents which outline direction of pharmacy for the next 5 years [44]. It must be acknowledged however, that the NHS system in the UK is considerably different to the current Irish model. NHS Trusts are well-established and have considerable autonomy so it is in their own interests to have pharmacy specific policy documents. Pharmacy is also given consideration in national frameworks which provide guidelines and quality indicators which drive improvement in pharmacy services at an individual trust level. While these measurements have their critics, they do foster a more progressive environment; unfortunately they have not yet become standard practice within the Irish healthcare system.

Up until now, the HSE has not invested in additional pharmacy services to any great extent. A review of the most recent HSE service plans 2014 and 2015 revealed that only one hospital pharmacy (Letterkenny) was to receive capital investment [45] [46]. A subsequent update for 2016 saw additional capital funding for new pharmacy in Ennis general hospital and development of an ePharmacy program as part of the overall eHealth Vision for Ireland [47, 48]. This project aims to deploy digital solutions across different care settings to make the delivery of pharmacy services safer and more efficient.

Only one additional pharmacy service, a needle exchange programme was being formally considered for evaluation [46]. This program was driven by social inclusion policies rather than a primary care or pharmacy orientated policy.

The current government (at time of writing February 2016) has outlined their plans for a primary care orientated healthcare system in but anticipated pharmacy input is minimal [39]. Evidence generated in this thesis will inform HSE strategists on the value for money (or lack of) to be gained from clinical pharmacy services.

If consideration has not yet been given to the benefits that pharmacists can provide, future projections have highlighted its importance. Irelands ageing population ensures that investment in preventative and public health measures is imperative in order to prevent our tertiary care systems collapsing. In 2011 it was estimated that 532,000 people in Ireland were aged 65 or older. By 2026 that figure is expected to be closer to 850,000 [49]. An inevitable consequence of an ageing population is an increase in age related illnesses. When this is combined with current and expected increases in chronic conditions caused by factors such as obesity, smoking and dietary deficiencies

it is reasonable to expect demands on Ireland's healthcare to multiply over the coming years.

1.4 Community pharmacy worldwide

As in Ireland, traditionally community pharmacists in other countries around the world have worked in isolation, with a focus on retailing and dispensing of medications. However, countries around the world are beginning to recognize this untapped potential and are beginning to integrate community pharmacists into their primary care strategy.

A recent systematic review has identified a range of community pharmacy services which are remunerated [50]. The majority of funding is obtained from government agencies, with the remainder of funding coming from private insurance companies, generally in the US. The most prevalent service identified was medication reviews with or without care plan development (n = 18). Other services identified which received support from a healthcare provider included contacting prescribers regarding drug therapy problems, smoking cessation counselling (n = 9), diabetes management (n = 5), emergency hormonal contraception counselling (n = 2) and inhaler device training (n = 2). Minor ailment schemes are operated in Scotland, Northern Ireland and isolated Canadian provinces [50] .

1.4.1 Pharmacy in the UK

Arguably the most progressive jurisdiction in the context of primary care pharmacy reform has been the UK. The development of pharmacy has received ongoing support from the state. The framework for the development of pharmacy service was outlined for England in the "Pharmacy in the Future" (2000) report [41]. The impetus for expansion in Scotland came from the publication of the "Right Medicine" report in 2002 [43]. Enhanced services provided include [34]:

- Provision of emergency prescription refills
- Renewal or extension of prescriptions
- Responsibility for adjustment of medication dosage or formulation
- Initiation of prescription drug therapy
- Minor ailment prescribing
- Therapeutic substituition
- Ordering and interpreting lab tests

Accredited pharmacists in England and Scotland have been allowed to independently prescribe since 2006 [51]. While this service was originally met with considerable resistance from the medical fraternity, it has remained in place and in 2012 was expanded to include prescription of certain controlled drugs [34].

Transfer of patients between tertiary and community care settings is a changeover which is fraught with danger and associated with exacerbations in patient conditions. This has been recognized by the NHS in Wales. Pharmacists are reimbursed for the provision of a structured Discharge Medicines Review Service [52].

Since 2011, a New Medicines Service has been provided in English pharmacies [53]. This service is also been made available to patients in Northern Ireland under the most recent pharmacy contract. Patients who receive a newly prescribed medication for a number of chronic conditions receive three consultation with a pharmacist during the first month of receiving their new therapy.

Scotland is perhaps the most advanced country in terms of a community pharmacy input into the primary care system. Smoking cessation is widely recognised as one of

the most cost-effective public health interventions and regularly provided as part of a pharmacist service in many countries. However, smoking cessation counselling is financially supported in Scottish pharmacies [54]. In addition, to recognised services such as medicine use reviews and minor ailment schemes, more novel services such as a community pharmacy heart failure programs are also supported in some Scottish districts [55].

1.4.2 Pharmacy in Europe

Community pharmacy services in Europe are less developed in comparison with the services available in the UK. A recent systematic review has only identified two enhanced pharmacy services which are eligible for reimbursement [50]. Danish community pharmacies provide inhaler assessment and training for asthma and chronic obstructive pulmonary disorder (COPD) patients [56]. Patients in Switzerland on ≥ 4 medication for more than 3 months can avail of a polymedications check [57]. This is a modified form of medication use review which focuses on medications management, adherence issues and other drug related problems. Efforts to reform the Dutch pharmacy system are progressing. Recently legislation has been passed which will allow pharmacists to access laboratory test results and prescribing indications [34].

1.4.3 Pharmacy in Australia and Asia

There is a history of engagement between healthcare payers and pharmacist representatives on the provision of pharmacy services. Since 1990, there have been regular agreements between the Australian government and the Pharmacy Guild of Australia. Originally, these specifically governed pharmacist reimbursement and regulations regarding the opening of pharmacy businesses. Over time, these

agreements have begun to incorporate designated funding for the provision of clinical pharmacy services [58]. These agreements provide an example of a coherent primary care strategy in which an agreed level of pharmacist services are reimbursed over a significant period of time. Up to $1.26 billion in funding will be available under the most recent agreement (6th version) for evidence-based, patient-focused professional pharmacy programmes and services. Pharmacists are provided reimbursement in the form of patient care fees or annual stipends for offering clinical pharmacy services targeting medication adherence, medication management and rural support projects. Another interesting funded provision is the "Pharmacy Trials Programme" which provides funding for new initiatives which seek to expand the role of pharmacy and improve patient outcomes [58].

Along with Scotland, New Zealand is oft cited as an example of a country with a similar population level to Ireland which has significantly developed its community pharmacy services. Since 2007, patients have been offered a medication use review and adherence support service [59]. Pharmacists receive a payment of $86.38 for an initial patient consultation, along with a fee of $21.60 for follow-up visits. Multi-disciplinary teams including community pharmacists are also encouraged to generate care plans for patients under a Medicines therapy assessment scheme.

However, despite these considerable incentives, uptake is disappointing. Only half of pharmacists who are qualified to perform medication use reviews regularly do so [60].

1.4.4 Pharmacy in North America

The development of community pharmacy services in the US is primarily influenced by the Medicare Prescription Drug Benefit Act which came into effect in 2006. This introduced a Medication Therapy Management (MTM) service, a variation of

medicine use review programs established in the UK. The objective of MTM is to prevent adverse drug events and improve adherence for Medicare beneficiaries. Studies analysing the impact of the program, concluded it was associated with improved clinical outcomes and cost savings [61]. Pharmacist-estimated cost savings in a large integrated healthcare system over the 10-year period were $2,913,850 ($86 per encounter). The total cost of providing this service was $2,258,302 ($67 per encounter) [61]. Further evidence from a meta-analysis comparing direct pharmacy care over comparative services indicated favourable therapeutic and safety outcomes for haemoglobin A1c, low-density lipoprotein cholesterol, blood pressure and adverse drug events were significant ($P<0.05$) [62].

There is considerable interstate variation in the availability of various community pharmacy services. Collaborative Drug Therapy Management agreements are in place in 33 states, which allow pharmacists to provide clinical services such as initiating and modification of drug therapy. They are also permitted to order laboratory tests in 31 states [34].

Canadian practice demonstrates considerable interprovincial variation. Pharmacists are independently allowed to prescribe in 70% of provinces [33].Alberta is the most advanced province in terms of additional dispensing functions. Accredited pharmacists are entitled to initiate and manage drug therapy[33].

Minor ailments schemes which include POMs are supported and reimbursed in 4 provinces. However remainder of provinces (9), limit scheme to non-prescription medication and do not provide financial incentives to provide the scheme.

1.5 Hospital pharmacy worldwide

Hospital pharmacy practice varies from country to country; however, challenges are similar regardless of population, location or wealth [63]. These barriers include shortage of qualified experienced staff, inadequate IT infrastructure and inability to monitor patient outcomes [63].

1.5.1 Hospital pharmacy practice UK

As with many pharmacy matters, hospital pharmacies in the UK were to the forefront of adopting of clinical pharmacy services. Even 10 years ago, a published survey indicated that clinical pharmacy was regarded as a core service in hospitals (94% of hospital provided clinical pharmacy services) [64]. As well as providing services at ward level, UK hospital pharmacists had significant involvement in the direction of drugs and therapeutic committees at NHS Trust or Directorate level [64]. Full-time specialist pharmacist positions have become the norm in many clinical wards including emergency departments [65].

1.5.2 Hospital pharmacy practice in Europe

Overall, clinical pharmacy services provided in the EU trail behind the level of service demonstrated in the US. A total of 34% US hospitals, employ pharmacists to work full time exclusively at ward level. The same level of care is not provided in Europe; only 6% of pharmacies have pharmacists spending at least 50% of their time on the ward. Developments in clinical pharmacy have been minimal over the past 10 years. A comparable survey conducted by the European Association of Hospital Pharmacists in 2005 and 2010 demonstrate minimal changes in the provision of clinical pharmacy services amongst hospital pharmacies. Despite the recognised dangers associated with transfer of patients from hospitals to other care settings, hospital pharmacies have not

become systematically involved in the discharge planning process, only 16.9% of pharmacies offer this service on admission and 22.1% at discharge [17].

1.6 Health Economic Evaluations

1.6.1 Introduction to Health Economics

Healthcare and government agencies must decide how to allocate their resources for a wide range of different medical interventions. Costs and outcomes of different healthcare interventions require evaluation to ensure the optimum health gain from any given budget. Economic evaluation is now a widely accepted tool for the appraisal of health care and this is reflected by the increasing number of research papers in this area in the medical literature. Economic evaluation of heath care programs has become increasingly important as resource constraints necessitate decisions regarding the allocation of heath care funding. Economic evaluation assesses the costs and benefits associated with an intervention or technology and only when this information is available should decisions be made regarding the availability of new services.

The application of the principles of economics are necessary to design health services that produce the best health care outcomes for society based on available resources. This is particularly applicable to pharmaceutical spending which in 2012 accounted for 20% of all health expenditure across European Union (EU) member states, with Ireland's ranked as third highest in terms of expenditure per capita.

Ireland's expenditure on healthcare will be €13.3 billion in 2014, and this accounts for 27% of total government expenditure [66]. Despite the high expenditure, resources are still limited. An aging population, in addition to an increase in expensive health technologies will continue to raise healthcare related expenditure. We will never

inhabit a utopian society with unlimited resources available to fund all healthcare requirements; therefore tough decisions on healthcare usage will have to be made.

Insufficient healthcare funding results in trade-offs between different potential healthcare interventions. These trade-offs result in an opportunity-cost; this refers to the benefits lost when potential therapy is foregone due to the choice of an alternative [67]. The decision on whether to provide funding for a particular healthcare intervention can be a painful and sensitive issue. It can also be politically contentious and the available evidence is not the only item taken into account. Health economics can help decision makers make informed decisions on complex and often emotive matters.

The influence of health economics is becoming pervasive in all areas of healthcare provision. Economic considerations have a significant influence on drug development, medication availability, clinician prescribing and service provision [67]. Historically, clinicians would have resisted the notion that cost would have an influence on patient treatment decision. In fact, some healthcare professionals would have initially regarded health economics as a marketing tool by pharmaceutical companies [68] however, the realities of the modern healthcare system have largely eradicated suspicions surrounding health economics.

Regardless of whether they are conducted in the health services sector or an alternative industry, two features characterise an economic analysis. An economic analysis accounts for both the inputs and outputs of a service, often called the costs and consequences of a proposed activity. Additionally, an economic analysis considers the alternative choices available. Therefore, an economic evaluation can be defined as the

comparative analysis of alternative courses of action in terms of both costs and consequences [69]. An economic evaluation will attempt to identify, measure, value and compare costs and consequence of a number of alternative initiatives.

Another important factor to account for when developing a health economic evaluation is the perspective or point of view from which the study will be conducted [70]. The two most common perspectives employed are the healthcare perspective or the societal perspective. The healthcare perspective only includes direct costs which are incurred by the relevant health service. The societal perspective takes a broader viewpoint and includes indirect costs such as loss of productivity and travelling expenses, in addition to direct healthcare costs. It also enables decision makers to be more informed regarding potential "shifting of costs" from one health area to another [71]. Government departments and hospital managers tend to favour a narrower perspective, although many health economic guidelines recommend utilisation of the broadest perspective available [70].

Health economic evaluation remains a relatively contemporary field of study. Although its origins can be traced back to the 17th century [72], it has really only risen to prominence in the past 30 years. Improvements in the methodologies applied and increased confidence in outcomes associated with research in the field has helped health economics become more acceptable to all stakeholders [73].

1.6.2 Health Economics in Ireland

As early as 1989 it was recognised that health economic evaluation was being ignored within the Irish Healthcare system [74]. Early attempts at economic evaluation of

services were very much isolated accountancy driven efforts [75, 76] and were retrospective in nature. The ethos of prospective health economic evaluation did not become ingrained within the Irish healthcare system until the establishment of the Health Information and Quality Authority (HIQA). The direction for health economic evaluation remains under the remit of HIQA. It provides guidance on economic evaluation on all health technology assessments including pharmaceuticals, procedures, medical devices, broader public interventions and service delivery models [77]. While these guidelines can be used across multiple settings, they are predominantly used to inform pharmaceutical reimbursement.

Economic evaluation for service provision within the Irish healthcare system is a less transparent process. A clear pathway and decision making process is available for economic evaluation of pharmaceuticals. Marketing authorisation holders can make their submission to the National Centre for Pharmacoeconomics (NCPE). The NCPE assess evidence for comparative effectiveness and cost-effectiveness of technologies for use by patients in Ireland. Their predominant focus is on pharmaceuticals. They then make a recommendation as to whether the drug should be reimbursed within the Irish healthcare system. There are guidelines in place regarding timelines and thresholds for reimbursement. Unfortunately, this does not yet exist for medical devices or services.

Published economic evaluations of services conducted by HIQA have focused on national screening and vaccination policies rather than individual services provided by healthcare professionals [78]. There are issues regarding the generalizability of pharmacoeconomic evaluations between different healthcare systems [79].

Interventions or technologies which prove cost-effective in one country could result in an unwanted outcome when applied to another healthcare system [80]. Therefore, localised research into the economic impact of healthcare interventions is sometimes required.

Economic evaluations of clinical pharmacy services in Ireland are minimal. While there have been significant publications detailing the clinical impact of pharmacists in the Irish healthcare system, these publications have variable relevance to those responsible for allocating resources within the healthcare system [81].

Research has shown conflicting evidence regarding the utility of economic evaluations on determining healthcare policy [73]. Health policy decision making is a complex multi-faceted process which should never be reliant on a single study or input to have an overriding influence on the final decision. However, as previously discussed, the establishment of bodies such as HIQA and NCPE have established a formal input for economic evaluations within the decision making process.

One of the fundamental tenets of health economics is that funding priority is given to interventions that have the greatest effect at the lowest cost [69]. However, despite the acknowledged importance of economic evaluations they are not always used in decision making [82]. An important aspect of the influence of health economic evaluation is accessibility for decision makers. Research needs to be made available to decision makers in an accessible format [83]. Suggestions have been made to produce simplified summaries of research for non-health economists or alternatively provide health economic training to relevant stakeholders [84]. Other decision makers

have indicated their reluctance to engage with health economic research for reasons of scientific, institutional and ethical acceptability [85]. Indeed, one of the main outcome measures used within UK and Irish health economic research the quality adjusted life year has been rejected for use within evaluations in the German health system [86].

1.7 Aims and Objectives

The primary aim of this doctoral thesis was to generate an evidence base for making future policy decisions in relation to the funding of pharmacy services and defining the role of the pharmacist within the Irish healthcare system. A secondary aim was to analyse a number of novel clinical pharmacy services in a more general manner, in order to provide evidence at an international level. The author of this thesis was the primary investigator for all research presented in this thesis. The author was responsible for devising research strategy and implementing methodologies required to complete research work. The five chapters described below, provide the main evidence for this thesis. The conclusions and recommendations forthcoming from this thesis are based on the findings of chapters 2 – 6 (inclusive). Chapter 2 – 6 have are all published or under review for publication in academic peer reviewed journals. The author of this thesis is listed as the lead author on all external publications generated from work presented in this thesis manuscript.

The specific objectives for each chapter were:

Chapter 2 - Systematic review of clinical pharmacist interventions on hospital inpatients

i) Systematically review and summarise the literature concerning clinical pharmacy services directed at hospital inpatients with an associated economic outcome.

ii) Identify any changing trends in the status of hospital-based clinical pharmacy services

iii) Utilise the Consolidated Health Economic Evaluation Reporting Standards to identify whether the economic evaluations of clinical pharmacy services were of an acceptable quality from a health economic perspective.

Chapter 3 - Cost-outcome description of clinical pharmacist interventions in a university teaching hospital

i) Identify the number and type of interventions made by hospital pharmacists on hospital inpatients in a major Irish teaching hospital

ii) Determine the cost avoidance associated with these interventions

iii) Determine the cost of providing this service from a healthcare payer perspective

Chapter 4 - Economic Evaluation of a randomised controlled trial of pharmacist-supervised patient self-testing of warfarin therapy

i) Determine whether a pharmacist-supervised model of warfarin testing is cost-effective.

ii) Perform additional analysis using multiple scenarios and perspectives

Chapter 5 - Structured pharmacist review of medication in older hospitalized patients: A cost-effectiveness analysis

i) Perform a cost-effectiveness analysis comparing the impact of the novel structured pharmacist review with usual care

ii) Use a multi-level mixed effect regression model to control for variables

iii) Construction of a cost-effectiveness acceptability curve based on a number of hypothetical thresholds

Chapter 6 - Clinical and economic benefits of a community pharmacy vaccination strategy

i) Evaluate the impact of a pharmacist-led vaccination campaign on a national scale

ii) Calculate the economic and health benefits associated with the vaccination campaign.

Chapter 7 - Systematic Review Update

i) Provide an update on any recent evidence not incorporated in chapter 2.

Chapter 8 - Discussion

i) Critically examine findings of previous chapters in terms of known information and consideration of new evidence generated by this research.

ii) Examine the strengths and limitations of the major research findings

iii) Outline the implications of this research at a societal level

Summary

Clinical pharmacy services have the potential to have a positive impact within the Irish healthcare system. Existing evidence indicates that a number of novel and newly established services have demonstrated positive clinical based outcomes. However, evaluations of the impact of these services from a health economic perspective are lacking. This thesis will attempt to address this knowledge gap. Output from thesis will help ensure decision makers can make informed decisions on the future direction of both hospital and community pharmacy in Ireland.

2 - Chapter 2: Systematic review of clinical pharmacist interventions on hospital inpatients

The work of this chapter has been published as Gallagher J, McCarthy S, Byrne S. Economic evaluations of clinical pharmacist interventions on hospital inpatients: a systematic review of recent literature. Int J Clin Pharm. 2014 Dec;36(6):1101-14. doi: 10.1007/s11096-014-0008-9.

2.1 Abstract

Background

Clinical and cost-effectiveness evidence are needed to justify the existence or extension of routine clinical pharmacy services in hospital settings. Previous reviews have indicated that clinical pharmacist interventions are likely to have a positive economic impact on hospital budgets but highlighted issues relating to the quality of studies.

Aim of the review

The primary aim of this review was to feature economic evaluations of clinical pharmacy services which targeted hospital inpatients. The review focused on the current cost-effectiveness status of different services, in addition to evaluating the quality of individual studies. Results of this systematic review were compared with cost-effectiveness and quality related findings of reviews which considered earlier time frames and alternative settings.

Methods

A systematic review of the literature included a review of the following databases: Academic Search Complete, Cochrane Library, EconLit, Embase Elsevier, NHS Economic Evaluation Database and PubMed. Only studies with an economic assessment of a clinical pharmacy service provided in a hospital setting were included. Data relating to the cost-effectiveness was extracted from eligible studies. Methodologies employed and overall quality of the studies was also reviewed. A grading system was applied to determine the quality of studies. Consolidated Health Economic Evaluation Reporting Standards statement was employed to determine which aspects of a high quality health economic study were employed.

Results

Twenty studies were deemed eligible for inclusion. Overall, pharmacist interventions had a positive impact on hospital budgets. Only three studies (15%) were deemed to be “good-quality” studies. No ‘novel’ clinical pharmacist intervention was identified during the course of this review.

Conclusions

Clinical pharmacy interventions continue to provide cost savings. However, the standard of studies published has stagnated or even deteriorated in comparison with those included in previous reviews. Utilisation of published guidelines at initial stages of future studies may help improve the overall quality of studies.

2.2 Introduction

The pharmacy profession has transformed from a dispensary-based role to one centred on the provision of clinical services. While still ensuring that medicines are sourced and dispensed to a high standard, hospital pharmacists have expanded their scope of practice [87], and pharmacy interventions include integral components of the enhanced role which pharmacists offer [88-90].

A pharmacist intervention is defined as the following "any action taken by a pharmacist that aims to change patient management or therapy" [91]. Clinical pharmacy services (CPS) employ the pharmacotherapeutic expertise of the pharmacist to ensure optimal patient outcomes [92, 93] and can improve the quality, safety and efficiency of care. Various pharmacist interventions including interaction with other healthcare teams, patient interviews, medication reconciliation and patient discharge counselling demonstrated improvements in patient outcomes [87].

In addition to clinical benefits, clinical pharmacist intervention have also demonstrated positive outcomes when measured using health-related quality of life assessments (HRQoL) [94]. This involves a multidimensional assessment of a patient's physical, functional, emotional and social well-being. Pharmacist interventions targeting specific conditions including asthma, hypertension and chronic heart failure have tended to show noticeable improvements in HRQoL [94].

However, there is an omnipresent danger that previous gains made by pharmacists will be eroded due to increased pressure on healthcare resources [1]. In order to vindicate the provision of additional pharmacy services, it is no longer sufficient to provide a justification exclusively based on clinical benefits. Cost-effectiveness data is also required [81].

Previous review articles have broadly reached the same conclusion, the operation of additional clinical pharmacy services results in cost savings to the healthcare payer [80, 81, 95-97]. However, many published studies have been of poor quality [95, 97], limiting the strength of any conclusions presented in previous reviews. Due to the previously highlighted quality concerns, it was decided to conduct a quality assessment of economic evaluations.

2.2.1 Aim of the Review

This systematic review will examine economic evaluations of clinical pharmacy interventions made on hospital inpatients published between 2008 and 2012. The review will focus on assessing the economic outcomes of eligible studies. Additionally, it aims to provide a description of the quality of included studies. There has been no previously published systematic review which has exclusively focused on services specifically targeted to hospital inpatients covering the stated time period. This systematic review will provide evidence to healthcare decision makers regarding the cost-effectiveness of various services. Additionally, it will highlight to academics and clinical practitioners study areas which have been poorly designed and could be improved upon in the future.

2.3 Method

2.3.1 Search strategy

This review of the literature was undertaken in April 2013. Searches were conducted of the following databases: Academic Search Complete, Cochrane Library, EconLit, Embase Elsevier, NHS Economic Evaluation Database and PubMed. The publication dates of articles included in search strategy ranged from January 2008 to December

2012. All authors were involved in the development of PubMed search strategy and appropriate Medical Subject Headings (MeSH) terminology was utilised. The following MeSH terms were employed: “drug information services”, “medication therapy management”, “drug toxicity”, “prescriptions”, “drug therapy”, “pharmacy services hospital” combined with “cost and cost analysis”, “economics, pharmaceutical”. Similar search strategies, with MeSH terms mapped to appropriate key words were used for additional databases. The full search strategy is detailed in Appendix 10.3. Search results from multiple databases were transferred to a reference manager, EndNote X6. Due to the broad remit of the search strategy, a ‘title review’ stage was conducted to remove obviously non-pertinent studies. This was conducted by the primary author. Studies were removed in a cautious manner. Abstract review was then performed. If a study clearly did not meet inclusion criteria it was excluded. Studies which had not been excluded following abstract review stage underwent full-text review. Full-text review was performed by the primary author. Studies selected for inclusion in the systematic review were reviewed by the co-authors to ensure they met eligibility criteria.

2.3.2 Review criteria and data extraction

Studies were required to meet multiple criteria specified in **Table 2.1**.

Table 2.1 Inclusion and exclusion criteria for systematic review

Inclusion criteria	Exclusion criteria
Published peer reviewed full-text articles	Non-peer reviewed literature e.g. government documents, technical reports, newspaper articles, letters to the editor, media releases
Study assessed an intervention performed by a pharmacist or team of pharmacists	Studies based on modelling effect of an intervention
Intervention must conform to the unabridged American College of Clinical Pharmacists (ACCP) definition of clinical pharmacy [3]	
Study must include an economic assessment (Measurement of costs to provide the service, outcomes expressed in monetary terms or both)	
Interventions must be conducted on inpatients in a hospital setting	Studies conducted in outpatient clinics, nursing homes, veteran's affairs clinics and any form of community level care
Study published in English language	

The references of eligible studies and previously published systematic reviews were systematically searched to ensure that they did not contain further relevant research. The heterogeneity of health economic studies prevented a meta-analysis being undertaken. Grey literature (e.g. government documents, technical reports etc,) was excluded.

Studies which met inclusion criteria were analysed with the aid of a data collection form (Appendix 10.4). Information collected included details of authors, type of intervention, study setting, study sample size, economic method, study period, outcome measures and results and multiple quality assessment related data. Completed data collection forms were reviewed by all listed authors.

2.3.3 Quality assessment

An established quality assessment of the economic methods employed was conducted [95]. Assessment comprised of a simple three question assessment, i) Was a comparator used? ii) Were program costs evaluated and described? iii) Were program outcomes evaluated and described? Studies were determined to be "good-quality" studies if they complied with all three criteria. Studies which lacked a comparator or had multiple flaws were labelled as "poor-quality". Studies which included a comparator but which did not evaluate either program costs or program outcomes were labelled as "fair-quality". This quality assessment was included as it provided a clear distinction on the standard of studies from a health economic perspective. Furthermore, it had been utilised in previous systematic reviews which enabled comparisons to be drawn with earlier time periods [95].

In addition to the previously described quality assessment, the authors decided it would be worthwhile to conduct a more comprehensive quality appraisal of included studies to provide an in depth analysis of study areas. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [98] ,was applied to eligible studies. The CHEERS statement contains a checklist detailing aspects of health economic methodologies which should be considered for inclusion in a study (Appendix 10.5). As The CHEERS statement was designed for use across all types of health economic evaluations, only items on the statement checklist relevant to studies under review will be examined in this review.

Descriptive statistics were used to summarise type of intervention, economic analysis, model, perspective and sensitivity analysis. A data collection form was initially completed by the primary author and then independently reviewed by another named author.

2.4 Results

Following elimination of duplicate titles, the search strategy yielded 6,815 titles for review. Reasons for exclusion are outlined in **Figure 2.1**. Twenty-two texts were considered eligible for inclusion in the systematic review. Studies were conducted in Asia [8], USA [8], Europe [5] and South America [1]. All studies were published in health related journals. **Table 2.2** contains a summary of studies which met inclusion criteria.

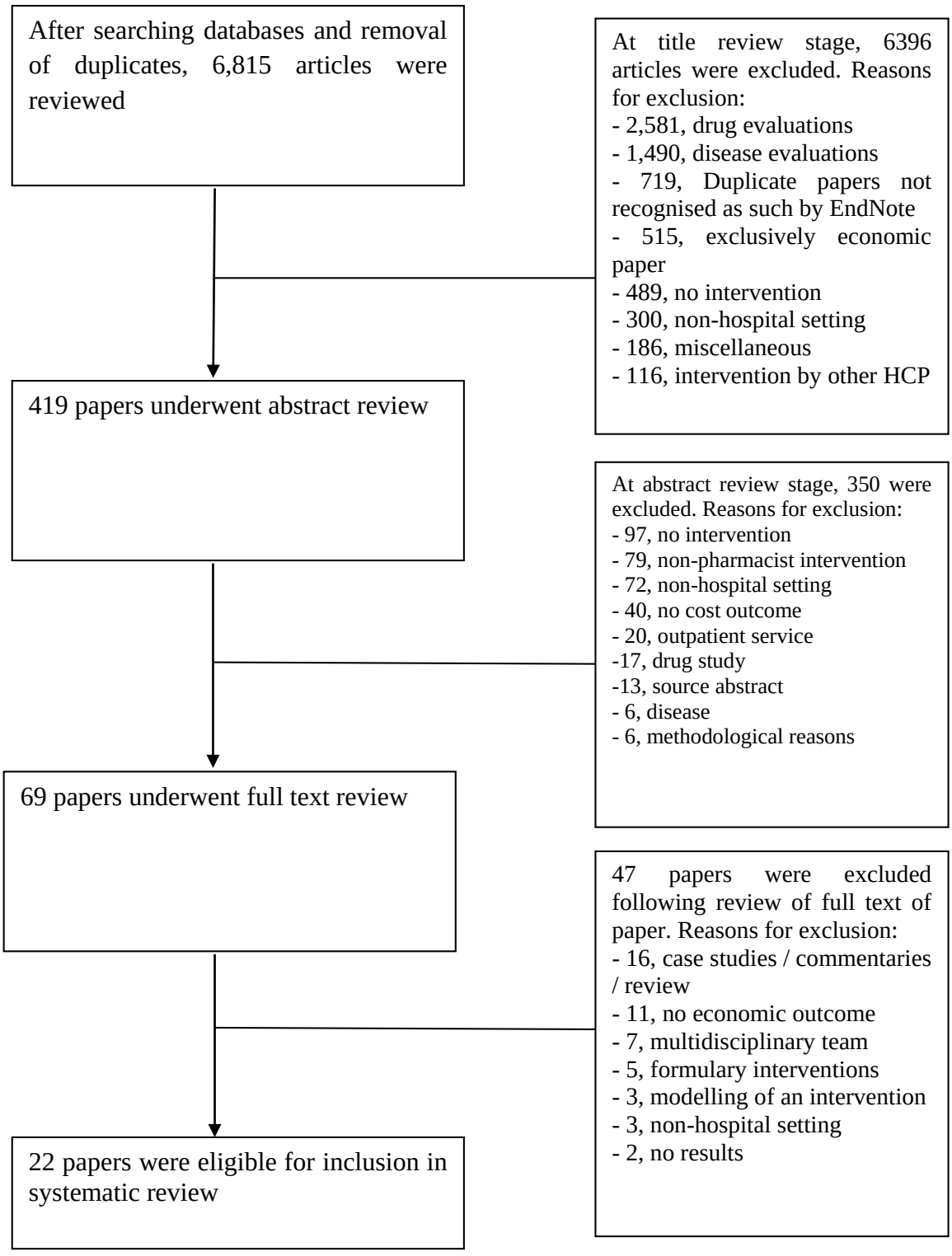


Figure 2.1 Literature search method and screening results

Table 2.2 Description of studies eligible for inclusion in this review

First Author (Year)	Title	Pharmacist Intervention	Setting	No of patients / Interventions	Economic Method	Period	Outcome Measures	Results	Quality	Type of study
Wallerstedt et al. (2012)	A cost-effectiveness analysis of an in-hospital clinical pharmacist service	Composite intervention of medication reviews, drug treatment discussion with the patient at discharge and medication report.	Two internal medicine wards in University Hospital in Sweden	181 control patients and 164 intervention patients	Cost-utility Analysis.	2007 - 2008. 6 month follow up on patient.	Effectiveness measured in gain in quality adjusted life years (QALY) as measured by EQ-5D.	Unlikely to be cost effective. Cost per QALY of €316243. No significant difference in total healthcare costs between study groups.	Good	Randomised controlled trial.
Magedanz et al. (2012)	Impact of the pharmacist on a multidisciplinary team in an antimicrobial stewardship program: a quasi-experimental study	Impact of a pharmacist on an antimicrobial stewardship program (ASP)	Cardiology hospital, Brazil	Not provided	Cost analysis	Pharmacy responsible for ASP: 19 months. ID Physician responsible for ASP: 21 months. Pre-implementation of ASP (Control): 30 months.	Mean monthly antibiotic costs	The mean monthly antibiotic cost, during the control stage, was US$30,727, US$ in the ID physician led ASP period and US$9623 in the pharmacist-led ASP period of study.	Fair (Missing cost of service)	Quasi-experimental study
Dunn et al (2011)	Implementing a pharmacist-led sequential antimicrobial therapy strategy: controlled before and after study	Intervention group consisted of application of stickers and implementation of criteria for switch to oral therapy Control was routine pharmacist care.	753 bed academic hospital in Ireland.	72 patients in intervention group and 44 in control group.	Cost analysis	Three data collection periods of 10 consecutive days	Direct cost savings were measured but it was not primary outcome	Antimicrobial costs reduced by a mean €6.41 per patient.	Fair (Missing cost of service)	Prospective, controlled before-and-after study design

Table 2.2 (continued) Description of studies eligible for inclusion in this review

First Author (Year)	Title	Pharmacist Intervention	Setting	No of patients / Interventions	Economic Method	Period	Outcome Measures	Results	Quality	Type of study
Shen et al. (2011)	Pharmacist interventions on antibiotic use in inpatients with respiratory tract infections in a Chinese hospital	Pharmacist making recommendations to clinical team of nurses and physicians. Control was absence of pharmacist involvement.	Respiratory wards in tertiary hospital in China	178 patients (control group), 176 patients (intervention group).	Cost analysis	July 2009 - April 2010	Total costs of hospitalisation and cost of antibiotics	The total costs of hospitalization in the intervention group were significant lower compared to the control group ($1442.3 ± 684.9 vs. $1729.6 ± 773.7).Cost of antibiotics ($832.0 ± 373.0 vs. $943.9 ± 412.0)	Fair (Missing cost of service)	Randomised controlled trial.
Winger et al. (2011)	Cost savings from dose rounding of biologic anticancer agents in adults	Cost savings from dose rounding of biologic agents	US	33 dose adjustments	Cost description	January 1 - March 1 2005	Direct cost savings	$15922, direct cost savings	Poor (No comparator, missing cost of service)	Retrospective database review
Steinberg et al. (2008)	Impact of Pharmacy Generated Recommendations on Antibiotic Therapy in Community Hospital	Pharmacist initiated antibiotic review service.	550 bed community hospital. Only undertaken in selected wards. USA	122 patients.	Cost analysis	10 weeks. Dec 2005 to Feb 2006	Total money saved based on interventions generated. Total antibiotic cost per patient	Overall savings of $12313.22. No significant difference in cost per patient between control and intervention groups.	Fair (Missing cost of service)	Pre and post intervention

Table 2.2 (continued) Description of studies eligible for inclusion in this review

First Author (Year)	Title	Pharmacist Intervention	Setting	No of patients / Interventions	Economic Method	Period	Outcome Measures	Results	Quality	Type of study
Moffett et al. (2008)	Medication dosing and renal insufficiency in a paediatric cardiac intensive care unit: Impact of pharmacist consultation	Pharmacist made recommendation to renal team regarding appropriateness of medication	Paediatric cardiac ICU, Houston, Texas, USA.	131 patients admitted during study period. 37 patient admissions required adjustment.	Cost description	January through March 2006 3 months	Monetary impact of pharmacist interventions was determined by calculating the number of doses saved	Cost savings of $12482.54.	Poor (No comparator, missing cost of service)	Retrospective analysis
Gillespie et al. (2009)	A comprehensive pharmacist intervention to reduce morbidity in patients 80 years or older	Compilation of meds on admission. Drug review. Patient education and discharge counseling. Contacted primary care physician.	2 acute medicine wards University Hospital of Uppsala, Sweden.	199 patients in intervention group. 201 patients in control group.	Cost analysis	October 1 2005 - June 30 2006 (9 months)	Secondary outcome was cost of hospital care	Total direct cost of secondary care during follow up year was $400 per patient in the intervention group vs. the control group. $230 per patient overall cost savings.	Good	Randomised controlled trial.
Mac Laren et al. (2009)	Effects of pharmacist participation in intensive care units on clinical and economic outcomes of critically ill patients with thromboembolic or infarction-related events	Direct patient care services provided by a pharmacist specifically devoted to an intensive care unit.	Multiple US hospitals	141,079 Medicare patients who experienced a thromboembolic or infarction related event. 77,857 were in hospitals with critical pharmacist care.	Cost analysis	Retrospective database review (01/09/04 - 31/08/05)	Medicare charges, drug charges and laboratory charges	Additional charges for control group in comparison with pharmacist group $215,397,354 in Medicare charges, $26,363,674 in drug charges, no difference in laboratory charges.	Fair (Missing cost of service)	Retrospective database review

Table 2.2 (continued) Description of studies eligible for inclusion in this review

First Author (Year)	Title	Pharmacist Intervention	Setting	No of patients / Interventions	Economic Method	Period	Outcome Measures	Results	Quality	Type of study
Hassan et al. (2009)	Impact of renal drug dosing service on dose adjustment in hospitalized patients with chronic kidney disease	Pre and post intervention period comparison. Pharmacist participation in nephrology team rounds.	35 bed nephrology unit, Penang General Hospital, Malaysia	Each phase had a random sample of 300 patients.	Cost analysis	4 months. Beginning of Feb to end of May 2007.	Drug cost savings of original physician regimen in comparison with pharmacist regimen	$2250 US for study. For all patients admitted to unit over 1 year, 13500 US$.	Fair (Missing cost of service)	Pre and post intervention
Campbell et al. (2011)	Analysis of cost avoidance from pharmacy students' clinical intervention at a psychiatric hospital	Retrospective database review of interventions made by pharmacy students.	Adult inpatient state psychiatric hospital, Missouri. 120 beds	320 interventions by 15 pharmacy students	Cost description	1 year. June 1, 2008 - May 31, 2009.	Estimated cost avoidance based on MediTrend values for adverse drug events and literature review.	Cost avoidance of $23000 (Literature calculation) or $4000 (MediTrend calculation)	Poor (No comparator, missing cost of service)	Retrospective database review
Ijo et al. (2011)	Pharmacy intervention on antimicrobial management of critically ill patients	Prospective pharmacy driven antimicrobial stewardship in the intensive care unit.	31 bed medical-surgical and cardiac ICU. US	70 patients.	Cost description	November 2009 - February 2010 (3 months)	Financial outcomes from drug discontinuation, streamlining, iv-po conversion, dose optimization, addition and substitution.	Service resulted in an additional cost of $192 to the pharmacy	Poor (No comparator, missing cost of service)	Prospective audit.

Table 2.2 (continued) Description of studies eligible for inclusion in this review

First Author (Year)	Title	Pharmacist Intervention	Setting	No of patients / Interventions	Economic Method	Period	Outcome Measures	Results	Quality	Type of study
Zhang et al. (2012)	Clinical pharmacists on medical care of pediatric inpatients	Clinical pharmacist active participation in paediatric ward rounds. Control consisted of no clinical pharmacist participation.	West China Second University Hospital	80 patients in each group.	Cost analysis	4 Months, Dec 1 2010 - March 31, 2011	Cost of drugs and cost of hospitalisation. This was a secondary outcome.	No statistical difference in costs of drugs and cost of hospitalisation.	Poor (Multiple flaws)	Randomised controlled trial
Wilkinson et al. (2011)	Impacting readmission rates and patient satisfaction: Results of a discharge pharmacist pilot program	Pharmacist driven discharge program for high risk patients. No control	University of Kansas Hospital. 525 beds average daily census.	229 patients received pharmacist evaluation.	Cost description	3 month study period beginning in Sept 2009	Cost avoidance calculated using Veterans affairs model.	Total cost avoidance €378,899	Poor (No comparator, missing cost of service)	Prospective, cohort, non-randomized trial.
Jing et al. (2009)	The impact of pharmacist intervention on the use of activated Vitamin D in a tertiary referral hospital in Malaysia	Retrospective review of activated Vitamin D use. Pharmacists discontinued unnecesary use.	University Malaya Medical Centre	557 patients	Cost analysis	1 year prior to intervention and 1 year post intervention.	Cost of Vit D in pre and post intervention periods.	Decease of RM400616.80(US$111,282.40) annually. P=0.002	Fair (Missing cost of service)	Pre and post intervention

Table 2.2 (continued) Description of studies eligible for inclusion in this review

First Author (Year)	Title	Pharmacist Intervention	Setting	No of patients / Interventions	Economic Method	Period	Outcome Measures	Results	Quality	Type of study
Nasser et al. (2010)	Cost reduction associated with restriction policy on dispensing intraveneous esomeprazole in Lebanon	Impact of pharmacist intervention on cost following implementation of restriction on esomeprazole iv dispensing. Physicians fill a form and pharmacists review prior to approval.	Inpatients of a Lebanese hospital	Not given	Cost analysis	12 months pre restrictions and 12 months post restrictions.	Measured reduction in IV vials dispensed, and calculated associated cost	Reduction of $21,233 per month.	Fair (Missing cost of service)	Pre and post intervention
Hou et al. (2011)	Retrospective evaluation of the outcomes of applying the renal dosing monitoring system in a medical centre	Computerised dosing system modifies dosing for patients with renal impairment. Pharmacist then decides whether to make recommendations. Retrospective analysis of outcomes.	Inpatients in a Taiwanese hospital.	12,057 cases reviewed. Pharmacists made recommendation in 202 cases and 173 suggestions were accepted.	Cost description	April 2007 - March 2008	Cost savings due to dosage adjustments	US$5377	Poor (No comparator, missing cost of service)	Retrospective evaluation
Klopotowska et al. (2010)	On-ward participation of a hospital pharmacist in a Dutch ICU reduces prescribing errors and related patient harm: an intervention study	ICU hospital pharmacist reviewed medications for ICU patients and noted issues for discussion with ICU physician. If consensus reached issues were scored as prescribing errors.	Adult medical and surgical ICU, in a 1,002 bed tertiary care academic hospital in Amsterdam	All patients admitted to ICU during study period.	Cost analysis	8 months (Intervention period). 3 weeks, (Baseline period). 3rd Oct 2005 and 30th June 2006.	Estimate of cost avoidance. Secondary outcome.	Cost savings of €26 -40 per patient per day.	Good	A prospective baseline vs intervention period study

Table 2.2 (continued) Description of studies eligible for inclusion in this review

First Author (Year)	Title	Pharmacist Intervention	Setting	No of patients / Interventions	Economic Method	Period	Outcome Measures	Results	Quality	Type of study
Chan et al. (2009)	Pharmacist intervention in activated protein C therapy for severe sepsis: influence on health and economic outcomes	Clinical pharmacists determine the appropriateness of prescribing activated protein C to a patient	Taiwanese hospital. Inpatiens. No further info given.	19 patients in each group.	Cost analysis	2 years pre intervention. 2 years post intervention. Jan 2003 to Dec 2007.	Total direct medical costs for both groups.	Intervention group US$20,632.3 vs control group US$24,785.8. Converted to US dollars from taiwanese currency but no conversion date give.	Fair (Missing cost of service)	Retrospective comparison
Yen et al. (2012)	Clinical and economic impact of a pharmacist-managed iv to po conversion service for levofloxacin in Taiwan	Pharmacist managed iv to po conversion programme for levofloxacin	Inpatients in a Taiwanese hospital. Tertiary hospital with 732 beds	37 patients in each group.	Cost analysis	Pre intervention 1/07/08 - 31/08/08 (2 months). Intervention period 01/10/08 - 31/12/08 (3 months).	Two cost outcomes, total inpatient expenditure and cost of antibiotics for both groups.	Antibiotics: Pre-intervention US$568.9 vs 449.0. Total inpatient expenditure:Pre-intervention US$6096.5 vs 3649.6. Converted to US Dollars but no conversion date.	Fair (Missing cost of service)	Retrospective comparison pre and post intervention
Swoboda et al. (2009)	Implementation of Practice Guidelines for Antifungal Therapy in a Surgical Intensive Care Unit and Its Impact on Use and Costs	Implementation of practice guidelines for antifungal therapy by a clinical pharmacist.	Surgical intensive care unit of the University Hospital of Heidelberg, Germany	372 patients in control period. 379 patients in intervention period.	Cost analysis	Control period January 2005 – June 2006 (18 months). Intervention period July 2006 – December 2007 (18 months)	Costs for antifungal agents during a period of 18 months before and after implementation.	Total of €557110 was spent on antifungal agents during the control period. Total of €258806 was spent on antifungal agents during the intervention period.	Fair (Missing cost of service)	Pre and post intervention

Table 2.2 (continued) Description of studies eligible for inclusion in this review

First Author (Year)	Title	Pharmacist Intervention	Setting	No of patients / Interventions	Economic Method	Period	Outcome Measures	Results	Quality	Type of study
Weant et al. (2009)	Cost effectiveness of a clinical pharmacist on a neurosurgical team	Monitoring and evaluating patients, participating in team rounds.	Neurosurgical service in a US hospital	1077 patients in control group. 1079 patients in intervention group.	Cost analysis	2 years pre implementation period and 2 years post implementation period.	Average pharmacy and intravenous cost of therapy per patient	The average pharmacy and intravenous therapy costper patient between the pre- and postimplementation groups decreased from $4833 to $3239	Fair (Missing cost of service)	Pre and post intervention

Type of economic evaluation

Only one of the studies was determined to be a full cost-utility analysis [99]. Fifteen of the studies included were labelled as cost-analysis [100-114] . While a further six were simple cost-description studies [115-120].

Clinical pharmacy interventions

Interventions were in the following areas antimicrobial management [100-103, 112, 118], targeted drug programmes [108, 109, 115, 121], multi-dimensional clinical pharmacy service [99, 104, 119], paediatric programmes [116, 122], renal specialist [106, 120], pharmacotherapeutic optimisation [110, 123], intensive care service [113, 124] and neurosurgery [114]. All intervention types have been identified in previous reviews of the literature [80, 81, 95, 96].

Antimicrobial management

Six antimicrobial interventions were identified. Five of the studies included a comparator, either in the form of a randomised controlled trial [102] or a pre- and post-intervention comparison [100, 101, 103, 112]. One study was a prospective audit [118]. Two studies evaluated antimicrobial stewardship programmes. A stewardship programme set in a Brazilian cardiology hospital, reported a reduction in mean antibiotic costs (Pharmacist present - US$9623.73 v No pharmacist - US$18034.89) when a pharmacist was included as part of a multidisciplinary team [100]. The study lacked information on the number of patients or interventions. An alternative antimicrobial stewardship programme was conducted in a US intensive care unit (ICU) [118]. On a sample of seventy patients, improved clinical outcomes were reported but associated antibiotic costs increased by US$192. An Irish study,

attempted to reduce antibiotic costs through pharmacists highlighting interventions to switch from the intravenous (iv) to the oral (po) routes of administration [101]. Antimicrobial costs were reduced by €6.21 per patient. A study focusing on iv to po switching of levofloxacin in Taiwan, reported a reduction in total inpatient expenditure of US$2446.9 [112]. Pharmacist provided antibiotic review services, showed overall cost savings in a US hospital but did not result in any significant reductions in cost per patient between control and intervention groups [103]. A similar programme in a Chinese hospital resulted in a reduction in total costs of hospitalization in the intervention group versus control group (US$1442.3 ± 684.9 vs. US$1729.6 ± 773.7) [102]. Antibiotic costs (US$832.0 ± 373.0 vs. US$943.9 ± 412.0) were also reduced. No study relating to antimicrobial management adequately assessed the costs of providing the service.

Targeted drug programmes

Four studies described cost outcomes associated with intervention on specific drugs or classes of drugs. Thirty-three interventions on biologic agents provided savings of US$15922 in a US hospital [115]. Pharmacists simply rounded the dose of anticancer agents to reduce medication waste. Pharmacists discontinued unnecessary vitamin D supplements over a 1 year period, resulting in cost savings of US$111,282.40 [108]. A group of hospital pharmacists reviewed the appropriateness of prescribing iv esomeprazole resulting in savings of US$21233 per month [109]. Pharmacists in Taiwan reviewing the appropriateness of activated protein C therapy in septic patients over a 2 year period, demonstrated a reduction in total direct medical costs [121]. Service costs were omitted in the above studies.

Multi-dimensional clinical pharmacy service

A multi-faceted pharmacist intervention programme incorporating medication reviews, patient counselling and discharge was reported as being unlikely to be cost-effective. This was based on a cost of €316243 per increase in quality adjusted life year (QALY) [99]. A similar study, also conducted in Sweden reported that the total cost of secondary care per patient was US$230 lower than in intervention group over a 12 month follow up period [104]. Significantly, both of these studies adequately described associated costs of providing a service.

A pharmacist-led discharge programme, consisting of patient counselling, medicines reconciliation and overall medication support resulted in cost avoidance of $378899 for a group of 229 patients [119]. Cost of service was not stated.

Paediatric programmes

Pharmacists review of medication appropriateness in a paediatric cardiac ICU resulted in cost savings of $12482 from 131 patients [116]. However, the study lacked a comparator and didn't assess cost of service. Pharmacists participated in ward rounds in a Chinese paediatric hospital. Intervention and control group showed no significant differences in terms of cost of drugs or cost of hospitalisation [122].

Renal specialist

Pharmacist participation in renal team ward rounds resulted in cost savings of US$2250 in comparison with control group [106]. The study size was 300 patients per group. Pharmacist recommendations on dosage adjustments for patients with renal

impairment resulted in savings of $5377 [120]. Savings were generated from 173 accepted interventions. Neither evaluation considered cost of providing the service.

Pharmacotherapeutic optimisation

Pharmacy students identified 320 interventions, resulting in a cost avoidance of $23000 due to the prevention of potential adverse drug events [123]. A study evaluating the participation of pharmacists in a Dutch ICU ward reported savings of $26 – 40 per monitored patient-day. Cost of providing the service was estimated [110].

Intensive care programme

A retrospective review of hospital databases indicated, presence of ICU specialist pharmacists resulted in improved clinical and economic outcomes in patients with thromboembolic events. Examining a total population of 141,079, patients who did not receive specific pharmacist care had additional Medicare costs of $215 million and drug charges of $26 million [124]. Implementation of antifungal practice guidelines by a clinical pharmacist member of an ICU team resulted in a 50% cost reduction in expenditure on antifungal agents [113].

Neurosurgery

A dedicated clinical pharmacist integrated as part of a neurosurgery team, resulted in total savings of US$1,718,260 from 11250 interventions implemented over the 2 year study period [114].

Quality appraisal

Three studies [99, 104, 110], achieved good-quality ratings. Twelve studies were described as being of fair-quality as they did not include the cost of providing the service or intervention as part of the evaluation. Seven studies were considered to be of ‘poor-quality’.

The relevant criteria identified from the CHEERS statement are listed in **Table 2.3**; the number of studies which successfully addressed individual criteria is also detailed. Only one study accommodated all relevant criteria [99]. The most common items to be included in studies were details of patient demographics (77%) and a comparator (68%). Statements on discount rates (measure of reduction in value of future costs and outcomes), horizon (period over which costs and outcomes were evaluated) and the perspective of the study were excluded in almost every study.

Table 2.3 Quality assessment of eligible studies

Item from CHEERS checklist	**% of studies included (n = 22)**
Demographics	77 (n = 17)
Comparator	68 (n = 15)
Estimating resources and costs	36 (n = 8)
Study parameter	32 (n = 7)
Incremental Cost-Effectiveness ratio	23 (n = 5)
Analysis of uncertainty	23 (n = 5)
Currency	18 (n = 4)
Perspective	9 (n = 2)
Horizon	4 (n = 1)
Discount	4 (n = 1)

2.5 Discussion

Based on the studies examined in this review, clinical pharmacist interventions remain economically beneficial. The majority of studies included in this review demonstrated

some degree of cost savings; however the disparate nature of evaluated interventions and outcome measures makes it impossible to determine the most beneficial intervention type. Furthermore, the methods used to calculate and report outcomes do not facilitate inter-disciplinary comparison.

Significant savings were generated through the prevention of ADEs; this concurs with findings of previous reviews which estimated that ADE prevention resulted in the highest cost-benefit ratio [81]. However, cost avoidance based results should be interpreted with caution, as it is difficult to predict the extent to which they will be reflected in real practice [80].

Clinical pharmacy services which targeted complex high cost environments such as ICUs, neurosurgery or biologic agents demonstrated promising results. While specialist training and experience is advantageous in this care area[125], interventions conducted in these settings have potentially a greater financial impact in comparison with interventions implemented in general wards. Furthermore, interventions deliver immediate savings which can be easily presented to administrators. Demands for critical care services are expected to increase [126]. Pharmacy education programmes should adapt accordingly to ensure graduates are suitably qualified for employment in these areas [127].

Multiple health technology assessment bodies have tended to favour cost-utility based evaluations which include measurements such as QALYs [128]. QALYs measure health as a combination of HRQoL and the expected duration of a patient's life, facilitating comparison between interventions in diverse healthcare settings [129]. QALYs were only used as the primary outcome in one included study [99]. This made

the comparison of outcomes between interventions impracticable. Other outcome measures which could be utilised to a greater extent are reductions in hospitalisations or mortality rates. These measures are more generalisable and facilitate inter disciplinary comparison.

The established trend in systematic reviews of economic analyses is the identification of a low number of 'good quality' studies [95, 97]. This issue is replicated in this review. The quality of studies from a health economic perspective has deteriorated in comparison with previous reviews. Perez *et al*. review established that 27% of studies were of good quality [95]. Only 13% of studies included in this review were labelled as good quality studies. The majority of studies did not make any attempt to calculate input costs for the study. When input costs are not appropriately estimated, it is impossible to make an informed decision on the true value of a service. Savings or associated benefits can be overestimated. Quality issues seem to be particularly prevalent in hospital studies. A recent systematic review which included community pharmacy, noted an improvement in standards of economic evaluations of clinical pharmacy services [96].

The application of the CHEERS checklist on eligible studies highlights the poor reporting standards from a health economic viewpoint. Basic components of a high quality economic evaluation such as estimation of resources and costs, uncertainty analysis and discount rates were absent from the majority of studies. The primary outcome of the majority of included studies was clinically orientated. This is reflected in the manner in which they were reported. Stating the perspective of the study, would be expected in a good quality health economic publication. However, this was only

quoted in two studies. It is expected that health economic studies would account for the uncertainty surrounding evidence used and some methodological assumptions [130]. The most basic way to address this issue is by conducting a sensitivity analysis. However, the issue of uncertainty was not considered in the vast majority of the studies.

The highest quality evaluation included in this study concluded that a composite clinical pharmacist intervention consisting of medication review, patient education and provision of a medication report, was unlikely to prove cost-effective. Wallerstedt *et al*. used the EQ-5D questionnaire which is a generic preference measure used to calculate QALYs [131]. For mild impairments, which most pharmacy interventions would be directed towards, condition specific preference measures have proven to be more sensitive (45). Despite their widespread use, QALYs are far from the perfect outcome measure and may exclude important health consequences (46). In addition, to issues around sensitivity mentioned previsously there are additional factors which increase the uncertainty surrounding their practicality[132]. Some researchers have questioned the validity of the underlying assumptions of a QALY based approach [133]. The QALY approach assumes that the value of being in a health state, for two years is twice that of being in the health state for one year [134]. Another assumption questioned, is that the value of a health state is independent of where a health state occurs in a sequence of health events [134]. On the contrary, the advantages of QALY based cost-effectiveness analysis are that they allow comparison across disparate therapy areas [129]. The widespread use of QALY based measurements has resulted in the availability of mapped algorithms to generate QALY values from disease specific questionnaires [129].

There were no new types of clinical pharmacist interventions highlighted in this review. This is a worrying finding for the future of pharmacy. While the profession has evolved, a constant stream of novel services will ensure that the profession does not stagnate. The lack of developments in economic evaluations of clinical pharmacy services is not just confined to a hospital setting. A recent review which included community, ambulatory and long-term care facilities did not unearth any 'novel' clinical pharmacy intervention [96].

A surprising aspect of this review was the increase in the number of studies reporting data from Asian healthcare systems. A number of these studies cited an underutilisation of pharmacy services in their jurisdiction. Production of economic evidence to augment clinical evidence is an excellent strategy to precipitate a change in mind-set within these countries.

There is an English language bias in this review. This is particularly important in health economic evaluations as the cost-effectiveness of a study is affected by the jurisdiction in which it is performed. The review may also be subject to a publication bias as grey literature was not evaluated.

As previously discussed, the lack of standardisation in reporting outcomes and poor quality of studies reduced the ability for comparisons between interventions.

2.6 Conclusion

Clinical pharmacy interventions continue to provide cost savings. However, the number of studies examining the subject has decreased and there is a dearth of good

quality studies. There was no novel clinical pharmacy service included in this review. The standard of studies published has stagnated or even deteriorated in comparison with those included in previous reviews. A number of reasons have been proposed to account for this, including lack of interest from academic journals due to the decline in 'novel' clinical pharmacy services. Alternatively, judgement may have been reached that established clinical pharmacy services are in general cost-effective and further research into them is unlikely to be necessary. Pharmacist interventions in complex high-cost healthcare settings have been supported by multiple studies included in this review and are an area of care which pharmacy research and education could be directed towards in the future. Economic analysis was not the main outcome measure in majority of studies and was added almost as an afterthought to the primary results. In order to increase their relevance, future economic evaluations should at the very least present the cost of providing a service in addition to economic and clinical outcomes in comparison with an alternative option. Utilisation of a checklist like the CHEERS statement has the potential to improve quality of studies; however previous published guidelines have not had a lasting impact.

3 - Chapter 3: Cost-outcome description of clinical pharmacist interventions in a university teaching hospital

The work of this chapter has been published as Gallagher J, Byrne S, Woods N, Lynch D, McCarthy S. Cost-outcome description of clinical pharmacist interventions in a university teaching hospital. BMC Health Serv Res. 2014 Apr 17;14:177. doi: 10.1186/1472-6963-14-177.

3.1 Abstract

Introduction

Pharmacist interventions are one of the pivotal parts of a clinical pharmacy service within a hospital. This study estimates the cost avoidance generated by pharmacist interventions due to the prevention of adverse drug events (ADE). The types of interventions identified are also analysed.

Methods

Interventions recorded by a team of hospital pharmacists over a one year time period were included in the study. Interventions were assigned a rating score, determined by the probability that an ADE would have occurred in the absence of an intervention. These scores were then used to calculate cost avoidance. Net cost-benefit and cost-benefit ratio were the primary outcomes. Categories of interventions were also analysed.

Results

A total cost avoidance of €708,221 was generated. Input costs were calculated at €81,942. This resulted in a net cost-benefit of €626,279 and a cost-benefit ratio of 8.64: 1. The most common type of intervention was the identification of medication omissions, followed by dosage adjustments and requests to review therapies.

Conclusion

This study provides further evidence that pharmacist interventions provide substantial cost avoidance to the healthcare payer. There is a serious issue of patient's regular medication being omitted on transfer to an inpatient setting in Irish hospitals.

3.2 Introduction

The traditional role of a pharmacist predominantly involved the dispensing of medications in both hospital and community settings; consequently the pharmacist was quite detached from other healthcare professionals. The profession has since evolved to become recognised as an essential part of the healthcare team [135]. While still ensuring that medicines are sourced and dispensed to the highest possible standards, pharmacists have diversified into alternative areas of care in hospital practice [87]. Interventions are integral components of the new enhanced role which pharmacists offer in a clinical setting [88-90, 102, 110, 136].

A pharmacist intervention is defined as any action taken by a pharmacist that aims to change patient management or therapy [91]. A pharmacist's expertise in pharmacology, pharmacotherapy and pharmaceutics ensures they have the requisite capabilities to offer suggestions to other healthcare staff on possible alterations to a patient's therapy [92]. This helps to ensure optimal patient outcomes, which has the potential to have an add-on economic benefit to the healthcare institution.

A myriad of studies have described the high rate of potential inappropriate prescribing and potential adverse drug events (ADE) in multiple healthcare systems [137-141]. An ADE is defined by the International Conference for Harmonisation as "any untoward medical occurrence in a patient administered a medicinal product which does not necessarily have to have a causal relationship with treatment". These issues cause repercussions in the form of increased resource utilisation [142]. Evidence of the clinical benefit and reduction in ADEs associated with enhanced roles for pharmacists in a hospital setting, are documented in the literature [80, 87, 88, 143].

Healthcare systems worldwide are coming under increasing pressure due to a combination of aging populations and the proliferation of new expensive technologies [67]. All healthcare services need to show that they provide value for money for the investment made in their provision [144][21]. Despite early scepticism, health economic evaluations are required for the establishment and continued provision of services and technologies [67].

The provision of a clinical pharmacy service in a hospital setting is an investment which utilises costs which could be used elsewhere in the health system. Economic evaluations of clinical pharmacy services will help policy makers make informed decisions on whether they are a worthwhile investment. Studies in other jurisdictions have indicated that they are cost-effective, however these findings are not generalisable [145, 146].

This paper will analyse the interventions made by a team of pharmacists in a university teaching hospital and evaluate the cost avoidance achieved through the prevention of an ADE. For the purposes of this study, cost avoidance refers to an intervention that reduces or eliminates additional expenditure that otherwise may have been incurred in the absence of the intervention [117]. It is a different measure to cost saving interventions, which refer to reductions in current spending due to changes in the expenditure on a patients treatment [147]. Cost avoidance interventions contain and control costs and over a longer period of time they can result in cost savings.

The study was based in an Irish university teaching hospital / tertiary referral centre setting over a period of one year. Similar studies have been performed, examining

shorter time periods or focusing on specific interventions [88-90, 110, 136, 147]. However, information which helps to evaluate the economic impact of pharmacist interventions over a longer period of time and covering an entire hospital domain is lacking. The authors have been unable to find a study where cost avoidance generated by a full department of clinical pharmacists in a full calendar year has been calculated.

3.3 Methods

3.3.1 Setting

This was a retrospective study based on a 1 year time period from 01/01/2012 to 31/12/2012 inclusive. Cork University Hospital (CUH) and the Cork University Maternity Hospital is a combined 850-bed hospital site. The hospital serves a population of over 620,000. In addition, it is a tertiary referral centre for over 1 million people, in the southern region of the Republic of Ireland. Approximately 32,000 inpatient admissions were recorded for 2012. All patients who were in receipt of a pharmacist intervention on their drug therapy were included in this study. There were no additional exclusion criteria. The Pharmacy Department consists of 15.8 whole time equivalent (WTE) pharmacists. As two WTEs are employed in managerial and administrative capacities, 13.8 WTE are available to document interventions as part of the daily pharmaceutical service. Interventions performed in all areas of the hospital, including the maternity unit, were included in this study.

3.3.2 Intervention analysis

Clinical pharmacist interventions are provided by many basic and senior grade pharmacists at CUH. Clinical pharmacist interventions are carried out at patient admission, during pharmacist-led patient chart review or at the request of another healthcare professional. As previously discussed, the primary goal of a clinical pharmacist intervention is to ameliorate patient therapy.

Interventions made by pharmacists were recorded on a duplicate paper form. One form is kept by the pharmacist and one is passed on to the attending physician who has the final decision on whether to accept or reject the intervention.

In addition to producing a paper record of the intervention, the pharmacist retrospectively enters the proposed intervention into the 'eClinical Pharmacy Suite'. The 'eClinical Pharmacy Suite' is a browser-based application, aimed at supporting clinical pharmacists to record, grade and report medication related interventions or errors. Interventions were assigned by the clinical pharmacist to the most appropriate category in the application. Due to time constraints, not all recorded intervention had been entered on the computerised database. The primary researcher inputted any outstanding interventions and verified data which had been previously entered by hospital pharmacists. Intervention categories were developed based on the recommendations of an advisory group of clinical pharmacists from Ireland.

3.3.3 Cost analysis

The cost of providing this service was calculated based on the average time it took to carry out an intervention and the hourly cost of employing a hospital pharmacist. The average time of an intervention was based on a previously published study, which showed that the majority of pharmacist interventions in a university hospital setting took between 15 – 30 minutes to complete [90]The hourly rate of employing a pharmacist at the mid-point of the salary scale was calculated based on an annual salary of €49,425 (Point 6 of 2010 salary scale) [148] This underwent upward revision to account for employer related costs and hospital overheads based on guidance for conducting an economic analysis within the Irish healthcare system [149-151]. Base

case scenario was calculated using the hourly cost of employing a basic level pharmacist at the mid-point of the salary scale and an average intervention time of 22.5 minutes.

Cost avoidance was calculated based on the probability that an ADE would have occurred in the absence of the proposed pharmacist intervention. Interventions were analysed by the primary author and a score was assigned based on the probability of a patient experiencing harm directly or indirectly from their prescribed/administered medicines, and also the potential of omission of regular medication, sub-therapeutic dosing or an ill-advised choice of therapy. Determination of the probability that a patient would experience harm in the absence of an action by a pharmacist was based on the methodology described by Nesbit *et al.* [147], description provided in **Table 3.1**. The cost avoidance for each individual intervention was determined as per equation 1 and total cost avoidance was accordingly calculated through summation of the individual interventions. A random sample of the interventions (n = 100) were reviewed by two academic pharmacists with hospital pharmacy experience and inter-rater reliability was calculated for the sample.

Equation 1

$$\boldsymbol{Cost\ avoidance\ for\ individual\ intervention}$$
$$= Probability\ of\ ADE\ occuring\ x\ Cost\ of\ ADE$$

Table 3.1 Nesbit method for calculating indirect cost-benefit

Probability of an ADE occurring	Probability score	Example
No harm expected	0.00	Pharmacist suggests changing patient from esomeprazole to omeprazole exclusively for economic reasons.
Very low	0.01	Patient regularly takes a bisphosphonate, but medication omitted from hospital kardex
Low	0.10	Patient takes an antibiotic twice daily, when recommended dose would be three times daily.
Medium	0.40	Metformin dose not reduced despite patient demonstrating renal impairment.
High	0.60	Patient prescribed amiodarone while currently taking digoxin without any reduction in digoxin dose.

Source Nesbit, T.W. et al.: Implementation and pharmacoeconomic analysis of a clinical staff pharmacist practice model. American journal of health-system pharmacy 58(9), 784–790 (2001)[147]

The authors were unable to find an estimated cost of an ADE, calculated based on data from the Irish healthcare system. The additional cost of treating an inpatient that experienced an ADE was taken from a recent study which utilised a micro-costing approach based on data from German hospitals [152]. This study also included a range of previously published ADE estimates (€934 – 5783). The majority of previously published studies which calculate cost avoidance used a cost of ADE determined by Bates *et al.* [88, 90, 117, 147]. Rottenkolber ADE valuation was deemed to be more appropriate for this study as it was published in 2012 while Bates study was published in 1997 using US data [153]. This removed the need to account for currency differentials and inflation. Purchasing power parities between Germany and Ireland were used to further minimise differentials between the two countries. Cost of an ADE used in base case scenario was €1057.

A micro-costing approach, assigns a valuation to each individual unit of resource consumed and is considered the most robust costing method [154]. Diagnosis related group (DRG) costs for toxic side effects of drugs based on Irish hospital data were available but were not chosen as the cost of an ADE. The DRG estimate exclusively measured toxic side effects of drugs [155], furthermore DRG costs are generally less accurate in comparison to micro-costing estimates [154]. DRG costs for toxic side effects for drugs (€887) were included in sensitivity analysis calculations.

Following estimation of the cost of carrying out the pharmacist interventions and the resulting cost avoidance, net cost-benefit and cost-benefit ratio for providing the service were calculated. Analysis was calculated from the perspective of the healthcare institution. Discounting was excluded as events were all considered to have taken place in a 1 year time period.

3.3.4 Sensitivity analysis

One-way deterministic sensitivity analysis was performed. Published ranges and confidence intervals where available determined the extent of the parameters. Sensitivity analysis was also performed using alternative published costs of an ADE [153], Irish DRG data and with various intervention acceptance rates.

3.3.5 Data analysis

Reports generated from the eClinical Pharmacy Suite database were in Microsoft Excel™ format. Summary statistics were calculated through Microsoft Excel 2010 (Microsoft Corp., Redmond, Washington). All other advanced analysis was conducted through IBM SPSS Statistics Version 18.

3.3.6 Ethical approval

Approval was obtained from the Clinical Research Ethics Committee of the Cork Teaching Hospitals, University College Cork, Ireland.

3.4 Results

A total of 4,257 interventions were documented on 2,147 individual patients (**Table 3.2**). The majority of the interventions were judged to have prevented potential ADEs (n = 3,417). The remaining interventions had no discernible impact on therapy or patient outcomes, based on the judgement of the primary author. Additional interventions required entry under multiple categories on the database, but were only evaluated once for potential prevention of an ADE.

Table 3.2 Intervention analysis

	Number of interventions
Total number of patients who received intervention	2147 patients
Total number of interventions	4257
Mean number of interventions per patient (St. dev.)	1.98 (1.60)
Median number of interventions per patient	1
Range of interventions per patient	1 - 18
Interventions accepted by physicians (%)	1275 (29.92)
Interventions rejected by physicians (%)	61 (1.43)
Interventions with unknown acceptance outcome (%)	2921 (68.81)

Recorded acceptance rate by physicians was 29.92% (n = 1275). Only 1.43% (n = 61) interventions were recorded as being rejected by a physician. However, the rate of interventions with an unknown acceptance outcome was high, 68.81% (n = 2921). Substantial cost avoidance of €710,000 was generated over a 1 year period from the perspective of the health care provider. Mean cost avoidance of €166 per intervention was generated. The cost of providing these interventions was €82,000. Substantial net cost-benefits of €626,279 and a cost-benefit ratio of 8.64 were generated based on this evaluation of pharmacist interventions as shown in **Table 3.3**.

Table 3.3 Cost analysis of pharmacist interventions

	Description	Base case (Range)
1.	Cost avoidance	**€708221** (625808–3874783)
2.	**Cost of Service**	
	- Pharmacist Wages	**€81942** (22402 –110389)
[a] 3 = (1–2)	**Net Cost-Benefit**	**€626279** (567173–3764394)
[b] 4 = (1/2)	**Cost-Benefit Ratio**	**8.64 : 1**

[a] (Cost avoidance – Cost of Pharmacy Services)

[b] (Net Cost-Benefit ÷ Cost of Service)

The number of interventions that potentially avoided ADEs were as follows: 119 (2.8% of all interventions) of the interventions were associated with a probability score of 0.6 (high likelihood of preventing an adverse event), 1101 interventions (25.86%) were associated with a probability score of 0.4 (medium), 1514 interventions (35.56%) were associated with a probability score of 0.1 (low), 683 interventions (16.04%) were associated with a probability score of 0.01 (very low) and 840 interventions (19.73%) were associated with a probability score of 0 (no harm expected). Results are presented in table 3.4

Table 3.4 Cost avoidance associated with intervention probability

Probability of an ADE occurring	**Example**	**No of interventions assigned to category**	**Cost avoidance generated (€)**
No harm expected	Pharmacist suggests changing patient from esomeprazole to omeprazole exclusively for economic reasons.	840	0
Very low	Patient regularly takes a bisphosphonate, but medication omitted from hospital kardex	683	7219.31
Low	Patient takes an antibiotic twice daily, when recommended dose would be three times daily.	1514	160029.8
Medium	Metformin dose not reduced despite patient demonstrating renal impairment.	1101	465502.8
High	Patient prescribed amiodarone while currently taking digoxin without any reduction in digoxin dose.	119	75469.8

The most prevalent type of intervention was the identification of omissions of patient's regular pre-admission medication, followed by requests to change the dose of medications and requests for the physician to consider whether it was appropriate to continue with a medication (**Table 3.5**). The most common categories of medications to require interventions were proton pump inhibitors (n = 259), statins (n = 208), beta-blockers (n = 165), corticosteroids (n = 161) and penicillins (n = 157).

Table 3.5 Intervention categorisation

Category of intervention	**N (%)**
Drug	2759 (64.81%)
- Drug, Omissions	*1820 (65.93% of Drug Category)*
- Drug, Review Therapy	*421 (15.24% of Drug Category)*
- Drug, Interaction	*124 (4.56% of Drug Category)*
- Drug, Other	*394 (14.27% of Drug Category)*
Doses	920 (21.61%)
Frequencies	354 (8.32%)
Routes	125 (2.94%)
Duration	47 (1.10%)
Other	27 (0.63%)
Date/Time	20 (0.47%)
Rates	5 (0.12%)

Inter-rater reliability indicated an acceptable level of agreement, based on a random sample of 100 interventions. Average agreement between 3 raters was 0.744. Individual pairwise agreement was over the significant level of 0.7 for all 3 comparisons: Primary Rater (PR) – Academic Pharmacist (AP) 1 = 0.763, PR – AP 2 = 0.761, AP 1 – AP 2 = 0.709.

In all scenarios examined, the cost-benefit ratio remained positive as outlined in **Table 3.6**. All known variables underwent a one-way sensitivity analysis based on known ranges or using variations used in previously published sensitivity analysis on the topic. Nesbit et al. conducted a sensitivity analysis where the ADE probability underwent an each way variation of 50%, an identical variation was undertaken in this paper [25]. The greatest variance in cost-benefit ratio was displayed in the cost assigned to an ADE. .

Table 3.6 Sensitivity analysis for cost-benefit ratios

Variable	**Lower limit *(Cost-Benefit Ratio)***	**Upper limit *(Cost-Benefit Ratio)***
Time	**30 minutes per intervention**	**15 minutes per intervention**
	6.48	12.96
ADE Probability	**−50% Probability score**	**+50% Probability score**
	4.32	12.96
Salary	**Highest point on senior pharmacist scale**	**Lowest point on basic pharmacist scale**
	6.42	12.07
ADE Cost[A]	**Lowest point on range**	**Highest point on range**
	7.63	47.28
Intervention acceptance	**50% Acceptance**	**Known Acceptance (29.92%)**
	4.32	2.59

[A] ADE range taken from a review of selected international studies regarding the economic consequences of ADEs which reported additional mean costs in the range of €934 to €5783 per case [156].

Two additional ADE cost estimates were investigated during the course of sensitivity analysis (**Table 3.7**). The estimated cost of an ADE calculated by Bates and adjusted due to change in setting and year resulted in a considerable increase in the cost-benefit ratio.

Table 3.7 Sensitivity analysis using alternative ADE estimates

Alternative ADE estimate	Cost-benefit ratio
DRG Toxic Side Effects [33]	7.25
Bates ADE Costing [31]	49.49

3.5 Discussion

Substantial cost avoidance was demonstrated in this study. Cost-benefit ratio and net cost-benefit remained positive under all conditions examined. To the authors' knowledge, this study is the first that has attempted to estimate the cost avoidance achieved in a total hospital environment over such an extended period of time. Direct comparison of savings generated in this study with previously published studies is difficult. Calculation of cost avoidance will have inter study variations in the cost assigned to an ADE, methodologies, healthcare settings, duration of study and number of pharmacists employed.

The original study which implemented the cost avoidance method used in this paper generated a net benefit of $392,660 [147]. This was over a similar 12 month period but only included 3 WTE pharmacists operating on three specific hospital wards. Study location was in a US hospital. These pharmacists had undergone specialist training and were to a large extent exclusively performing interventions during their participation in the study. Cost-benefit ratio of 3.1:1 was considerably smaller in the Nesbit study. Cost-benefit ratio was influenced significantly by the method used to calculate the cost of the service. The complete pharmacist salary was used to calculate the cost of providing the intervention rather than apportioning part of the salary based on the time pharmacist spent enacting the interventions.

A study by Olson et al. conducted in a 360 bed US hospital has the greatest methodological agreement with this paper [90]. This was conducted over a 3 month period and estimated the cost-benefit ratio to be 1.2. Only 5 pharmacists provided interventions in this study. Although, substantial savings ($84,631) was generated from a small number of interventions, the cost-benefit ratio was lower than expected. As with the Nesbit study, cost-benefit ratio was reduced as full pharmacist salary was used to calculate the cost of providing the service. The results in this study provides evidence that the positive cost-benefit ratio of clinical pharmacists' interventions is maintained over a longer period of time, with additional pharmacists and in a wider hospital setting.

Cost avoidances are impacted significantly if they are focused in specific departments. Cost avoidance per intervention generated in our study was decidedly lower in comparison to a study conducted in an intensive care unit. The addition of a single critical care pharmacist to a 16 bed intensive care unit produced an average cost avoidance of $1596.27 - $1615.67 per intervention [88]. Input costs were omitted in this study so further comparison was not feasible.

While the cost-benefit ratio in this study was positive, it needs to be reiterated that this ratio was based on estimates of time and avoidance of cost rather than actual monetary valuations. Therefore, the ratio could potentially be an overestimate. Furthermore, an evaluation of a clinical pharmacy service is strengthened when it also includes an assessment of the clinical and humanistic outcomes involved [81].

This high degree of omissions of patient's regular pre-admission medications (43% of all interventions) highlights the need for a dedicated system of medicines reconciliation at a tertiary healthcare level in Ireland. A pilot study of pharmacist-led medication reconciliation in two university teaching hospitals, elsewhere in Ireland, also identified omission of a pre-admission medication as the most common discrepancy [157]. These findings are replicated in other healthcare settings [158]. Medication omissions can have potentially serious consequences for patients depending on the nature of the drug omitted [159].

An argument could be presented not to include medication omissions as an ADE, based on a strict interpretation of the definition, as the patient did not receive the drug [160]. However, the decision was taken to include them in this study. Similar studies in the past have included the identification of medication omissions as a potential ADE [90, 161]. The probability of a patient incurring harm is increased if they do not receive their regular medication, resulting in a related increase in hospital resource utilisation [162].

Medium and low scores were the most frequent probabilities assigned to the interventions. This reflects findings obtained in the majority of previous studies which implemented the same method of calculating cost avoidance [88, 147, 161]. The frequency of these scores were influenced by the number of medication omissions (39% of omissions were assigned a medium probability score and 37% assigned a low probability score.) Interventions designated with a high probability of preventing an ADE were largely composed of omissions of essential medications (e.g. anti-epileptic drugs) or known serious drug interactions.

The most common medication classifications requiring intervention were unsurprising. Proton pump inhibitors (PPI) were the medication classification requiring the most frequent intervention. Interventions on PPIs were largely suggestions to change to lower cost equivalents, highlighting therapeutic duplication, excess of therapy or suggestion for switching from intravenous to oral administration. The majority of these interventions resulted in cost savings to the healthcare provider. Inappropriate prescribing of PPIs is a significant issue in the Irish healthcare system and a significant drain on resources [163, 164]. This demonstrates the pivotal role can play as cost containers in the healthcare system.

Another method of increasing the number of interventions would be the provision of further training for clinical pharmacists which would enable them to become specialists in various areas of patient care. This practice is common in other countries and has been shown to provide substantial monetary savings from interventions enacted by specialist pharmacists [88]. Specialised anti-microbial pharmacists have been shown to be of value and are now established in many hospitals in Ireland [164, 165].

A significant level of agreement was found between three of the listed authors. Assignment of probabilities is subjective; therefore a high level of agreement is unlikely. On review of samples, almost all were within 1 score of each other, further indicating that probabilities were assigned by the primary author in a manner consistent with fellow professionals. Although, inter-rater reliability was not examined for all interventions, the clinical background of the primary rater and the

significant agreement level demonstrated in the sample indicate the ADE probabilities were assigned in an appropriate and consistent manner.

There was a high rate of interventions where the outcome was unknown at time of analysis. However, review of interventions where status was determined indicated that only a small minority of pharmacist interventions were rejected. This indicates that other healthcare professionals are receptive to pharmacist interventions on patient medication. The high level of unknown outcomes was most likely due to time constraints on the pharmacist. Following acceptance or rejection, system requires manual updating. It is understandable that an administrative task such as this may be neglected.

The importance of an accurate estimation of ADE cost was emphasized from the dramatic increase in cost-benefit ratio if Bates *et al.* estimate of ADE was used. As previously stated, there is an absence of data on ADE costs in Ireland. The validity of estimated cost avoidance would be improved through application of local data on excess costs associated with ADE. Until this issue has been addressed, imperfect data is the only viable option. Sensitivity analysis undertaken in this study was deterministic in nature; performing probability sensitivity analysis would have been a more robust method to determine whether pharmacist interventions would have maintained a positive cost-benefit ratio.

The primary limitation was the limited availability of additional patient information (medical record, medical history, outcome of intervention etc.) when assigning adverse drug event probabilities. As this study contained a large number of patient

interventions, it was not feasible to retrospectively retrieve this information from medical notes.

Another major limitation was the exclusion of some potential input costs. In order to conduct an intervention, problems must be located which takes up pharmacist time and therefore has an associated cost. Screening of a patient's medication may not be exclusively for the purpose of discovering interventions but it is one possible outcome from it. Additionally, other healthcare professionals are required to spend time reviewing suggested pharmacist interventions. This was also excluded from analysis.

Utilisation of a scoring system which also accounts for the severity of the potential ADE would significantly enhance this study. Such scoring systems exist but they do not assign a cost with the scoring outcome generated. There is no ideal system for assigning probabilities to adverse events but the widespread adaptation of one system would add to the ability to compare studies across jurisdictions. The classification of interventions is subjective. Generation of local guidelines on the classification of interventions would help reduce this variation.

While the interventions included in the study represented the majority of work conducted by clinical pharmacists, it is possible that some interventions were not inputted on to the eClinical System. Therefore, the current data may under-represent the cost avoidance produced. The overall return on investment associated with clinical pharmacist interventions could potentially be increased if some interventions were omitted from entry into eClinical System.

The interventions were assigned scores by an individual rater. While sample of interventions examined for inter-rater reliability indicated that the primary author was assigning probability scores in a manner consistent with other pharmacists, review of complete dataset by additional pharmacists and other medical professionals would have enhanced the study.

3.6 Conclusion

Previous reviews have indicated that pharmacist interventions generate significant cost avoidance when measured under certain criteria and conditions [18]. This study has confirmed previous opinions and supplemented the body of evidence that the provision of clinical pharmacy services in an entire hospital provides value for money to the healthcare payer. An excessive amount of omissions of regular medications has been highlighted by this study. The estimation of cost avoidance would be improved by the development of a method which incorporated the potential severity of an ADE into the evaluation and an evaluation of excess costs associated with ADEs in an Irish healthcare setting.

4 - Chapter 4: Economic Evaluation of a randomised controlled trial of pharmacist-supervised patient self-testing of warfarin therapy

The work of this chapter has been published as Gallagher J, McCarthy S, Woods N, Ryan F, O' Shea S, Byrne S. Economic evaluation of a randomized controlled trial of pharmacist-supervized patient self-testing of warfarin therapy.

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4.1 Abstract

Introduction

The increase in numbers of patients requiring oral anti-coagulation testing in outpatient clinics has focused attention on alternative flexible systems of anti-coagulation management. One option is pharmacist-led patient self-testing (PST) of international normalised ratio (INR) levels. PST has demonstrated improvements in anti-coagulation control, but its cost-effectiveness is inconclusive. This study reports the first cost-effectiveness evaluation of a randomized controlled trial of an automated direct-to-patient expert system, enabling remote and effective management of patients on oral anti-coagulation therapy.

Method

We conducted an economic evaluation alongside a randomised controlled trial investigating a pharmacist-led PST method. The primary outcome was to determine the cost effectiveness of PST in comparison with usual care (management in a hospital-based anti-coagulation clinic). Long term anti-coagulation patients were recruited to a 6 month cross over study between PST and routine care in an anti-coagulation clinic. Economic evaluation was from the healthcare payer perspective.

Result

On a per patient basis over a 6 month period, PST resulted in an incremental cost of €59.08 in comparison with routine care. Patients achieved a significantly higher time in therapeutic range (TTR) during the PST arm in comparison with routine care, (72 ± 19.7% vs. 59 ± 13.5%). Overall cost of managing a patient through pharmacist-supervised PST for a 6 month period is €226.45. Additional analysis of strategies from a societal perspective indicated that PST was the dominant strategy.

Conclusion

Pharmacist-led patient self-testing is a viable method of management. It provides significant increases in anti-coagulation control for a minimal increase in cost.

4.2 Introduction

Despite the development of new oral anticoagulant agents (NOACs), warfarin remains an integral treatment option in anticoagulation management strategies. In Ireland in 2010, 57,000 patients were in receipt of a prescription for warfarin [166]. This constitutes 1.7% of the population. The majority of patients (55%) required warfarin for treatment of atrial fibrillation [166].

Warfarin is a well-established medication with a relatively low cost. However, unusually for an oral medication, it has significant expenses associated with the monitoring and management stage of the therapy. Warfarin is a medication with a narrow therapeutic index, requiring close management and regular dosage adjustments can be necessary. Currently in Ireland, the majority of management is provided by dedicated hospital-based anticoagulation clinics [166].

There are documented limitations to hospital-based clinics, especially from a patient's perspective which include the requirement to make regular and frequently, time consuming visits to the clinic [167]. Furthermore, previous studies have shown that alternative management strategies can improve anticoagulation control in comparison with hospital-based anticoagulation clinics [168]. The development of NOACs will decrease the overall proportion of patients' dependent on warfarin as a long term anticoagulant, however some patients will remain on warfarin therapy and therefore require an anticoagulation management service [169].

Patient self-testing (PST) of warfarin therapy is a concept which allows the management of warfarin therapy to move away from already overburdened hospital-based clinics to management at a primary care level. The PST model involves the

patient measuring their international normalised ratio (INR) levels using a portable point-of-care (POC) device. There are clinical benefits associated with the application of PST over usual care in anticoagulation management. Evidence ranging from randomised controlled trials (RCT), meta-analysis and full systematic reviews indicates that PST is associated with improved outcomes [7, 170-174]. PST of oral anticoagulation is proven to be a safe option in all age groups [175].

Input from healthcare professionals is still a fundamental requirement for the success of any PST strategy. Ryan *et al*. demonstrated that a single pharmacist could favourably oversee the management of a group of patients managing their INR using a PST strategy [7]. Pharmacists have a broad clinical and therapeutic knowledge and are using these skills to diversify into new areas of patient care [176]. With additional training in the area of anticoagulation management and accreditation of required standards, pharmacists have shown they are capable of providing an anticoagulation management service [177].

The method by which results are communicated to the responsible professional is another crucial part of warfarin PST. Telephone-based communication has been proven as a viable method and is widely utilised in the US [178]. However, availing of technological developments can reduce the cost, time and risk of errors associated with verbal communication [179]. 'Expert' software systems have been developed to assist in patient management and data recording. The RCT examined in this evaluation utilises the CoagCare™ system (ZyCare Inc. Chapel Hill, NC, USA). CoagCare™ combines a direct-to-patient expert system accessed via the internet with PST to provide a novel model of pharmacist-supervised tele-health [7].

This study is the first cost-effectiveness evaluation of an internet based, direct-to-patient expert system in anticoagulation management. The direct-to-patient expert system employs a rule-based algorithm to inform patients how to adjust warfarin therapy based on INR data which has been recorded and inputted by the patient [7]. Previous cost-effectiveness analysis has been inconclusive as to whether similar systems offer "value for money" to the healthcare payer [180].

In this paper, a cost-effectiveness analysis was undertaken based on the outcomes and resource utilisation from a RCT of pharmacist-supervised PST of warfarin therapy using an internet based system [7]. The primary aim of this study was to determine the incremental cost-effectiveness of PST in comparison with usual care.

4.3 Methods

4.3.1 Trial protocol

This cost-effectiveness analysis was based on data from an RCT which is documented elsewhere [7]. In summary, the trial was a prospective, randomized controlled crossover study. Patients were initially assigned to either six months of routine care or six months of PST. At the end of the six month period, the patient was transferred to the alternative arm. The crossover design of the study eliminated the potential for covariate disparities. The primary outcome was the difference in the time in therapeutic range (TTR) between the two arms. Overall TTR for each arm was calculated using the Rosendaal method [181]. For the purposes of this trial, TTR was defined as the time spent within 0.5 units of the targeted INR value [7]. Patients were required to have been on warfarin therapy for at least two months prior to the start of the study and expected to have a requirement for warfarin for the duration of the 12-month study. Patients were excluded from the trial if they were unable to use a POC

device, if they missed attending more than two clinic appointments in a six month period prior to recruitment screening or if the patient was taking an additional anticoagulant other than warfarin. Furthermore, patients were excluded if they had experienced a haemorrhagic complication in the preceding six months, or if they were unable to attend the hospital clinic at short notice. Following recruitment, patients received comprehensive training from the research pharmacist.

Initially INR levels were measured in the PST arm twice weekly. Following stabilisation of INR levels, intervals between tests were increased to a maximum of once every two weeks. Management of deviations from the targeted INR value or other patient issues were the responsibility of the research pharmacist, assisted by the CoagCare™ system. During the course of routine care, patients attended the anticoagulation management service (AMS) for INR measurement every 4 - 6 weeks. Any necessary dosage adjustments were calculated by a doctor or nurse associated with the clinic.

Ethical approval was obtained from the Clinical Research Ethics Committee of the Cork Teaching Hospitals, University College Cork, Ireland.

4.3.2 RCT information

Patient recruitment and provision of routine care was provided at the AMS of Cork University Hospital (CUH). Currently, the AMS has approximately 850 regular patients. Additionally, the clinic is responsible for short-term anticoagulation patients and the processing of INR tests which are taken at other locations. In 2012, 120,000 INR tests were processed at the medical laboratory in CUH.

The total patient enrolment was one hundred and sixty-two patients, 132 of whom completed both the AMS and PST arms of the trial. Only patients who completed both arms of trial were included in final analysis. Mean age of the patient was 58.7 ± 14.3 years. Indication for oral anticoagulation therapy consisted of prosthetic heart valve – 49 (37.1%), atrial fibrillation – 43 (32.6%), deep vein thrombosis (DVT) / pulmonary embolism (PE) – 29 (22%) and other - 11 (8.3%). Patients withdrew from the trial for the following reasons: warfarin therapy discontinued (n = 8), patient found PST stressful (n = 5), left the AMS (n = 5), issues with internet access (n = 4), poor correlation between PST meter and laboratory INR results (n = 3), non-anticoagulant related death (n = 2), difficulty obtaining sample of blood using lancet (n = 1).

4.3.3 Pharmacoeconomic analysis

The analysis has a time horizon of six months which is the duration of the intervention arm. Discounting of costs or outcomes was not required as the time horizon was less than one year. Base case analysis is from the narrower perspective of the healthcare payer. Base case analysis used mean values determined during the RCT. Resource utilisation was over a six-month time period. The effect measurement was TTR in both the routine care and intervention arms. The duration of the trial was unsuitable for the adequate measurement of patient orientated outcomes such as death and non-fatal thromboembolic events. However, TTR is a documented marker for haemorrhagic and thrombotic complications [182]. Kaatz reasons that TTR should be the standard quality indicator for anticoagulant control as there are pragmatic issues affecting the completeness and accuracy of adverse event gathering [183].

Costs associated with the control and intervention groups are described in **Table 4.1**. The cost of processing an INR test at the CUH laboratory had previously been

calculated as part of an internal CUH evaluation. Costs of staff were calculated based on expert guidance from staff of CUH, internal CUH data and published HSE salary scales [184]. Patients received a 90 minute education and training session from the pharmacist. These were carried out in groups of one to three people; the pharmacist conducted 44 separate sessions [7]. Mean daily time required to manage a group of 80 patients was 23.2 minutes (± 9.5 minutes standard deviation). Therefore, an estimated 20 hours per month would be required for management of 132 patients. A cost of €30 per hour was applied to pharmacist time required for the study. The cost of the POC system was sourced from Roche Diagnostics, the manufacturer of the device used in the RCT.

The cost of warfarin therapy was excluded from both arms as significant differences in usage between groups were not anticipated; furthermore warfarin is a relatively cheap medication. Referenced unit cost prices are from 2012. Value added tax (VAT) was excluded from study costs based on recommendations for conducting health technology assessments in Ireland [185].

Table 4.1 Costs associated with anticoagulation management

Anticoagulation Management Service*	**€**
Cost per laboratory INR test	2.00
Medical Staff [ab]	8.08
Nursing [ac]	62.67
Clerical Officer [a]	8.17
Senior Medical Scientist [a]	9.43
Phlebotomy [a]	52.51
Healthcare Assistant [a]	5.11
Patient self-testing group	**€**
Cost per Coaguchek strip	*3.66*
Lancets (200)	*12.62*
Pharmacist supervision [a]	*27.27*
Cost of education session per patient	*15.00*
Coaguchek® XS Meter (Purchase cost)	*588.00*
CoagCare - 6 month license cost	*2500*

** - Costs calculated based on internal CUH data and expert guidance*
a – Mean cost per patient per 6 month period
b – Four senior house officer hours and three consultant haematologist hours per week
c- One whole time equivalent (WTE) clinical nurse specialist and 2.5 WTE's staff nurse

4.3.4 Sensitivity analysis

One-way sensitivity-analysis was conducted on all known variables. Standard deviations and confidence intervals were employed where possible. In the absence of any indication of variability, a ±50% variation was applied. Additional evaluations which were inclusive of societal benefits such as travel costs and patient time foregone through attendance at AMS were also included in a supplementary evaluation. An argument for evaluation from a societal perspective can be made as significant costs can be accrued due to patients' requirement to attend an anticoagulation clinic. Societal benefits were calculated using resource consumption and patient data obtained in the RCT [7]. Cost per km travelled by car was calculated using recommended Irish reimbursement rate for a mid-sized car [186]. Working time sacrificed due to attendance at anticoagulation clinic was calculated using national average wage per hour (Q3 2013) [187]. Leisure time lost through attendance at clinic was valued at 35% of the local average gross wage. This methodology had been used in previously published attempts to calculate cost of attending an anticoagulation clinic [167]. The cost to the HSE for provision of POC devices to patients was also investigated. Machine costs were spread over a five year period using a straight line depreciation method. This was deemed acceptable as five years is recognised as the minimum lifespan of these machines [188]. The year one purchase cost of a CoagChek XS meter was included in this scenario.

4.4 Results

Patients achieved a significantly higher TTR during the PST arm in comparison with routine care, (72 ± 19.7% vs 59 ± 13.5%). Increases in TTR were achieved for both patients who were initially randomized to PST group (16.6%) and AMS group (12.3%). The effect of order of management was non-significant (P = 0.412).

There was a substantial difference in the frequency of testing between the trial groups. The PST group tested their INR almost four times more frequently than the AMS group over a 6 month period as described in **Table 4.2**. The mean frequency of testing days for PST was 4.6 days, which was a considerably shorter time period than the 19.6 days between each test in the control group.

Table 4.2 Cost Effectiveness of 6 months of PST versus AMS (Usual Care)

	Patient Self-Testing	**Anticoagulation Management Service**
Mean % TTR (95% CI)	72 (+/- 2.32%)	59 (+/- 3.36%)
Median % TTR (IQR)	74 (64.6 – 81)	58.6 (45.5 – 73.1)
Mean INR tests / patient ± SD (Range)	41.7 +/- 6.6 (24 – 60)	10.7 +/- 5.2 (5 – 35)
Cost of 6 months of patient management	€226.45	€167.38
Incremental cost of 6 months of PST therapy versus AMS	€59.08	

The base case cost-effectiveness analysis indicated that on a per patient basis, PST was slightly more expensive than AMS (**Table 4.2**). On a per patient basis over a six month period, PST resulted in an incremental cost of €59.08 in comparison with routine care. Overall cost of managing a patient through pharmacist-supervised PST for a six month period is €226.45. Difference in overall cost was minimal and PST

was the dominant strategy in some scenarios examined during sensitivity analysis, specifically if analysis was conducted from a societal perspective or at the maximum estimate of the cost of AMS staff as demonstrated in **Table 4.3**. Unsurprisingly, the most expensive scenario evaluated was if full cost of POC meter was reimbursed by healthcare payer.

Table 4.3 One-way sensitivity analysis

Testing frequency	€
- Minimum value 95% CI	34.92
- Maximum value 95% CI	83.23
Point of care device reimbursement	
- 5 Year Straight Line Depreciation	176.68
AMS Staff	
- Minimum value (15% of workload)	-13.91 (Dominant)[1]
- Maximum value (5% of workload)	132.07
Societal perspective	-13.44 (Dominant)[2]
Excluding pharmacist training	44.08

1 Based on expert guidance, sensitivity analysis of +/- 50% was applied
2 This scenario was both less costly and more effective in comparison with management at AMS. Therefore, PST is dominant over usual care.

4.5 Discussion

Based on the results of this study, on a per-test basis, PST is marginally more expensive in comparison to centralized laboratory testing. This is similar to the established trend of previous publications [189]. However, it does offer additional benefits to the healthcare payer in exchange for this extra cost. It is speculative to determine whether this strategy is cost-effective, as no threshold has previously been suggested for an increase in TTR. However, the relatively small value of the incremental cost increases the probability that a healthcare payer would surmise that it is a worthwhile strategy to finance. The fact that multiple scenarios examined in the sensitivity analysis, including an evaluation from a societal perspective concluded that PST was the dominant strategy, gives further credence to this prospect.

The cost-effectiveness of PST is dependent on the method of evaluation used, choice of comparator and the setting. As far as the authors are aware, this is the first economic evaluation of a pharmacist-supervised direct-to-patient system. Furthermore, this is the first evaluation of PST that has been undertaken in an Irish population.

The strategy evaluated in this paper is favourable on a cost per patient basis to a number of other PST strategies which have undergone economic evaluation. Claes *et al*. evaluated a similar method which involved a CoaguChek device, dosing software and GP management in Belgian GP practices, however, this method was more expensive and achieved an inferior TTR level to our study. Perhaps the most comprehensive evaluation of PST strategies was a health technology assessment conducted in Canada. This concluded that PST was not cost-effective based on a threshold of €50000 (CAN) per Quality Adjusted Life Year (QALY). However, when calculated from a societal perspective, PST was determined to be cost saving [190].

While QALYs attempt to give an overall measurement of the impact of a therapy or intervention on a patient, they can lack sensitivity when used in the comparison of two similar treatment strategies, as is the case with PST and AMS.

TTR is a reliable indicator of the performance of any method of anticoagulation management and therefore is a suitable effect measurement for this cost effectiveness analysis. The current study showed a difference of 13% between the means of both groups and a 15.4% difference between the two median values. The Stroke Prevention using oral thrombin inhibitor in atrial fibrillation (SPORTIF) III and SPORTIF V studies suggest that the incidence of death, major bleeding and stroke may be halved by a 15 % improvement in TTR [191]. Similar increases were obtained during the course of this study.

Significantly, the TTR levels associated with this study were greater than the 70% range which would be considered a good level of control. A retrospective review of 6108 patients with non-valvular atrial fibrillation showed that patients with INR control of 70% of time in range had a significantly reduced risk of stroke [192].
The cost of managing a patient using PST based on our trial data was determined to be €226 for a six month period. In comparison, the net ingredient cost of six months of therapy of either of the two NOACs currently licensed for the prophylaxis of thromboembolic events in Ireland is between €456.06 (Dabigatran 150mg x 60 tablets per month) and €384.66 (Rivaroxaban 20mg x 28 tablets per month) [193]. Previous studies indicate that these are cost-effective in comparison with conventional warfarin management [194]. However, the comparator used in both of these trials was conventional warfarin management which is associated with reduced TTR levels and

overall poorer patient outcomes. No significant effect has been shown between patients treated with dabigatran and those who are treated with warfarin and have TTR levels >65.5% [195]. The management strategy evaluated in this paper has an overall TTR of 72%. Improvements in warfarin control may force a reappraisal of the cost-effectiveness of NOACs.

Although, the increase in testing frequency has been hypothesised as the reason for the observed benefits of PST [196], it does not offer a comprehensive explanation. Similar testing frequencies in control and intervention groups resulted in better outcomes in the groups using POC monitoring [197, 198].

Patient self-testing is not a suitable strategy for all patients. This is reflected in the reasons given by patients for dropping out of the trial. Thirteen patients did not complete the trial for reasons which could be attributed to difficulties with PST management. Future research should attempt to investigate which patient groups would benefit most from self-testing or self-monitoring strategies. Some studies have suggested focusing on those with mechanical heart valves or those under 55, however conclusive evidence is lacking [199].

The limited duration of the RCT restricts the utility of the data as initial costs such as patient training and purchase costs of the POC devices are loaded into a six month time period, even though they will have a longer term benefit to the patient which is not captured during this study. The duration and sample size did not allow for a significant level of haemorrhagic and thromboembolic complications to be detected.

Optimal management of warfarin therapy in the form of PST has a long-term benefit to the patient in terms of reduced thromboembolic events and deaths [170]. The benefit is not one that is conclusively detectable after six months data collection.

Some of the costs calculated were based on expert guidance and internal hospital data. Workload of AMS staff was based on expert guidance from senior staff in the anticoagulation clinic at CUH; however variation of this estimate had the greatest effect on outcome. Wide variations were employed to any assumptions based on expert guidance during sensitivity analysis. Analysis based on micro-costing techniques, would considerably reduce uncertainty around outcomes. Additionally, there was a self-selective nature to patient recruitment. Therefore, the group studied may not be representative of the actual population. The estimated percentage of patients who are prescribed warfarin for atrial fibrillation was lower in this study compared to national levels.

As with all economic evaluations based on a single RCT, there are considerable issues associated with the generalizability of the results reported. However, this has been partially addressed through the application of a sensitivity analysis.

4.6 Conclusion

PST provides a significant increase in anticoagulation control for a modest increase in expenditure. This is maintained in all situations evaluated in sensitivity analysis. The associated increase in INR control for a modest increase in expenditure demonstrated in this study provides further evidence that optimally managed warfarin therapy remains a viable strategy for anticoagulation management. Therefore, pharmacist-supervised patient self-testing should be considered as an alternative to NOACs which are both more expensive and not established.

5 - Chapter 5: Structured pharmacist review of medication in older hospitalized patients: A cost-effectiveness analysis

The work of this chapter has been published as Gallagher J, O'Sullivan D, McCarthy S, Gillespie P, Woods N, O'Mahony D, Byrne S. Structured Pharmacist Review of Medication in Older Hospitalised Patients: A Cost-Effectiveness Analysis.

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5.1 Abstract

Introduction

A recent cluster randomised controlled trial (RCT) conducted in an Irish hospital evaluating a structured pharmacist review of medication (SPRM), supported by computerised decision support software (CDSS), demonstrated positive outcomes in terms of reduction of adverse drug reactions (ADR). The aim of this study was to examine the cost-effectiveness of pharmacists applying a SPRM in conjunction with CDSS to older hospitalised patients compared to usual pharmaceutical care.

Method

Cost-effectiveness analysis was based on data from a cluster RCT. The trial was conducted in a tertiary hospital in the south of Ireland. The intervention arm patients (n=361) received a multi-factorial intervention consisting of medicines reconciliation, deployment of CDSS and generation of a pharmaceutical care plan. Control arm patients (n=376) received usual care from the hospital pharmacy team. Incremental cost-effectiveness was examined in terms of costs to the healthcare system and an outcome measure of ADRs during an inpatient hospital stay. Uncertainty in the analysis was explored using a cost-effectiveness acceptability curve (CEAC).

Results

On average, the intervention arm was the dominant strategy in terms of cost-effectiveness. Compared to usual care (control), the intervention was associated with a decrease of €807 (95% Confidence intervals (CI) -3443, 1829) (p = 0.548) in mean healthcare cost and a decrease in the mean number of ADR events per patient of -0.064 (95% CI -0.135, 0.008) (p = 0.081). The probability of the intervention being cost-effective at respective threshold values of €0, €250, €500, €750, €1000 and €5000 was 0.707, 0.713, 0.716, 0.718, 0.722 and 0.784.

Conclusions

Based on the evidence presented, SPRM/CDSS is likely to be determined to be cost-effective in comparison with usual pharmaceutical care. However, neither incremental costs nor effects demonstrated a statistically significant difference so results of this single site study should be interpreted with caution.

5.2 Introduction

Interventions targeting medication optimisation in older persons have the potential to significantly improve patient outcomes and reduce unnecessary expenditure [200, 201]. Therefore, any potential improvements in prescribing and medication use in this expanding group could have a substantial positive impact on resource consumption.

Multiple approaches have been proposed to minimise the prevalence of inappropriate prescribing and preventable adverse events in older patients. Methods include prescriber education initiatives, use of screening tools to highlight inappropriate medications, medication review by health professionals and structured protocols for medication review [202]. A recent clinical trial which incorporates a number of these elements into a structured medication review programme has demonstrated promising clinical outcomes [203].

Medication review in a hospital setting is generally conducted on an ad-hoc basis and can vary depending on the experience and ability of the professional conducting the review [204]. The structured medication review implemented by O'Sullivan *et al*. was designed with the aim of reducing inappropriate prescribing and adverse events in a geriatric population. It is based on the application of a clinical decision support system (CDSS), which incorporates patient data from multiple sources and clinical guidelines [205]. Application of CDSS in a hospital setting is associated with fewer patient complications, lower mortality rates and lower costs [206]. However, a review of the evidence highlighted that CDSS does not appear to reliably prevent adverse drug events (ADEs) and in some instances can have a negative influence on work practices [207].

The evidence-based guidelines included in our unique CDSS system include the widely used STOPP/START (Screening Tool of Older Person's Prescriptions / Screening Tool to Alert doctors to Right Treatment) criteria (version 1) [208]. STOPP/START attempts to optimise pharmacotherapy in older patients by identifying medications which may be inappropriate to use (STOPP) and suggesting medications which patients should be receiving according to current available evidence (START) [209]. A recent cluster randomised controlled trial (RCT) sought to apply a structured pharmacist review of medication (SPRM) which was supported by CDSS. The intervention has demonstrated improvements in terms of adverse drug reactions (ADR) [203] and medication appropriateness measures [210].

Uncertainty still remains around the cost-effectiveness status of medication reviews [80, 97] Research examining net ingredient costs within health systems is simple to measure and often quoted. These studies simply provide a summary of the overall cost of drugs based on their list prices. However, they do not offer an accurate reflection of changes in patient outcomes. The cost of prescribing, dispensing and monitoring must also be taken into consideration [211]. There is also a potential that the outcome of a medication review will have negative consequences for a patient. Effectiveness of medication reviews can be difficult to evaluate due to the overlapping effects of polypharmacy and the highly complex and transient health status of patients.

Prior to recommending a general adoption of any intervention, investigation of the economic and budgetary impact of this method is a prerequisite. Despite some promising evidence [203, 210], a comprehensive economic evaluation of the implementation of the programme has not yet been conducted. The aim of this study

is to perform a cost-effectiveness evaluation of the SPRM/CDSS program based on its application in a RCT in an older population in order to reduce in-hospital ADRs. This is the first economic evaluation of a programme which is based on the application of STOPP/START.

5.3 Methods

5.3.1 SPRM/CDSS Intervention

Comprehensive details of this trial have been published elsewhere [203]. In summary, the RCT was conducted in an 810 bed teaching hospital in Ireland between June 2011 and June 2012. This trial was cluster-randomized with consultants from each speciality represented in each trial arm. Patients were randomised into either intervention or control group based on the consultant with primary responsibility for their care during their hospital stay. The intervention arm consisted of 361 patients. Patients in the control arm of this study received usual pharmaceutical care (n = 376). Usual pharmaceutical care consisted of ad-hoc pharmaceutical review from a hospital pharmacist employed at the study site. This involved hospital pharmacists performing an unstructured pharmaceutical review with communication of any suggested interventions to the attending medical team via hand written notes attached to the patient's hospital Kardex. In some cases, medicines reconciliation was also performed. The baseline characteristics of the recruited patients are presented in **Table 5.1**. No significant differences existed between the groups in terms of age, sex, functional status, cognitive function or number of medications at entry to the study.

Table 5.1 Baseline characteristics of patients in the randomised controlled trial.

Variable	**Measure**	**Intervention (n = 361)**	**Control (n = 376)**
Age	Median (IQR)	77(71-83)	78 (72-84)
Male	n (%)	180 (49.9%)	190 (50.5%)
Female	n (%)	181 (50.1%)	186 (49.5%)
Length of hospital stay	Median (IQR)	8 (5 – 13.5)	9 (5 – 16)
Hospital mortality rate	n (%)	17 (4.7%)	17 (4.5%)

Key: IQR – Interquartile range

The SPRM/CDSS intervention consisted of four elements. The first of these was direct contact with the patient's community pharmacy and or general practitioner in order to reconcile the patient's medication history, from available medical and pharmacy records.

The second element was deployment of the CDSS to review the patient's list of medications in order to identify any drug related problems, such as incorrect drug omission, dosage, frequency and formulation. The CDSS also identified problems with drug appropriateness, non-indication, drug-drug interactions, excessive doses for the level of renal or hepatic impairment, potential prescribing omissions as defined by the START criteria [208]and potentially inappropriate prescribing (PIP) as defined by the STOPP [208], Beers [212] and PRISCUS criteria [213]. Potential drug-drug interactions in the CDSS were informed using British National Formulary 61 [214].

The CDSS allowed standardization of the data collection, medication review and ADR detection process.

Thirdly, the intervention pharmacist then reviewed CDSS output and interpreted which potential interventions were clinically relevant. Clinical relevance was informed by accounting for clinical status, number of prescription drugs and the likely risk: benefit ratio of each recommendation. Finally, a written pharmaceutical care plan was presented to the attending medical team, which decided whether suggested alterations would be implemented.

SPRM/CDSS was applied to patient profiles within 48 hours of admission. All patients aged ≥ 65 years admitted under the care of the medical or surgical services through the emergency department were eligible for inclusion. Additional exclusion criteria included i) admission to psychiatric services, intensive care unit, specialist geriatric or clinical pharmacology services, ii) anticipated length of stay (LOS) <48 hours iii) elective admission.

5.3.2 Economic evaluation

This economic evaluation consisted of a trial-based analysis conducted alongside the RCT. The perspective of the healthcare provider (Health Service Executive – HSE) was adopted with respect to trial- related costs and outcomes. Evidence on resource use and patient health outcomes were collected by the intervention pharmacist during the course of the study and retrospective review of patient medical records. The time horizon for this evaluation was confined to patient discharge or 10 day follow-up, whichever came first. This was informed by average length of stay for elderly patient

in the Irish hospital system [215]. The average length of stay for patients aged 65 – 74 years is 7.9 days and 10.4 days for patients aged 75 – 84 years. The study was not designed to measure the medium/long term impact of this intervention. Discounting of costs or outcomes was not required due to the limited follow-up period. Statistical analysis was conducted on an intention to treat (ITT) basis, in accordance with guidelines for conducting cost-effectiveness analysis alongside cluster RCTs [216]. Missing data were not an issue in this evaluation, as follow-up was facilitated by a unique hospital number identifier and confined to a single centre over a short time period.

5.3.3 Cost analysis

Multiple cost components were included in the analysis and are described in **Table 5.2**. Costs are expressed in euros (€) using 2012 prices (unless otherwise stated). The primary component was the cost of employing and training a pharmacist to implement the programme. We took the mid-point of the HSE pharmacist scale (new entrant) and adjusted according to guidelines for conducting economic evaluation in Ireland [217, 218]. Salary was adjusted for employers' insurance cost, pension payments and general overheads. Based on discussion with the intervention pharmacist, it was agreed that one hour was an appropriate duration to assign for pharmacist time spent implementing the intervention.

The second component consisted of the associated follow-up time for other healthcare professionals to implement the suggested interventions. Costs associated with physician and nurse review of pharmaceutical care plan were included. Expert guidance dictated that it would take approximately 5 minutes for both physician and nurses respectively to review written communication and approve or reject suggested

interventions. The mid-point on the specialist registrar scale was used in cost-analysis. Nursing salary was based on the cost of a senior staff nurse.

The third major component was the cost of a hospital inpatient stay; this cost was obtained from aggregated national data [219]. In general, micro-costing estimates of patient estimates are preferable. However in the context of this piece of research a broader cost like the diagnosis-related group cost, is a justifiable choice as patients are admitted due to a diverse range of primary indications. The fourth component consisted of the support structures necessary to implement the intervention including software and training required to implement SPRM / CDSS.

Table 5.2 Costs associated with care of patients

Cost Component	Unit Cost	Description	Reference
Pharmacist	€40.00	Per application of SPRM/CDSS	HSE Salary Scales [218]
Non-consultant hospital doctor	€5.06	Per review of pharmaceutical care plan	HSE Salary Scales [218]
Senior staff nurse	€3.55	Per review of pharmaceutical care plan	HSE Salary Scale [218]
Inpatient day	€850.00	Cost of care per hospital in patient day	HSE Inpatient Ready Reckoner [155]
Software costs	€1000.00	One off installation of software programme	Investigator estimate
Training costs	€2000.00	Training costs of trial pharmacist	Investigator estimate

Key: SPRM - Structured pharmacist review of medication; CDSS - Computerised decision support software; HSE – Health Service Executive

5.3.4 *Effectiveness analysis*

It has been established that conducting economic evaluation based on data from RCTs is a suitable methodology [220]. 'This approach has dual advantages; first, internal validity is maintained due to the comprehensive nature of data collection during the trial; second, there is a modest marginal cost associated with collecting required data alongside a trial which is predominantly clinically orientated [220].

While a cost-utility analysis with a health-related outcome measure is recommended as the reference case in Ireland [217], it was not a realistic outcome measure for this study. The population under consideration has multiple co-morbidities and often an initially poor health status. Therefore health-related quality of life (HRQoL) is inappropriate in this case [221]. The primary outcome measure of this RCT was the difference in the proportion of patients in the two groups who experienced a non-trivial ADR during the course of their hospital stay. ADRs were identified by a trained clinical pharmacist and verified by a physician. A comprehensive description of ADR identification and outcomes is provided elsewhere [203].

5.3.5 *Cost-effectiveness analysis*

Techniques were adopted to account for the effect of clustering and correlation of cost and effect data collected alongside cluster RCTs. Cost-effectiveness analysis was presented in the form of an incremental cost-effectiveness ratio (ICER). An ICER is an additional cost per unit effect, in the case of this study, the cost of preventing an additional non-trivial ADR in hospital. In an economic evaluation, one treatment or method is considered more cost-effective than its comparator if it meets one of the following conditions [69];

a) Less costly and more effective;

b) More costly but more effective, with an ICER which is considered acceptable by decision makers;

c) Less costly and less effective, but the additional cost per unit of effect of its comparator is not considered worth paying by decision makers.

While threshold ICER values exist for some generic measures of health (eg cost per quality-adjusted life year (QALY)), acceptable values for cost per ADR prevented have not yet been proposed. In this paper, we examine a number of hypothetical thresholds.

Incremental analysis was undertaken using a multilevel mixed-effect regression model for both cost and effect data. The model was designed to control for treatment arm, age, sex, number of medications at admission and consultant (cluster group). This form of regression analysis is appropriate for normal and non-normal distributional forms of clustered data [222]. Regression for total costs was estimated using multilevel mixed-effects linear regression models; while regression for ADR event used mixed effect logistic regression models.

The estimated treatment arm effects represent the difference in means for control patients compared with intervention patients, with 95% confidence intervals and p-values reported to examine the statistical significance of these coefficients based on standard errors estimated using the mixed command in STATA 13.

Uncertainty in the analysis was addressed by estimating confidence intervals and a cost-effectiveness acceptability curve (CEAC), which link the probability of a

treatment being cost-effective to a range of potential threshold values (λ) that the health system may be willing to pay for an additional unit of effect [223].

Nonparametric bootstrapping with 1,000 replications was conducted on the difference in mean costs and mean ADR events to generate ICER replicates. The ICER replicates were used to generate a CEAC [224]. Analysis was performed using STATA (IBM SPSS Statistics 22) and Microsoft Excel (2010). A scenario analysis was performed which varied the time required by all healthcare professionals to complete intervention by +/- 50%.

5.3.6 Guidelines and ethical considerations

This manuscript followed the CHEERS guidelines for reporting health economic evaluations [98]. A completed CHEERS checklist details compliance with guidelines (Appendix 10.6). Original clinical cluster randomised trial conformed to Consolidated Standards of Reporting Trials (CONSORT) guidelines [216]. The biomedical ethics committee (institutional review board) of the University College Cork teaching hospital network approved the trial protocol and the trial was registered with the United States National Institutes of Health (NCT01467128 - http://clinicaltrials.gov/show/NCT01467128). Written consent was sought and obtained from all participating patients, prior to enrolment in the study. Approval for an ethical amendment submission was received for research presented in this manuscript from the Clinical Research Ethics Committee Of The Cork Teaching Hospitals.

5.4 Results

There were no significant demographic differences between the two treatment arms. Fifty-six percent of patients in usual care received some form of pharmacist review of medication. Demographic analysis is presented in the original RCT paper [203].

SPRM/CDSS strategy was dominant in comparison to usual pharmaceutical care. It showed improved outcomes in terms of ADRs experienced, alongside a reduction in associated costs, see **Table 5.3**. The mean cost of caring for an intervention patient during a single admission was €13250 (standard deviation (SD) €15530). The control group showed a mean cost of care of €15465 (€19310). Median costs also favoured intervention arm (€8954) in comparison with usual care (€10029). Following application of a multi-level mixed effects model in STATA and accounting for baseline differences across groups, the adjusted incremental difference in costs of -€807 was non-significant.

The effectiveness measures similarly favoured the intervention strategy. The odds ratio for experiencing an ADR was 0.655 when comparing SPRM/CDSS to usual care. This related to an adjusted difference in mean number of ADRs of -0.064, (95% CI = -0.135, 0.008, p = 0.081).

As both mean health costs and outcomes scores favoured the intervention arm of trial, it was unnecessary to calculate an ICER. It can be stated that SPRM/CDSS was dominant to usual care during the course of this RCT. However, as with all attempts to calculate the cost-effectiveness of an intervention, there is a degree of uncertainty surrounding this outcome. Even if the healthcare payer was unwilling to pay any money for the prevention of an ADR, the intervention strategy is still likely to be cost-effective (probability of being determined cost-effective = 0.707) (**Table 5.4)**.

Table 5.3 Incremental cost effectiveness analysis

	Intervention (n = 361)	Control (n = 376)
Cost analysis		
Total cost (€)		
Mean (SD)	13,250 (15,530)	15,465 (19,310)
Median (IQR)	8,954 (5,618 – 14,515)	10,029 (5,572 – 17,830)
Effectiveness analysis		
Total ADRs [n (%)]	50 (13.85)	78 (20.74)
ADRs per patient [n (%)]		
0	311 (86.15)	298 (79.26)
1	40 (11.08)	66 (17.55)
2	9 (2.49)	12 (3.19)
3	1 (0.28)	0 (0.00)
ADRs per patient [mean (SD)]	0.169 (0.456)	0.242 (0.503)
Incremental analysis	Intervention vs control	
Difference in mean total costs	−807 (95% CI −3443, 1829); p = 0.548	
Difference in odds ratio for ADR events	0.655 (95% CI 0.431, 0.994); p = 0.047	
Difference in mean ADR events (n)	−0.064 (95% CI −0.135, 0.008); p = 0.081	

Notes:
1. Reported estimates for incremental differences in costs and effects adjusted to account for baseline differences between groups.
2. Regression for total costs estimated using multilevel mixed-effects linear regression models and controlling for treatment arm, age, sex, number of medications at admission and clustering.
3. Regression for ADR event estimated using mixed effect logistic regression models and controlling for treatment arm, age, sex, number of medications at admission and clustering.

Key: IQR = interquartile range; SD = standard deviation; ADR = adverse drug reaction; CI = confidence interval.

Table 5.4 Threshold analysis of cost-effectiveness of intervention

Threshold value (λ) per ADR averted (€)	Probability that intervention is cost-effective
0	0.707
250	0.713
500	0.716
750	0.718
1,000	0.722
3,000	0.759
5,000	0.784
10,000	0.833
20,000	0.878
25,000	0.898
50,000	0.918

1. Probabilities for cost-effectiveness estimated parametrically using net benefit regression models for analysis at each threshold value.
Key: IQR = interquartile range; SD = standard deviation; ADR = adverse drug reaction; CI = confidence interval.

A graphical representation of the probability of the intervention being cost-effective is given in **Figure 5.1**. The majority of entries are in the south-east quadrant, indicating that the intervention group is likely to be considered cost-effective.

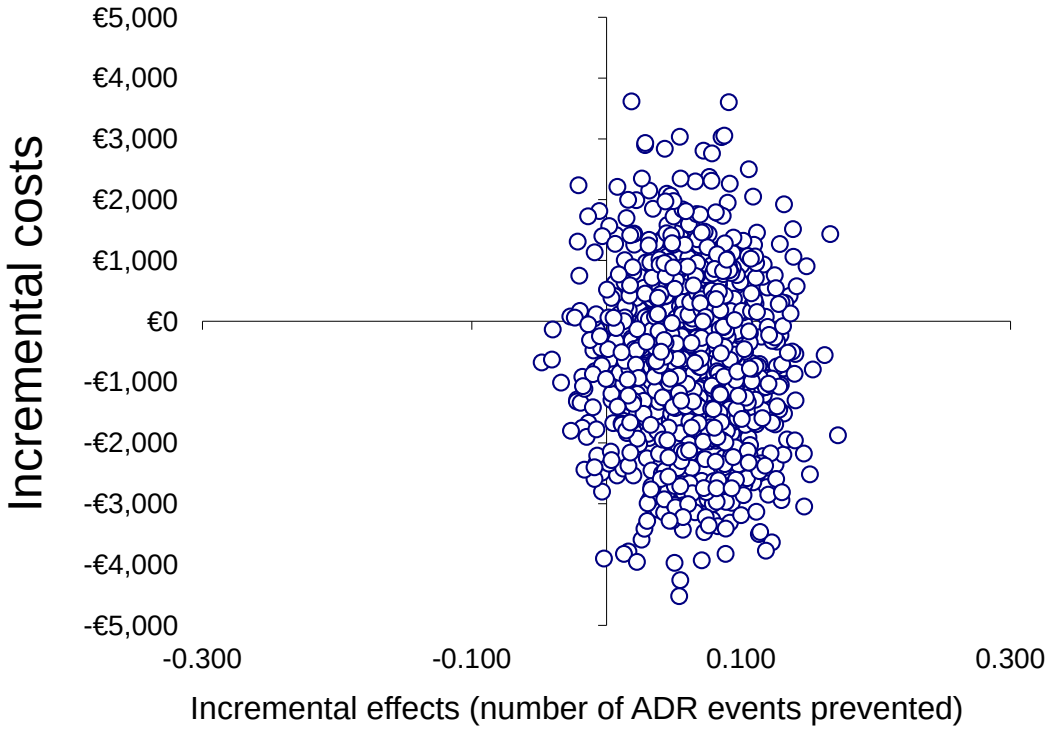


Figure 5.1 Graphical representation of the incremental cost-effectiveness ratio of structured pharmaceutical review of medication / clinical decision support system in comparison with usual care.

Key: ADR – Adverse drug reaction.

Scenario analysis demonstrated that if healthcare professional time associated with intervention was increased by 50% , SPRM/CDSS remained the dominant strategy as seen below in **Table 5.5**.

Table 5.5 Scenario analysis 1: 50% increase in healthcare professional time

	Incremental Analysis *Intervention versus Control*
Incremental Cost: Total Cost *Difference in Mean (95% CI's) (p-value)*	-760 (-3466, 1804) (0.537)
Incremental Effect: No. of ADR Events *Difference in Mean (95% CI's) (p-value)*	-0.064 (-0.135, 0.008) (0.081)
Incremental cost-effectiveness ratio	SPRM/CDSS dominant

SPRM remained dominant when healthcare profession time was reduced by 50%, see **Table 5.6.**

Table 5.6 Scenario analysis 2: 50% decrease in healthcare professional time

	Incremental Analysis *Intervention versus Control*
Incremental Cost: Total Cost *Difference in Mean (95% CI's) (p-value)*	-830 (-3466, 1804) (0.537)
Incremental Effect: No. of ADR Events *Difference in Mean (95% CI's) (p-value)*	-0.064 (-0.135, 0.008) (0.081)
Incremental cost-effectiveness ratio	SPRM/CDSS dominant

The overall cost of applying the intervention to a group of 361 patients was estimated to be approximately €20000 or €55 per patient. The majority of the SPRM/CDSS intervention costs were associated with the cost of the trial pharmacist's time in conducting the intervention (€40 per patient). Length of stay in the hospital was responsible for the majority of the cost associated with management in both arms. The majority of the SPRM/CDSS intervention costs were associated with the cost of the trial pharmacist's time in conducting the intervention (€40 per patient).

5.5 Discussion

Combining a CDSS with a medication review incorporating STOPP/START is likely to be cost-effective. This is predominantly based on the premise that even at a €0 threshold; the probability of the intervention being cost-effective is 0.707. The probability of the intervention being cost-effective, increases to 0.759 if a €3,000 threshold is applied. The thresholds applied were arbitrary but when one considers that the mean cost associated with a single ADR event has been estimated at €2250 [225], the threshold values presented in **Table 5.4** are a reasonable measure of what could be considered value for money. Similar increases in the cost of care could be imputed from this study, as patients who experienced a suspected ADR had their average length of stay increased by three days [203].

ICER results are not presented in the regular form of cost per additional unit of health. Our results show that SPRM / CDSS is likely to result in reduced costs and improved health outcomes. If it were to be plotted on an ICER plane, it would be located in the "south-east" quadrant. It is possible to represent this in ICER traditional terms; however it would be a "negative ICER". This is ambiguous as a "negative ICER value" would also be possible with a method of care that cost more but resulted in reduced health outcomes, i.e. was plotted in the "north-west" quadrant. When a cost-effectiveness analysis finds that option A is associated with decreased costs and increased health outcomes compared with option B, it is considered more practical to state that option A is dominant in comparison with option B.. Therefore, we have stated in our results section that SPRM/CDSS intervention was dominant in comparison to usual care in the context of this randomised controlled trial.

This is the first study to evaluate the economic impact of a novel SPRM/CDSS based intervention. The CDSS element of the intervention was highly influenced by the application of the STOPP/START criteria. We are unaware of any study which has included the practical application of the STOPP/START criteria as part of a comprehensive cost-effectiveness evaluation. Since their development in 2008, STOPP/ START criteria have become a widely used method of identifying and improving instances of potentially inappropriate prescribing. This study provides further evidence for the adoption of STOPP/START guidelines as a fundamental part of any healthcare review conducted by a healthcare professional in an older population.

The principal barrier to the application of SPRM/CDSS at a wider level is capacity. This RCT demonstrated that a single pharmacist could recruit 3 trial patients each day; however it should be noted that the pharmacist in question was not employed on a full-time basis applying SPRM/CDSS interventions to patients. If all older hospitalised patients are to receive this method of care, increased pharmacy staff numbers will be required. However, we believe that this will be a worthwhile investment, since healthcare payers will likely be rewarded in the form of substantial cost avoidance from a reduction in ADRs. Previous reviews have concluded that for every €1 invested in clinical pharmacy services, a saving of €4.80 is achieved [95]. Furthermore a correlation exists between increased clinical pharmacy services/pharmacy staff numbers and reduced mortality [145].

The results of this study are aligned with previous evaluation of clinical pharmacist services. Pharmacist interventions are generally considered to be cost-effective [226],

however a recent Cochrane review declared that it is difficult to make a generalised conclusion on the efficacy of pharmacist interventions due to the heterogeneity in study comparison groups, outcomes and measures evaluated [227]. Moreover, a recent systematic review highlighted issues with the general quality of economic evaluations of pharmacist interventions from a health economic perspective [226]. The present study has implemented recommendations from the CHEERS statement to ensure that this manuscript presents a transparent high quality evaluation.

It has been established that conducting economic evaluation based on data from RCTs is a suitable methodology [220]. This approach has dual advantages; internal validity is maintained due to the comprehensive nature of data collection during the trial. Furthermore, there is a modest marginal cost associated with collecting required data alongside a trial which is predominantly clinically orientated [220]. While a cost-utility analysis with a health-related outcome measure is recommended as the reference case in Ireland [217], it was not a realistic outcome measure for this study. The population under consideration has multiple co-morbidities and often an initially poor health status. Therefore health-related quality of life (HRQoL) is inappropriate in this case [221].

A very similar assessment to our study recently evaluated the Lund Integrated Medicines Management Model (LIMM), an alternative structured protocol designed to optimise drug treatment [228]. A modelled economic evaluation was determined to be dominant in comparison to usual care. The model estimated costs and utility loss from medication errors needing medical attention within a 3-month time period. Gillespie *et al*. evaluated a model of unstructured pharmaceutical care in older patients

on a hospital ward [104]. The total cost per patient in the intervention group was lower than the control group. Patient outcomes in terms of reduction in hospital visits and emergency department visits were also reported.

Conversely a similar structured clinical pharmacy service in a Swedish hospital setting was labelled as unlikely to be cost-effective [99]. The study generated an ICER of €316,243 per unadjusted QALY. This highlights the effect which a small increase in QALY values can have on the cost-effectiveness status of an intervention or therapy. Reasons hypothesised for the negative verdict on cost-effectiveness included the previously mentioned lack of specificity associated with generic outcome measures, the conduct of the study in a pharmacist naïve environment with relatively inexperienced pharmacists and non-attendance of medical rounds by intervention pharmacist.

It is likely that the intervention acceptance rates in our study were negatively affected by non-attendance of medical rounds by the research pharmacist. Similar intervention methods which included a pharmacist as a member of a multi-disciplinary team have demonstrated higher intervention acceptance rates [104, 229]. Other factors which have been proposed as having an influence on the acceptance rate of pharmacist interventions include ward type and pharmacist grade [230].

Methods used to investigate the economic evaluation were appropriate for the type of data available. Multi-level mixed effect models are a suitable method for estimating the incremental net benefits for a clinical trial of this nature. Clustered data can potentially lead to biased results [231]. Normal statistical analysis are generally unsuitable, however the methods employed for our analysis overcome this issue [222].

These techniques account for both the clustering and correlation of cost and effect data.

There are several limitations to the present cost-effectiveness analysis, predominantly relating to the extrapolation of the findings to routine clinical practice. Training costs and software costs were not recorded at time of event and were solely informed by investigator estimate It is likely that some costs associated with this intervention were overestimated. For example, the 1-hour period allocated to conducting the intervention included time required to obtain the patient's consent to participate in the intervention. Since minimal time would be required to obtain patient consent for a medication review (if indeed this was in fact considered necessary at all), the time spent with each patient is likely to be less in routine practice than was estimated for this analysis.. A time in motion study which gathered data on healthcare professional time required to complete the intervention, would have reduced uncertainty surrounding this input. In addition, as healthcare professionals become more familiar with the application of the SPRM/CDSS programme, they will be able to apply it more efficiently and come to quicker decisions regarding the relevance of a suggested intervention.

This study is based on the work of one pharmacist in a single centre. Aspects of the intervention which would be variable between settings include the ability of the pharmacist involved and the extent of the uptake of interventions by the associated medical team. The fact that the trial pharmacist was singularly responsible for determining whether an intervention is clinically relevant is a subjective decision. However, there are previous examples of medication optimisation due to the application of STOPP/START and other variations of SPRMs [209, 232].

Furthermore, the single study site also increases the potential for cross-over learning between healthcare professionals within the hospital environment. Ideally, this study would be conducted on a larger scale involving multiple hospital sites however this was not possible due to limited resources available to implement this RCT.

Zermansky and Silcock have suggested a gold-standard method for economic evaluation for medication review [211]. Ideally, evaluation should be conducted with a 1 year follow-up period from a health service perspective. Health related quality of life should be the effectiveness measure of choice, facilitating comparison with established societal values. The ideal comprehensive evaluation would be a cost-benefit evaluation over a 5-year period from a societal perspective. It would be valuable to compare a number of alternative medication review strategies using these suggested methods.

5.6 Conclusion

Based on the information available from the corresponding RCT, a software-supported structured pharmacist intervention is likely to be cost-effective even if the healthcare payer is unwilling to assign any additional finance for the prevention of ADR. However, as the authors are unaware of decisions previously made based on the cost per ADR prevented, there is some degree of uncertainty regarding the cost-effectiveness status of the intervention from a policy perspective. In addition, the difference in incremental costs and effects on an individual basis did not demonstrate statistical significance. To date, medication reviews conducted by pharmacists have primarily received funding at a primary care level [204]. At a minimum, this study

further adds to the growing body of evidence that a structured form of medication review and reconciliation incorporating STOPP/START criteria is superior to current medication review based on a pharmacist's individual clinical knowledge.

6 - Chapter 6: Clinical and economic benefits of a community pharmacy vaccination strategy

The work of this chapter has been submitted as Gallagher J, Byrne S, O'Dwyer S, McCarthy S. Clinical and economic benefits of a community pharmacy vaccination strategy

International Journal of Clinical Pharmacy. Under review

6.1 Abstract

Introduction

Influenza places a significant burden on healthcare systems worldwide. Seasonal influenza vaccination is the most effective method of preventing or reducing the symptoms of influenza. However, vaccination uptake rates remain below targeted levels, especially amongst high-risk population groups. Legislation was implemented in Ireland to allow pharmacists to partake in the Seasonal Influenza Vaccination Programme at a national level. The aim of this research is to evaluate the impact of introducing a pharmacist-led vaccination campaign on the Irish healthcare system. The clinical and economic benefit obtained by a cohort of patients who obtained an influenza vaccination in a pharmacy setting will be estimated.

Method

Data was collected from patients who availed of an influenza vaccination service offered by a community pharmacy chain at multiple locations in the Republic of Ireland during the 2013/14 influenza season. Demographic information from sample data was applied to national population levels. A method described by Preaud *et al.* was adapted to estimate the clinical and economic benefit gained from vaccination of patients by a community pharmacist in Ireland in 2013/14 [233].

Results

Implementation of pharmacist-led influenza vaccination has resulted in substantial clinical and economic benefits to the healthcare system. The majority of patients (64.9%) who availed of this service had identifiable influenza-related risk factors. Of patients with influenza-related risk factors, age ≥65 year was the most commonly cited risk factor. Pharmacist vaccination services averted a total of 848 influenza cases across all age groups during the 2013/2014 influenza season. Due to receipt of

vaccination in a pharmacy setting, 444 influenza-related GP visits were prevented. In terms of more serious influenza-associated events, 11 hospitalisations and five influenza-related deaths were averted. Costs averted were approximately €305,000. These were principally wider societal-related costs associated with lost productivity

Conclusion

Community pharmacy vaccination has proved to be a successful addition to the Irish society. Vaccination services are being predominantly utilised by patients who are classified as being 'at-risk' for influenza. The number of influenza-related events averted due to vaccination in a pharmacy setting is a welcome benefit to the Irish healthcare system, especially in winter months where services are already overburdened.

6.2 Introduction

Influenza places a significant burden on the Irish health system. Internationally, annual rates of influenza illness vary between 5 – 10% in adults and 20 – 30% in children [234]. Irish specific data presented by the Health Protection Surveillance Centre indicates that during the 2013/14 influenza season 693 patients were hospitalised with a confirmed case of influenza [235]. In addition, 43 people were considered to have an influenza associated death during the same time period [235]. Similar event rates are replicated at a European and global level [236]. Influenza also imposes a substantial burden on society, in terms of loss of productive working days and overall increased use of healthcare resources [237].

Seasonal influenza vaccination is the most effective method of preventing or reducing the symptoms of influenza. Influenza vaccination has been linked with a reduction in hospital admission by as much as 60% and a reduction in mortality of 50% [238, 239]. However, vaccination effectiveness varies substantially depending on circulating strains and host characteristics [240].

The potential positive influence of seasonal vaccines is further tempered by poor uptake levels. It is estimated that 180 million people across the 27 EU countries are considered members of influenza vaccination target groups [233]. However, only 44% of the eligible target population is vaccinated annually [233]. Ireland is amongst the group of countries with suboptimal vaccination uptake levels [241]. Despite the best efforts of policy makers, influenza vaccination uptake rates have remained steadfastly below the EU recommended level of 75% [242]. Influenza vaccination uptake rates are currently at 59% in population over 65 years of age [243]. Vaccination coverage

among those with chronic medical disease is approximately 30%, one of the lowest uptake rates in Western Europe [244].

Comprehensive evidence is available to advocate the utility and success of pharmacist administered vaccination services. The service was initially provided in California in the early 1990s [245]. Since 2009, it has been implemented in fifty US states and other health systems including England, Scotland, Portugal and Canada [246]. Evidence supporting provision of vaccination services has been generated based on clinical data, economic evaluations and patient preference [247-249].

In 2011, legislation was implemented in Ireland to allow pharmacists to partake in the "Seasonal Influenza Vaccination Programme" at a national level [250]. Numbers of patients availing of this service have been steadily growing since its establishment [251]. While the feasibility of the system is established, limited evidence is available regarding whether the service is reaching patients in relevant risk groups. In addition, the overall benefit of the service to the health service and society in general has not been quantified.

The aim of this research is to evaluate the impact of introducing a pharmacist-led vaccination campaign on the Irish healthcare system. The clinical and economic benefit obtained by a cohort of patients who obtained an influenza vaccination in a pharmacy setting will be estimated. In addition, analysis will be performed on the demographic details of a sample of patients who availed of community pharmacy vaccination services. These outcomes will provide a quantitative estimate of the

impact of an important community pharmacy service and will also help inform future public health policy decisions in the area.

6.3 Methods

6.3.1 Sample Data collection

Data was collected from patients who availed of an influenza vaccination service offered by a community pharmacy chain at multiple locations in the Republic of Ireland during the 2013/14 influenza season. Pharmacists performing vaccination completed externally accredited training, in addition to education on internal operational procedures. All participating pharmacists were assessed as competent in undertaking the service prior to receiving authorisation. Procedures were also in place for dealing with potential adverse reactions to the vaccinations.

Vaccination service had been especially targeted through various media campaigns at patients with the following risk factors:

- Aged 65 and over.
- Long-term medical condition such as diabetes, heart or lung disease.
- Impaired immune system due to disease or treatment.
- Body Mass Index (BMI) over 40.
- Pregnancy (the vaccine can be given at any stage of pregnancy).
- Residency of a nursing homes or another long-stay institution.
- A healthcare worker.
- A carer and
- Regular close contact with poultry, waterfowl or pigs.

Influenza vaccination is available free of charge in the pharmacy to patients who are eligible for General Medical Services (GMS) scheme or GP visit scheme. GMS

scheme entitles patients to free medical care (e.g. GP visits, supply of medications with a small patient co-payment). GP visit scheme has similar entitlements but patient will have greater out of pocket payments for medications. In 2013, approximately 40% of the population were eligible for the GMS scheme [252]. A further 3% of the population qualified for GP visit cards. Private patients (those not eligible for GMS or GP Visit schemes) are required to pay an out of pocket payment of approximately €20.

Only patients who had agreed to have their information analysed by external bodies had their data included in this study. No patient identifiable information is presented in this study or was transferred to any external parties.

6.3.2 Estimate of influenza related clinical burden

The following formula was used to calculate the number of influenza-like events prevented:

$$Number\ vaccinated \times Rate\ of\ influenza\ illness\ x\ Vaccine\ effectiveness$$

This formula was varied to account for age and risk factors. Health related outcomes such as GP visits, lost days at work, hospitalizations and death were then calculated by applying the probability of experiencing these influenza related events to the overall number of cases of influenza prevented. Age and risk status were accounted for in transition probabilities. Input data is presented in **Table 6.1**.

Table 6.1 Age specific data used to estimate clinical and economic burden

Model Input	**18 - 64**	**18 - 64, risk**	**≥65**	**Ref**
Patients vaccinated in pharmacy setting	14154	10975	15270	Study sample data / PSI [253]
Influenza attack rate	3.64%	3.64%	4.91%	Preaud *et al.* [233]
Probability of influenza related GP visit	0.31	0.62	0.62	Prosser *et al.*[248]
Probability of lost work days	0.90	0.90	-	Carrat *et al.* [254]
Mean number of days off work	4	4	-	Carrat *et al.* [254]
Annual Influenza related hospitalisations per 100,000 population	4.9	17.9	130	Preaud *et al.* [233]
Annual influenza related mortality per 100,000 population	0	3.87	66.9	Preaud *et al.*[233]
Vaccine effectiveness (%)	51%%	51%%	51%%	CDC [255]
Lower vaccine effectiveness – 95% CI (%)	43%	43%	43%	CDC [255]
Upper vaccine effectiveness – 95% CI (%)	58%%	58%	58%	CDC [255]

6.3.3 Economic analysis

A method described by Preaud *et al.* was adapted to estimate the clinical and economic benefit gained from vaccination of patients by a community pharmacist in Ireland in 2013/14 [233].

Analysis was performed from a wider societal perspective to capture the considerable burden associated with influenza related work absences. Estimates for the number of days taken off work due to influenza were informed by a study conducted by Carrat *et al* [256]. All unit cost data were obtained from Irish sources, references are provided in **Table 6.2**. All costs are expressed in euros (€) at 2013 levels.

Table 6.2 Influenza related unit resource use

Resource Variable	Unit	Reference
GP Visit	€50.00	ORC
OTC Treatment	€7.00	Investigator estimate
Prescription medicine	€15.00	Investigator estimate
Inpatient hospitalisation for acute upper respiratory tract infection and influenza (age specific) - Adult, 18 – 64 - Adult, ≥65	 €2056.80 €3599.40	 HPO
Average wage (per day)	€138	CSO Q3 2015
ORC - Office of the Revenue Commissioners, HSE - Health Service Executive, HPSC - Health Protection Surveillance Centre, HPO – Healthcare Pricing Office, CSO - Central Statistics Office		

6.3.4 Ethical Approval

Ethics approval for the research was received from the Clinical Research Ethics Committee of the Cork Teaching Hospitals and University College Cork, Ireland. All patient information was managed in accordance with established data protection procedures.

6.4 Results

Overall, 40,443 patients were vaccinated in a community pharmacy setting during the 2013/2014 influenza vaccination season [253]. Demographic analysis was performed on a sample of 3,949 patients. This sample represented 10% of national pharmacy based vaccinations during the 2013/2014 influenza vaccination season. All of these patients had obtained vaccinations from source outlined in methods section. **Figure 6.1** provides detailed breakdown of patient demographics. Based on sample analysed, females, over 65 years of age, who had previously received an influenza vaccination were the most frequent type of user of this scheme.

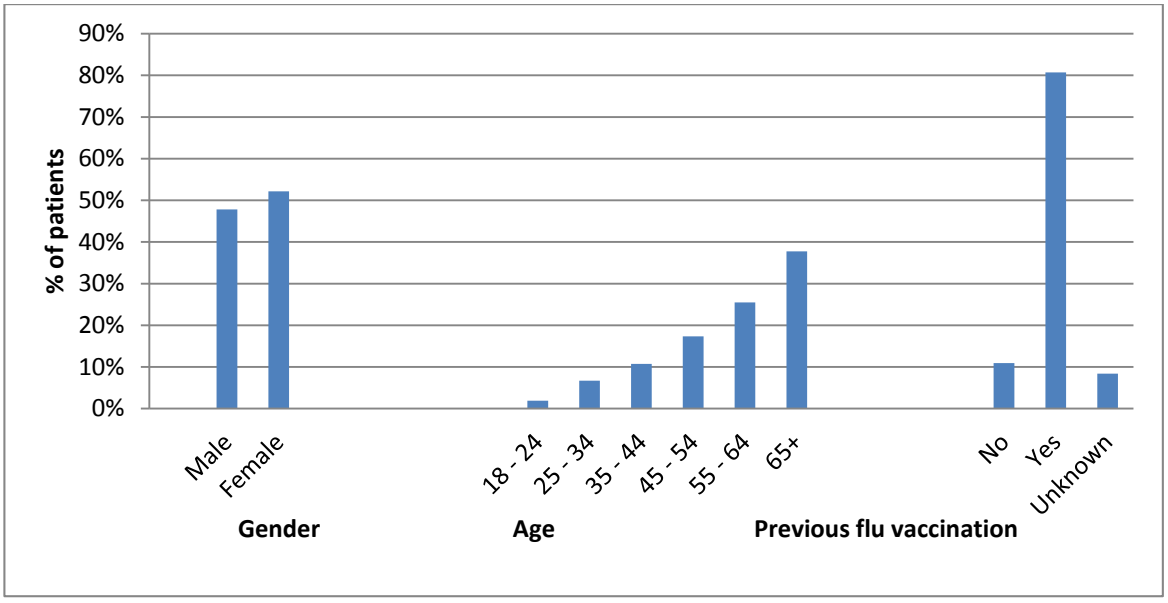


Figure 6.1 Demographic details of sample patients accessing pharmacy vaccination services (n=3,949)

The majority of patients (64.9%) who availed of this service had identifiable influenza-related risk factors. Of patients with influenza-related risk factors, age ≥65 year was the most commonly cited risk factor; followed by history of respiratory illness or diabetes (**Figure 6.2**). A combination of risks (e.g. over 65 and concurrent respiratory illness) were recorded for 148 patients.

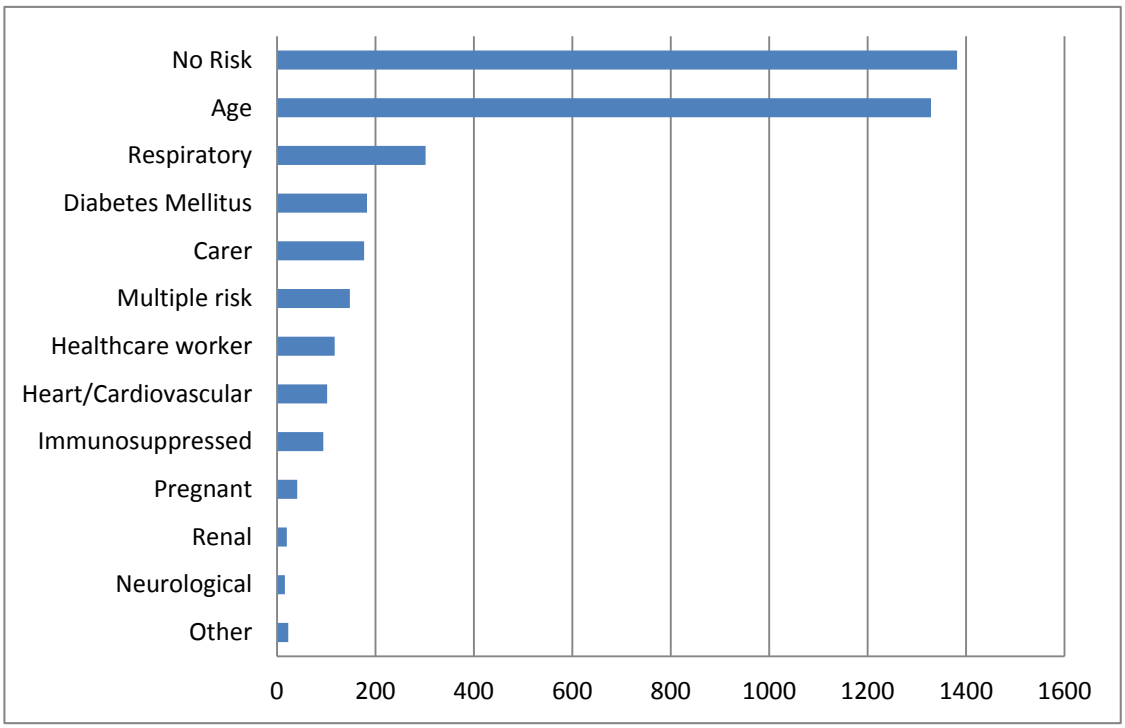


Figure 6.2 Risk factors analysis of pharmacist vaccinated patients (n=2561)

Pharmacist vaccination services averted a total of 848 influenza cases across all age groups during the 2013/2014 influenza season, as described in **Table 6.3**. Unsurprisingly, patients who are over 65 years of age represented the group of patients who were responsible for the largest number of cases averted (n=382). A total of 1679 days of lost productivity were averted in patients aged 18 – 64. Patients aged ≥ 65 years of age were not included in this productivity analysis, as they were deemed unlikely to be in full time employment. Due to receipt of vaccination in a pharmacy setting, 444 influenza-related GP visits were prevented. In terms of more serious influenza-associated events, 11 hospitalisations and five influenza-related deaths were averted.

Table 6.3 Clinical / economic benefits of pharmacist influenza vaccination

Category of influenza-related events averted (Based on total pharmacist vaccinated population in Ireland, n = 40,433)	**18 – 64 years (Range)**	**18 – 64 years, Risk (Range)**	**≥ 65 years (Range)**	**Total economic burden**
Influenza-like illness	263 (222 –299)	203 (172 – 232)	382 (322 – 435)	-
OTC Treatment	-	-	-	€5,942
Lost days of work	946	733	-	€231,346
Influenza-related GP visit	81	126	237	€22,242
Prescription medicine treatment	-	-	-	€6,673
Influenza-related hospitalisation	0	1	10	€38,501
Influenza-related mortality	0	0	5	-
Overall influenza related costs (Range)				€304,703 (€256,907 - €343,630)

Costs averted were approximately €304,000. These were principally composed of wider societal-related costs associated with lost productivity. Therefore, the majority of economic benefits were driven by patients in the 18 – 64 years age category. Elderly patients were responsible for the bulk of direct healthcare costs (€51,849). Due to the inter-seasonal variation in vaccination effectiveness, a range of averted events and other associated impacts is presented in **Table 6.3**.

6.5 Discussion

Based on the study sample pharmacist-led vaccination services are being predominantly used by patients in 'at-risk' categories for influenza. Uptake of influenza vaccination by any patient group is to be welcomed; however engagement of patients in at risk categories is maximizing the benefit of the vaccination service as these patients are more vulnerable and more likely to have outcomes which require use of higher levels of healthcare resources. It is also assisting with Ireland's aims of reaching EU and WHO recommended levels of vaccination for patients with risk factors for influenza [242].

The fact that the majority of users being identified are classified as at-risk to influenza has been replicated elsewhere. A similar study conducted in the Isle of Wight primary care trust (PCT), also demonstrated that a majority of users availing of a pharmacist administered influenza vaccination were in an at-risk category[257]. Pharmacist vaccinations increased the overall patient numbers receiving vaccination in the Isle of Wight PCT. However, there is no evidence that availability of a pharmacist service has improved overeall influenza vaccination uptake levels.

Pharmacist-delivered influenza vaccination numbers have increased annually since initiation of the scheme [251]. However, overall uptake of influenza vaccination has not increased in terms of percentage of patients over 65 years who are being vaccinated. Ireland remains below recommended vaccination levels [242]. As described in **Figure 6.1**, the majority of the patients availing of influenza vaccination have previously received it. While it is a positive development that evidence indicates a large number of patients are convinced of the benefit of vaccination and avail of service on a regular basis, there remains a substantial number of patients who are not

engaging with the service either at a pharmacy or GP level. More targeted initiatives need to be utilised in order to identify patients reluctant to avail of vaccination services and to convince them of their benefit.

To date, health policy has relied on general media campaigns to attempt to increase influenza vaccination uptake. However, it appears that their influence has plateaued. The time may have come to take a different approach to patient recruitment. Utilisation of the proposed electronic healthcare record may offer a means to identify reluctant patients and consolidate resources on improving uptake rates amongst these patients. Electronic healthcare records have demonstrated utility amongst other populations reluctant to engage with vaccination [258].

Considering government funding for pharmacist vaccination programme in 2013 was in region of €250,000 [252], the overall economic benefit to society of €305,000 is a satisfactory return on this investment. The majority of the economic benefit is composed of indirect costs benefitting the working adult population. This finding supports the argument that greater support should be directed towards encouraging vaccination amongst this category of patients. Absenteeism has been estimated to cost the Irish economy up to €1.5 billion annually so any reduction will be a welcome development to the state [259].

While direct healthcare costs may appear insignificant considering overall expenditure on healthcare in Ireland, these benefits should not be appraised in isolation. Influenza tends to reach peak levels during December / January period. This period is generally one where demands on the Irish healthcare system reach crisis levels [260]. The

prevention of influenza-like events reduces demand on hospital services at a time when they do not have capacity to deal with additional strains associated with vulnerable patients. Increased demand due to influenza-related events can affect other areas of the healthcare system due to cancellation of routine procedures in order to deal with crises events. Moreover, vaccination outcome measures evaluated in this study are an under estimate of the overall benefit to society as the additional benefit of herd immunity associated with vaccination has not been captured.

Research is on-going to develop more targeted vaccinations but the continued antigenic drift associated with influenza strains complicates the process [261]. Both clinical and economic benefits are highly dependent on the effectiveness of the influenza vaccination, which is reflected in the large range of economic costs averted (€257,000 – €344,000). While awaiting developments in vaccine technology, increasing influenza vaccination coverage remains the best method of reducing the impact of influenza.

While the economic and clinical benefit derived from pharmacist-led vaccination is currently a satisfactory addition to the Irish healthcare system, it is a resource which could be further developed. Currently, vaccination in pharmacies is limited to patients over 18 years of age. Legislation allows for pharmacist vaccination of patients less than 18 years of age [250]. However, healthcare payer does not currently provide funding for the provision of the service to cohort of patients less than 18 years of age.

The large number of patients under 65 years of age (62%) indicates that pharmacy could be a good location for enabling vaccination of the children of time pressurised working parents. Convenience of location and opening hours were the two most cited reasons for utilisation of pharmacy vaccination services from recent research in the UK [249]. Evidence also indicates that it is a cost-effective public health intervention [262]. In addition to reducing clinical burden of illness amongst the childhood population, increased vaccination of this cohort has potential to reduce school absenteeism and parental industrial absenteeism [263].

One policy which could be considered to increase overall vaccination uptake is the additional provision of government funding to reduce out of pocket payments for patients who want to avail of influenza vaccination. Any increase in overall national vaccination uptake will help provide additional indirect protection to unvaccinated sectors, due to a reduction in risk of transmission. Research at a EU-27 level has indicated that if influenza vaccination was utilised by all at-risk patients versus current uptake levels, an additional 1.6 to 1.7 million cases would be prevented, with influenza-related costs averted increasing by an additional €190 -226 million annually [233].

The success of pharmacist-provided influenza vaccinations has highlighted the possibility of extending the range of vaccinations which can be provided in a community pharmacy setting in the future. Pneumococcal and various travel vaccinations have been provided in a community pharmacy setting in other jurisdictions [264, 265]. Potential barriers to the implementation of vaccination services have been identified in a previous literature review [266]. The recognized

challenges include competent response to adverse reactions, record keeping, liability, legal regulations and quality of service. The clinical governance standards enacted during the establishment of influenza vaccination services largely overcomes these barriers. In addition, the evolved powers of both the Pharmaceutical Society of Ireland and the Health Information and Quality Authority ensure that the appropriate regulators are in place to assist with the development of potential future vaccination programmes.

There is a potential for sample bias in the data collection phase. Patients were all attendees of the same pharmacy chain. While pharmacies were located in both urban and rural locations, throughout the country, sample demographic data may not be representative of the entire Irish population.

Input data used in estimates of the clinical and economic burden averted, is sourced from various international sources. Influenza rates and vaccine effectiveness vary annually, therefore broad estimates were thought to be more appropriate to use and similar methodology had been employed in similar previously published studies.
A further limitation is the exclusion of potential adverse drug reactions (ADR) associated with influenza vaccination from overall analysis. ADRs would not be expected to have a major impact on overall benefits associated with influenza vaccination provision. PSI evaluation of service for 2013/2014 vaccination season indicated 12 ADRs were reported by pharmacists [253]. None of these related to serious events such as anaphylaxis.

6.6 Conclusions

Community pharmacy vaccination has proved to be a successful addition to the Irish society. Vaccination services are being predominantly utilised by patients who are classified as being ‘at-risk’ for influenza. The number of influenza-related events averted due to vaccination in a pharmacy setting is a welcome benefit to the Irish healthcare system, especially in winter months where services are already overburdened. While clinical benefit of the vaccination scheme is primarily experienced by older patients, working adults obtain the majority of economic benefit in the form of reduced out of pocket expenses and averted absenteeism from work. Expansion of government funding for this scheme to support additional patient groups and disease campaigns would result in further substantial benefits to society. The successful establishment of influenza vaccination services within a community pharmacy setting highlights that pharmacies are still a relatively untapped potential source within the Irish healthcare system for implementation of public health policy initiatives.

7 - Chapter 7: Systematic Review Update

7.1 Objective

A systematic review entitled “Economic evaluation of clinical pharmacist interventions on hospital inpatients: a systemic review of recent literature” was conducted in April 2013 and published in February 2014. The objective of this chapter is to re-conduct the search in order to update the thesis.

7.2 Methods

The search used the same search terms and databases as the original searches and was conducted in January 2016. The publication dates of articles included in the search strategy ranged from January 2013 to December 2015. Eligible studies underwent the same quality assessments outlined in chapter 2.

7.3 Results

The updated search results are outlined in the below flowchart **(Figure 7.1**). Of 2695 potential articles, 16 studies were eligible for inclusion. **Table 7.1** provides details on the included studies.

Antibiotic specific interventions were the most common type of clinical pharmacy service identified following systematic review. A total of six studies were identified, which highlighted various degrees of cost savings and cost avoidance, which can be gained from implementation of targeted antibiotic interventions [107, 267-270]. Specific details are given in **Table 7.1.**

General medication optimisation interventions were identified in two studies [176, 271]. Benefits associated with these interventions were impressive but were judged to be of poor quality due to the lack of available comparators.

Inappropriate prescribing of stress ulcer prophylaxis is a considerable burden on healthcare payers, Buckley*et al.* and Mosavi *et al* have separately described interventions where hospital pharmacists can lead efforts to reduce unnecessary expenditure in this area [272, 273].

A number of more innovative speciality areas were identified. Pharmacists have identified niche roles for themselves in surgery[274], paediatric cystic fibrosis [275], intensive care[276] , infectious diseases [136], organ transplants [277] and heart failure[278].

General IV to oral conversions, are a long established area of potential influence for hospital pharmacists, additional evidence relating to the topic was described by Hohlfelder *et al* [279].

From a quality perspective, only two studies could be labelled as “good-quality” studies. Lack of comparators and disregard for costs associated with providing the service were once again an issue with majority of studies.

7.4 Conclusion

The findings of the updated systematic review were broadly in line with the conclusions of chapter 2 (Chapter 2, section 2.5). The majority of clinical pharmacy interventions provide direct cost savings or generate positive outcomes in relation to cost avoidance. This thesis update adds to the growing body of evidence which highlights the issue of poor study design from a health economic perspective. The vast majority of studies do not address simple but important issues such as quantifying the cost of providing the service.

A positive development is new evidence indicating that pharmacist involvement is improving economic outcomes in specialized care areas such as cystic fibrosis [275]. These studies have potential to improve chances of establishing pharmacist positions on specialist multidisciplinary teams.

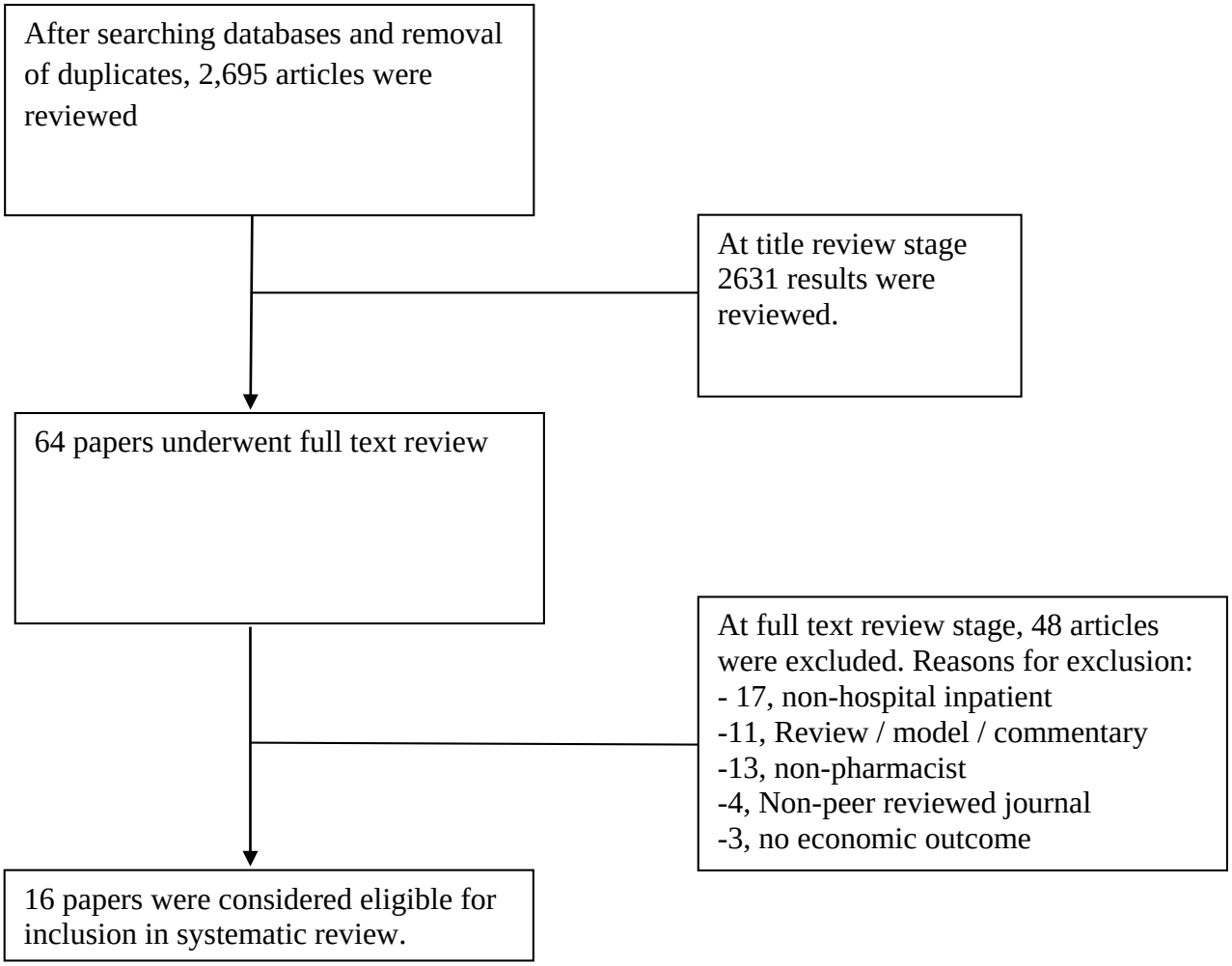


Figure 7.1 Literature search method and screening results

Table 7.1 Description of studies eligible for inclusion in updated review

First Author (Year)	Title	Pharmacist Intervention	Setting	No of patients / Interventions	Economic Method	Period	Outcome Measures	Results	Quality	Type of study
Maldonado *et al.* (2013) [277]	Changing transplant recipient education and inpatient transplant pharmacy practices: Single centre perspective	Medication management, reconciliation, discharge planning and patient education.	USA. 628 bed tertiary care hospital with focus of study on interdisciplinary transplant care team	Intervention group = 54 patients. Control group = 60 patients	Cost analysis	3 years	LOS, readmission rates.	Annual cost savings of $279,180	Fair (Missing cost of service)	Retrospective database analysis
Neville et al. (2013) [274]	Clinical benefits and economic impact of post-surgical care provided by pharmacists in a Canadian hospital	Addition of clinical pharmacy services to general surgery wards. Medication management of surgical patients.	Canada. 950 bed adult tertiary care hospital.	Prospective observational study. 1097 interventions evaluated.	Cost avoidance	6 months	Cost avoidance per intervention	$0.68–1.36 million	Poor (No comparator)	Prospective observational study
Cies et al. (2014) [275]	Clinical pharmacist impact on care, length of stay, and cost in pediatric CF patients	Clinical pharamcist is responsible for aminoglycoside dosing, adjustments and monitoring.	USA. 189 bed tertiary care childrens teaching hospital.	Intervention group = 29 patients. Control group = 22 patients	Cost analysis	Intervention period, September 2008 to May 2009. Comparator period, January 2007 to August 2008.	Compare the number of pediatric CF patients achieving AG PK/PD targets when therapy is managed by a clinical pharmacist (CP) versus usual care (UC)	Cost saving of $287,877	Fair (Missing cost of service)	Retrospective cohort study.

Table 7.1 Description of studies eligible for inclusion in updated review

First Author (Year)	Title	Pharmacist Intervention	Setting	No of patients / Interventions	Economic Method	Period	Outcome Measures	Results	Quality	Type of study
Khalili *et al.* (2013) [136]	Evaluation of clinical pharmacist's interventions in an infectious diseases ward and impact on patient's direct medication cost	Patient medical chart review and direct interventions.	Iran. 60 bed infectious diseases ward.	Post-intervention group = 956. Pre-intervention group = 1040.	Cost analysis	1 year pre and post intervention.	Direct medication cost for patients.	direct medication cost per patient was decreased about 3.8%. Decrease was non-significant.	Fair (Missing cost of service)	Prospective, interventional study
Claus et al. (2014) [276]	Expected net benefit of clinical pharmacy in intensive care medicine: a randomized interventional comparative trial with matched before and after groups	Clinical pharmacist provided recommendation on drug therapy and follow up from clinical pharmacist	Belgium. 22 bed surgical ICU.	Intervention group = 75patients. Control group = 60 patients	Cost-benefit analysis	April to mid June 2012	Comparison of mean daily drug costs between patients with or without a clinical pharmacy service.	Excluding outlier drugs mean daily cost per patient was decreased from €184.4 to €90.5 (P<0.001).	Good	Randomized interventional comparative trial.
Buckley et al. (2015) [272]	Impact of a Clinical Pharmacist Stress Ulcer Prophylaxis Management Program on Innappropriate Use in Hospitalized Patients.	Clinical pharmacists initiate, modify, or discontinue stress ulcer prophylaxis.	USA. 700 bed major academic medical centre.	Post-implementation period = 371. Pre-implementation period = 763.	Cost-analysis	October 2011 to January 31 2012.	Total inpatient costs associated with acid suppression therapy.	Pre-implementation inpatient costs $20,052. Post-implementation costs $3280. Estimated annual savings of >€200,000.	Fair (Missing cost of service)	Retrospective pre- and post-implementation study.

Table 7.1 Description of studies eligible for inclusion in updated review

First Author (Year)	Title	Pharmacist Intervention	Setting	No of patients / Interventions	Economic Method	Period	Outcome Measures	Results	Quality	Type of study
Mousavi et al. (2013) [273]	Impact of clinical pharmacy services on stress ulcer prophylaxis prescribing and related cost in patients with renal insufficiency	Stress ulcer prophylaxis developed by clinical pharmacists.	Iran. 60 bed infectious diseases ward.	Post-test phase = 236 patients. Pre-test phase = 375 patients.	Cost analysis	6 month pre-intervention stage. 6 month post-intervention stage.	Costs due to innappropriate acid suppression therapy.	67% reduction in cost per patietns of inappropriate stress ulcer prophylaxis.	Fair (Missing cost of service)	Pre- and post-intervention study.
Wang et al. (2015) [267]	Impact of pharmacist interventions on rational prophylactic antibiotic use and cost saving in elective cesarean section	Pharmacists made recommendations on prophylactic antibiotic prescribing, in addition to physician education and monitoring of clinical records.	China. Patients who underwent elective cesarean section in a tertiary hospital.	197 patients were enrolled in both pre- and post-intervention period.	Cost analysis		Antibiotic cost reduction	Antibiotic cost reduction = $68,024. Cost:Benefit ratio = 27.23 : 1.	Good	Pre- and post-intervention study.
Bartlett et al. (2014) [268]	Implementation and first-year results of an antimicrobial stewardship program at a community hospital.	Implementation of an antimicrobial stewardship program by a team of pharmacists.	USA. 155 bed hospital.	797 interventions during study period.	Cost analysis	Intervention period January - December 2011.	Antimicrobial acquisition costs.	Cost savings of $145,353.	Poor (Quasi-experimental).	Pre- and post-intervention study.
Sallach-Ruma et al. (2015) [269]	Correlates and Economic and Clinical Outcomes of an Adult IV to PO antimicrobial conversion program at an academic medical centre in Midwest United States	Pharmacist initiated IV to PO conversions.	USA. 635 bed tertiary teaching care center.	237 patients	Cost analysis	40513	Cost savings due to iv to po switch.	$5242 in December 2010.	Poor (Multiple flaws)	Retrospective observational study.

Table 7.1 Description of studies eligible for inclusion in updated review

First Author (Year)	Title	Pharmacist Intervention	Setting	No of patients / Interventions	Economic Method	Period	Outcome Measures	Results	Quality	Type of study
Szkiladz et al. (2013) [278]	Impact of pharmacy student and resident-led discharge counseling on heart failure patients	Discharge counselling to patients provided by students and residents to patients with heart failure related symptoms	USA. 659 bed tertiary care academic teaching hospital.	Intervention group = 86 atients. Control group = 94 patients	Cost avoidance	Oct 2011 to March 2012	Cost avoidance of medication errors likely to be prevented.	$4241 per intervention period.	Fair (Missing cost of service)	Retrospective, non-randomized intervention study.
Zhang et al. (2014) [107]	Pharmacist interventions for prophylactic antibiotic use in orological inpatietns undergoing clean or clean-contaminated operations in a Chinese Hospital	Pharmacist interventions included real-time monitoring of medical records and controlling of the prescriptions of prophylactic antibiotics	China. Tertiary hosptial.	Post-intervention group = 174 patients. Pre-intervention group = 196 patients	Cost-benefit analysis	Pre-intervention January 2011 - June 2011. Post-intervention January 2012 - June 2012.	Mean antibiotic cost savings	$239.64 for intervention period. Benefit to cost ratio 18.79 : 1	Good	Retrospective, pre- / post-interventions study.
Shogbon et al. (2014) [271]	Student pharmacists' clinical interventions in advanced pharmacy practice experiences at a community nonteaching hospital	Interventions on following areas: Therapuetic, safety, quality assurance and education.	USA.	2107 interventions	Cost analysis	June 2009 - December 2012	Cost savings to institution	$280297	Poor	Retrospective database analysis

Table 7.1 Description of studies eligible for inclusion in updated review

First Author (Year)	Title	Pharmacist Intervention	Setting	No of patients / Interventions	Economic Method	Period	Outcome Measures	Results	Quality	Type of study
Gallagher et al. (2014) [176]	Cost-outcome description of clinical pharmacist interventions in a university teaching hospital	Clinical interventions identified during pharmacist chart review	Ireland. 850 bed hospital site.	4257 interventions	Cost description	January 2012 - December 2012	Cost avoidance	Cost avoidance due to prevention of ADEs - €708221. Cost-benefit ratio 8.64 : 1.	Poor (No comparator)	Retrospective database analysis
Tachi et al. (2013) [270]	Impact of levofloxacin dose adjustments by dispensing pharmacists on adverse reactions and costs in the treatment of elderly patients	Pharmacists evaluated patient kidney function and suggested appropriate doses of levofloxacin.	Japan. 609 bed acute-care general hospital.	Intervention group = 142 patients. Control group = 98 patients	Cost analysis	March 2011 to August 2011	Cost savings to institution	Intergroup difference in total cost per patient was ¥465.60.	Fair (Missing cost of service)	Retrospective comparative study.
Hohlfelder et al. (2015) [279]	Improvements in a program to convert i.v. to oral medications at an academic medical center	Addition of targeted interventions to a pharmacist initiated iv to po oral conversion program	USA. 793 bed academic acute tertiary hospital.	Mean number of interventions: post intervention = 57, pre-intervention = 25.	Cost analysis	Post-intervention = October 2014 - January 2015. Pre-intervention = January 2014 - August 2014.	Cost saving	No significant difference in overall cost savings. Mean monthly (±SD) cost savings, post intervention = $2068.49±143.32 versus pre-intervention = $1276.75±1217.43 (P=0.12).	Fair (Missing cost of service)	Before- and after-intervention analysis.

8 - Chapter 8: Thesis Discussion

8.1 Discussion Summary

This thesis primarily examined the health economic impact of a series of interventions by pharmacists within the Irish healthcare system.

This chapter will assess the overall implications of the evidence presented earlier in this thesis. Discussion will focus on the following areas:

- Key findings from each of the research chapters,
- Overall findings of thesis,
- Potential impact of evidence on national policy,
- Strengths and limitations of the evidence presented,
- Future research and
- Conclusion

8.2 Summary of chapter 2

A systematic review was conducted at the early stage of the research to provide an overall evidence base and structured background on the topic of health economic evaluations of clinical pharmacy services at a global level.

The principal finding from the systematic review indicated that clinical pharmacist interventions are associated with positive economic outcomes within healthcare systems, a finding also reported in previous systematic reviews and in the new evidence produced in chapter 3 – 6 of this thesis.

The second key finding related to the overall quality issues with much of health economic research produced in relation to pharmacy services. This had been previously highlighted but it is an aspect that has not been improved upon in recent studies. Even with a robust study design, there is always likely to be some uncertainty associated with decisions on the cost-effectiveness of interventions.

However, greater input of health economists at an earlier point in the research process would assist in reducing some of the quality issues and subsequently increase the generalizability of the findings. Health economic expertise needs to be included from an early stage of the study design, rather than being seen as a 'bolt-on' after the main clinical study has been published. Greater adherence to guidance documents such as the 'CHEERS' statement utilised in this study may be beneficial. Similar guidance documents are commonly used in other areas of research but have perhaps been underutilised or under promoted in the field of health economics research (Chapter 2, page 60).

While, similar systematic reviews have been published in the past, the current review does provide a timely update on the recent developments within clinical pharmacy services at a hospital level. On commencement of this systematic review, the time period covered had not been included in a formal published review focusing on health economic evaluations. Subsequent reviews covering a similar time period have been published [96]. An ACCP-led collaborative study had a slightly wider remit and alternative means of assessment but came to similar conclusions relating to the paucity of studies which could be considered high quality in terms of health economic methodology [96]. Findings such as these have been discussed for over 20 years and in multiple jurisdictions [80, 95, 96, 280]. However, based on evidence from chapter 2, clinical pharmacy orientated researchers have not really engaged with previous advice.

Chapter 2 was an example of research which successfully adopted the use of 'CHEERS' statement within a systematic review. This approach has been

subsequently used by authors of other systematic reviews [281-283] , further endorsing the utility of this approach. The use of the CHEERS approach enabled definite recommendations on research methodologies which required greater consideration in future clinical pharmacy studies.

An update on the published systematic review has identified 16 studies of relevance published between 2013 and 2015. Quality assessment outcomes were similar to original systematic review.

8.3 Summary of chapter 3

Chapter 3 of the thesis provides detail on an article titled ‘Cost-outcome description of clinical pharmacist interventions in a university teaching hospital’ published in BMC Health Services Research [176].

This research offers an insight into the impact of pharmacist ward rounds, a fundamental-component of a clinical pharmacy service. As they have already been established, to a variable degree within the Irish health system, an established data source was available for analysis. The most stimulating finding of the hospital intervention study was the sheer volume of interventions implemented by a single pharmacy team and the significant level of cost avoidance estimated to be generated as a result of their clinical interventions. While the costs averted from the study were based on a subjective method, the cost : benefit ratio of 8.64 : 1 indicates that this service would likely to be considered to be value for money even in the event that an ultra-conservative approach is taken to assigning ratings to various interventions (Chapter 3, Table 3.3)

Another major highlight of this study was that the impact was measured over a full calendar year. Other studies have attempted to measure the benefit of clinical pharmacist interventions over a short period and extrapolate finding over a longer period of time [88, 90, 147]. However, evidence provided in this study provided a more realistic evaluation of the impact over an entire year within a hospital environment.

In addition, the large amount of data evaluated and Irish setting of the study has meant that this research has been used by multiple hospital departments in internal submissions for additional funding for hospital pharmacy staff. Appendix 7 and Appendix 8 also outline the application of this research methodology in two other hospitals. Similar levels of cost avoidance were highlighted in both a national major paediatric tertiary referral hospital and an additional University Teaching Hospital.

A limitation of Chapter 3 was the large element of unknown acceptance rates associated with the interventions (68.81%) (Chapter 3, Table 3.2). At an Irish hospital level, ward reviews conducted by pharmacists have become an established practice. However, evidence indicates that it can be intermittent or confined to certain wards or areas of the hospital [16]. As pharmacists may not get a chance to perform a follow-up review on the patient, it can be difficult to determine whether the suggested intervention was implemented. Furthermore, lack of pharmacist integration on core medical teams may limit the acceptance rates of suggested interventions.

Drug omissions were the most frequent intervention highlighted in chapter 3 (Chapter 3, Table 3.5). Drug omissions have been continuously highlighted as an issue within the Irish hospital system. Examples have been highlighted in various hospitals, ranging from omissions at admission to discharge [157, 203]. The targeting of dedicated pharmacist staff members towards completion of medicines reconciliation at both entry and exit from care institutions would help to reduce this problem. Establishment of similar roles in other jurisdictions have been associated with improved outcomes [284].

8.4 Summary of chapter 4

Health policy in Ireland is shifting towards a strategy promoting management of chronic diseases at a primary care level [39]. While it is anticipated that the majority of these services will be provided by GPs in purpose-built primary care centres, it is well documented that GPs are overworked and in short supply and the purpose-built centres have not yet been built. Pharmacist involvement in the management of chronic illness offers a partial solution to these ongoing resource issues. Chapter 4 outlines one such example where pharmacists can have a positive impact on chronic disease management. Earlier research conducted by academics within the UCC School of Pharmacy and wider Southern Hospital Group had demonstrated the clinical promise of a novel form of pharmacist-led patient self-management of INR therapy. However, establishment of a service requires local economic data to attract new funding or force a revision of established funds or resources.

Results outlined in chapter 4 indicate that for a marginal increase in expenditure, a clinically significant improvement in management of warfarin therapy is achieved. On a per-patient basis over a 6 month period, PST resulted in an incremental cost of

€59.08 in comparison to routine care. The intervention arm of care resulted in a significantly increased mean TTR in comparison with routine care (72% ± 19.7% vs 59 ± 13.5%) (Chapter 4, Table 4.2). This conclusion is supported by similar results in all scenarios evaluated. Research outlined in chapter 4 is the first economic evaluation of a pharmacist-supervised direct to patient system of INR management.

A recent publication by the HSE Medicines Management Program has indicated that at a >70% level of TTR [285]; warfarin is the preferred method of management for atrial fibrillation, even in comparison to the new oral anti-coagulant agents. TTR level in the usual care control group evaluated in this research was 59%. The overall mean level of care in the community in Ireland is unknown, however evidence in this study indicates that care may be sub-optimal. Supporting pharmacist-led management of warfarin therapy would be a potential method of ensuring that patients receiving warfarin receive optimal care.

Cost of management of a patient using PST strategy for a six month period was €226 (Chapter 4, Table 4.2). In comparison, the net ingredient cost of six months of therapy with a NOAC agent ranges from €384.66 to €456.06 [193]. Previous studies have indicated that NOACs are cost-effective in comparison to warfarin [194]. However, the level of anticoagulation control demonstrated through pharmacist-supervised patient self-testing of warfarin therapy may force a re-appraisal of these conclusions.

Examples of variations of this service have been provided in a number of locations around the country. Appendix 9 of this outlines research conducted in a community

pharmacy which is providing a similar system of pharmacist-led anticoagulation control. However, the successful establishment of this service without any support from the HSE / DoH indicates there is a demand and capacity to deliver the service at a community pharmacy level.

It has also formed part of various submissions by the IPU to government departments as an example of a service which could be provided at a community pharmacy level [286]. To date, the service has remained isolated to private provision in a handful of community pharmacies. Government funding has not yet been provided for either pharmacy fees or to support patient with cost of test strips or medical devices. Evidence described in this chapter will help ensure that informed decisions are made regarding the provision of the service.

8.5 Summary of Chapter 5

STOPP/START is a prescribing guideline which has generated quite a deal of interest at an international level in the field of geriatric pharmacotherapy research. The main contribution of Chapter 5 is that it is the first time the practical application of a structured pharmacist review of medication incorporating STOPP/START has been adequately examined in a cost-effectiveness analysis. Chapter 5 indicates that application of SPRM/CDSS is dominant in comparison to usual pharmaceutical care (Chapter 5, Table 5.3).

Evidence provided in this thesis combined with the previous work presented by O'Sullivan *et al [203]*, demonstrates that revision of service provision within Irish hospitals to include the intervention in Chapter 5 will not alone improve clinical

outcomes but also result in cost-savings directly to the healthcare payer. Compared to usual care, the intervention arm was associated with a reduction of €807 in mean healthcare costs, in conjunction with a reduction in the mean number of adverse events. Even at a threshold of €0, the probability of the intervention being cost-effective was 0.707 (Chapter 5, Table 5.3). The single site nature of the study warrants caution when the above results are interpreted.

Research presented in this chapter outlining the cost-effectiveness of a pharmacist medication review in a hospital setting is in concordance with a number of other similar pharmacist-led medication review interventions. Two Swedish-based studies support our findings, concluding that a structured pharmacist medication review was a cost-effective intervention [228, 287].

Irish hospitals have moved towards a policy of activity based funding. Incorporation of a pharmacist-led SPRM/CDSS could have further benefits to hospital groups. Previously, reducing the length of stay of patients offered no financial reward however, new funding mechanisms will remedy that problem. If hospitals can reduce the incidence of adverse drug events, and thereby reduce the overall length of stay of patients they will improve their score in an important metric which will assist in their overall funding level. It may also facilitate efficiency improvements and enable hospital trusts overcome capacity issues. Commencement of activity based funding is an opportunity to enable implementation of the interventions proposed in this thesis.

The application of this structured intervention, along with the unstructured interventions highlighted in Chapter 3, demonstrate the important role that pharmacists can have on a patient's transition in a hospital setting from admission to discharge. The cost-saving nature of this intervention in comparison to *ad-hoc* pharmaceutical care, which itself is likely to be beneficial to the overall hospital budget based on the level of cost-avoidance generated in chapter 3, further supports the value of employing a large number of hospital pharmacists dedicated to medication optimisation.

The abolition of the recruitment moratorium and move towards greater use of electronic health records and electronic discharge may mean that it is an opportune time to redesign systems to include SPRM/ CDSS as a crucial component of hospital medication management strategy.

8.6 Summary of Chapter 6

The final research chapter describes a relatively new community pharmacy service and the benefits being derived from it within the Irish health system while also highlighting the unfulfilled potential which could be realised if further financial support was forthcoming from healthcare payers.

The main contribution of Chapter 6 relates to the clinical and economic benefits of a community pharmacy vaccination service following evaluation at a national level. Previous papers have provided general estimates of more broad vaccination strategies rather than the focusing on a pharmacist-specific vaccination campaign [233].

While previous chapters have focused on pharmacists' skills being applied in an elderly or chronically ill population, this chapter is an example of the pharmacist offering a more public health-orientated intervention. Even with modest vaccination numbers, significant illness burden is prevented at higher and more expensive levels of care. The other notable aspect was the worthwhile contribution of pharmacist vaccination to the economy due to the prevention of influenza-related absences from employment. While clinical benefit associated with the vaccination scheme is primarily experience by older patients, working adults derive the majority of the economic benefits in the form of reduced out-of-pocket expenses and averted absenteeism from work (Chapter 6, Table 6.3).

Another important element of the vaccination process was the effectiveness rate of the annual vaccination. Both clinical and economic benefits are highly dependent on the effectiveness of the influenza vaccination, which is reflected in the large range of economic costs averted, €193374 – €533,218 (chapter 6, Table 6.3). While awaiting developments in vaccine technology, increasing influenza vaccination coverage remains the best method of reducing the impact of influenza.

This service has been successfully provided at a community pharmacy level for a number of years, demonstrating steady growth in terms of patient uptake. However, without further investment from healthcare payers to support vaccination in a broader population, the value of this service may quickly reach its limit in terms of numbers of patients who will avail of service. Pharmacist vaccination has much greater potential to help Ireland reach its overall goals of vaccination of 70% of at-

risk patients. A recent welcome development for this service has been the introduction of new legislation for pharmacists to vaccinate patients against pneumococcal infection and shingles [288]. It remains to be seen what kind of assisted access patients will be provided by the state to avail of this service.

8.7 Overall summary of research findings

A common identifiable trend across the research chapters was the level of economic benefit these services are / can provide to society in comparison with the investment cost required to provide them. The level of savings and averted costs that could be generated through a national application of various services evaluated or increased funding to provide additional support for existing services is considerable and at the very least this research will highlight the interventions for consideration.

The burden of ADEs and the potential for pharmacists to have a positive impact in the area is highlighted initially in the systematic review and further developed in Chapters 3 and 5. The combination of ageing demographics, increased co-morbidity and polypharmacy ensures that greater consideration will have to be given to patient care pathways to ensure the negative burden of ADEs is minimized. This has been previously highlighted as a unique area of expertise for pharmacists and research provided in this thesis further documents the potential (Chapter 3, page 85) (Chapter 5, page 128).

Another trend identified across the research chapters is the minimal cost associated with set-up of these services. Chapter 3 requires no additional costs other than pharmacist time. Chapter 4 does require some initial funding for purchase of the PST

software and meters but once the project has been established further expenditure was confined to payment for pharmacy services. Chapter 5 apart from some training costs is reliant on pharmacist experience and availability. Flu vaccination by pharmacists simply requires a fee for provision of the service. The network of established community pharmacies provides the readymade location and willing workforce to implement the scheme. Expansion or implementation of these four services outlined in this thesis would be expected to have a minimal budget impact with substantial medium to long term benefits anticipated. In terms of balance, it should be noted that other healthcare professionals are capable of offering some of the services outlined. However, this thesis is focused on whether clinical pharmacy services are providing value for money to Irish society and will thus remain focused on this particular topic.

Another learning element apparent from all research chapters is the urgent requirement for investment in IT at all levels of the healthcare system. While evidence presented in this thesis indicates that pharmacists having greater involvement in patient care is a positive development, steps must be taken to maintain GP oversight of the overall patient care pathway. To ensure clinical governance is maintained the establishment of a functioning patient electronic health record is vital. As previously mentioned the application of SPRM/CDSS type intervention would be enhanced through the establishment of an e-prescribing system at all levels of care.

8.8 Strengths and limitations of the evidence presented

All of the research chapters (2 – 6) outlined have generated full publications in peer-reviewed academic publications or is currently under assessment for future publication. Additionally, research has been presented at multiple conferences in both poster and oral format (Appendix 10.1). While publication is not the definitive goal for investigating a problem, it is an outcome which reflects the impact of this thesis overall and the interest in the topic from the wider academic community. The author adopted a pro-active approach to ensuring that a wider audience was made aware of any work undertaken (Appendix 10.1).

This PhD thesis utilised a variety of rich data sources to inform the overall outcomes of this thesis. The findings from the influenza vaccination analysis (Chapter 6) in particular are based on a national based sample of the patients, facilitating an accurate reflection of the influenza patients who availed of the service. Cost-effectiveness analyses (Chapters 4 and 5) were based on primary data collected from two randomised controlled trials. This enabled the accurate identification of resource use associated with both intervention and control arms. Chapter 3, an evaluation of the economic impact of pharmacists' interventions was informed by direct access to a database outlining all recorded pharmacist interventions conducted in a major tertiary care centre over a 12 month period. This facilitated an appraisal of the long-term value of the service, in comparison to previously published shorter term evaluations.

Chapter 5 is perhaps the most comprehensive economic evaluation of a proposed pharmacist intervention provided in this thesis. CHEERS guidelines were adopted as guidance for the generation of the paper. In addition the methodologies used are

highly suitable for use alongside cluster RCTs. The use of multi-level mixed effect models are becoming a prominent method of evaluating data which may be clustered in nature.

Individual chapters elaborate on the specific limitations of each study. On a more general level, while the trial-based economic evaluations (chapters 4 and 5) are an established and relevant form of assessment. They do give rise to their own methodological challenges. While datasets utilised were considered trustworthy and generally complete, all manually generated datasets will have some degree of missing data. Moreover, in the case of both the patient self-testing and medication review research, trial follow-up period was shorter than the period during which differences in health effects and use of healthcare resources between interventions persist; increasing the uncertainty surrounding whether investing in these intervention programmes would be a good use of healthcare resources over a longer period of time.

Ireland is a country which has a health technology assessment system that favours an emphasis on cost-utility analysis [185]. While the primacy of QALY-based assessments is not universally recognised [134], the main advantage of QALY-based assessments is the fact that they enable comparison across different areas of the healthcare system. While the cost-effectiveness of the majority of services outlined in this thesis appear to be positive, broader decision on allocation of healthcare budget may be better informed by QALY-based methodology.

Recommendations outlined previously to incorporate health economic research early in a study design were not adhered to during the course of this thesis. The research was predominantly incorporated around retrospective evaluation of data sources or as an add-on to previously completed clinical trials. While chapters presented in this thesis were not majorly impacted by this issue, reductions in uncertainty surrounding some of the input data could have been reduced through earlier engagement with primary researchers.

8.9 Impact of evidence on national policy

This principal contribution of this thesis has been the identification of new strategies by which pharmacists can have a more influential role in patient care; and evidence which indicates that these services may have added value for the health system at both a clinical and economic level. The interventions evaluated in this thesis can have a significant impact on national health policy if implemented.

Evidence generated in this thesis is being published at an opportune time. The current Minister of Health (at time of writing – February 2016) has indicated a desire to expand community pharmacy services [289]. However, any expansion of services will not be met with universal agreement. Other healthcare practitioners will have their own views on whether any expansion to the role of pharmacists should occur similar to the debate globally. Just because a service has been delivered elsewhere does not automatically mean that it will be the correct fit for a very unique healthcare system. The robust economic evidence generated over the course of this thesis will assist healthcare payers determine in an objective manner whether it is worth pursuing a policy of expanded clinical pharmacy care.

Interventions described in this thesis will influence healthcare policy decisions, through conference publication nationally and internationally and through peer reviewed publications. Fortunately, implementation of the proposed interventions will not require a substantial capital investment. The reallocation of funds for additional employment or additional payment of services, in addition to agreement of all stakeholders involved in the provision of care to the relevant patient group, may be challenging.

While dissemination of research through the medium of academic journals and conferences is an important aspect of any research thesis, communication through these channels may not be reaching the correct audience if we want to see the research influencing policy at a national level. It is just as vital that if this research is to make an impact, it is brought to the attention of key decision makers within the healthcare system. The author of this thesis has ensured that throughout the course of his research he has attempted to engage the wider pharmacy and healthcare community. This thesis resulted in collaboration with three major teaching hospitals, a national independent community pharmacy representative group and a large community pharmacy chain. Moreover it is the intention to submit a policy briefing document to the Department of Health in order to make them fully aware of the Irish specific evidence generated over the course of this thesis, see Appendix 12.

The Pharmacy 2020 report has been cited on numerous occasions throughout this thesis. However, it is a document which is losing its relevance since its publication in 2008[9]. This has been recognised by the Pharmaceutical Society of Ireland, who

are in the process of commissioning a new policy document on the future of pharmacy in Ireland [290]. To ensure that the research can be incorporated into a wider pharmacy development framework, a draft copy of this thesis has been submitted to the working group. For communication to a non-clinical audience, incorporation of health economic evidence such as that produced in this thesis will assist in the decision-making process surrounding any recommendation that are made from report.

8.10 Barriers to implementation of research

High quality evidence alone is not sufficient to enable change of pharmacy system. Zellmer described a number of external barriers to the development of clinical pharmacy services [291]. We will now discuss these in an Irish context.

The national economy in Ireland is currently in a recovery phase and any new health initiatives will be heavily reliant on the continued recovery of our economy [292]. It is possible to implement through redistribution of resources [293], but development of clinical pharmacy services will be much more likely to prosper with specific designated funding for new initiatives. Recent examples from Belgium have described how development of clinical pharmacy services within a hospital should not be predicated on receipt of new funding and can be established through realignment of staff within a pharmacy department [293].

As outlined in the introductory chapter and in research in other jurisdictions, pharmacist influence on major policy decisions is arguably under-represented given their involvement in the overall process of medicine and health policy [294, 295].

Pharmacy groups at both hospital and community level need to become better advocates for their profession. A coherent and realistic policy on pharmacy services needs to be developed and presented to wider stakeholders within the health system. Evidence presented in this thesis is a step in the right direction to achieve this.

Any service expansion needs to incorporate the correct skill mix. It is quite easy to recommend that additional pharmacists should be employed in hospitals to implement the services outlined in chapter 3. However, the recruitment embargo within the healthcare system in recent years has meant that senior staff with hospital experience may not be available within the system to facilitate the roll out of additional services. The residency type training programs offered in the United States ensures that there is an ongoing stream of highly qualified staff available to take up highly skilled hospital-based roles. The redesign of pharmacist curriculum to include greater focus on hospital placements at an undergraduate level is a positive step in overcoming this problem [296]. At a community level it may be easier to implement services such as pharmacist vaccinations and absorb them into everyday workload. More complex services such as the New Medicines Service offered in the NHS have also being implemented without any provision of additional resources or reduction in other responsibilities [53].

Alteration of work practices may also be required. Currently pharmacy services in Irish hospitals are largely confined to office hours. If pharmacy services are to become integral to hospital care in Ireland, negotiation with hospital pharmacists will be required. Significant capital investment is also needed to update pharmacy sites within

hospitals. They are very much antiquated environments, which do not offer sufficient space to facilitate even the current services provided [16].

Whilst not necessarily a problem confined to the pharmacy department within the Irish healthcare system, the lack of access to IT resources or an integrated IT strategy is nonetheless a barrier to the development of pharmacy services and an on-going source of waste within the system. The on-going reliance on paper based documentation is responsible for a major waste of healthcare resources [297].

8.11 Recommendations for policy implementation

The following section proposes a five point plan which is a potential mechanism to develop the pharmacy profession in Ireland, incorporating evidence presented in this thesis and from other sources.

1. **Finalisation of Future Pharmacy Practice Project** – Completion of evidenced based review of potential future pharmacy contribution to Irish healthcare system. Formal conference launch with invites sent to key stakeholders from a wide range of healthcare, political and public arenas. Public engagement plan to generate wider awareness of the potential for both community and hospital pharmacists to maximize health outcomes in the population.
2. **Implementation plan** – Following an example from Northern Ireland [42]. Establish an implementation advisory group with members drawn from community, hospital, industry, academia, regulatory bodies and experts on implementing change at a national level. Also ensure that pharmacy representative groups are in alignment with overall strategy to develop pharmacy. Agree on timelines for achieving strategic goals.

3. **Task force** – Source seed funding from PSI to ensure that adequate resources can be made available to allow for a viable attempt at implementation of 'Pharmacy Futures' plan. Consider employment of a team whose sole focus is successfully achieving objectives outlined in implementation plan. Continue to fund external public relations firm to assist in keeping media and public focus on potential for pharmacy to improve public health. This will increase pressure on Department of Health to engage in meaningful discussions with pharmacy task force regarding the future direction of pharmacy in Ireland.
4. **Framework agreement** – This type of negotiated agreement has been in place for many years between the Irish Pharmaceutical Healthcare Association (IPHA) and the Department of Health. IPHA agreement allows for projections on drug spending and savings to be made and specific budgets for new therapies to be made available. Proposed pharmacy framework agreement would seek agreement on funding for provision of new services over a period 3 – 5 years. Similar initiatives have been implemented successfully in Australia[58]. A coherent long term strategy for pharmacy would reduce the possibility of disputes between DoH and community pharmacies, which could potentially put safety supply at risk.
5. **Multi-annual pharmacy budget** – To ensure commitments made in framework agreement are adhered to, it is important to have guaranteed funding for the duration of agreement. As payments to pharmacy are not a fixed expense, they have traditionally been an easy target for budgetary cuts [298]. Pharmacy task force should engage early with other healthcare professional representative groups and indeed the HSE senior leadership

team. All of these parties would mutually benefit from establishment of multi-annual budgets to allow for proper planning and implementation of gradual healthcare reform.

8.12 Future work

Research presented in this thesis gives rise to a number of questions which could be adequately addressed through future research.

i) Qualitative interviews with senior healthcare payers to determine the utility of local health economic data.

ii) Application of SPRM/CDSS intervention in a community setting.

iii) Longer term outcomes associated with SPRM/CDSS intervention.

iv) Economic evaluation of pharmacist-led warfarin management in comparison to NOACs.

8.13 Conclusion

Overall, clinical pharmacy services are adding value to the Irish healthcare system, but provision of additional funding for new services would enable them to offer a great deal more.

This thesis has added substantially to the overall evidence surrounding the impact of pharmacists within the Irish healthcare system. In the past, much of the valuable research produced in relation to pharmacist innovations had focused on the clinical elements of an intervention. This thesis has overcome a large element of the knowledge deficit associated with the cost analysis and cost-effectiveness of implementing a viable clinical pharmacy service at community and hospital level in Ireland.

However, the scarce resources available for development within the Irish healthcare system will potentially be a major barrier to any further development of the profession. Consideration should be given to development of a framework agreement between pharmacist representative groups and healthcare providers to enable development of a coherent medium to long term development plan.

Research and evidence presented will assist decision makers make informed decision about the future direction and engagement of pharmacists within the Irish healthcare system.

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10 Appendices

10.1 Appendix 1: PhD Research Dissemination

10.1.1 Published Papers as 1st author

Title and authors	Reference
Cost-outcome description of clinical pharmacist interventions in a university teaching hospital. **Gallagher J**, Byrne S, Woods N, Lynch D, McCarthy S.	BMC Health Serv Res. 2014 Apr 17;14:177. doi: 10.1186/1472-6963-14-177.
Economic evaluations of clinical pharmacist interventions on hospital inpatients: a systematic review of recent literature. **Gallagher J**, McCarthy S, Byrne S.	Int J Clin Pharm. 2014 Dec;36(6):1101-14. doi: 10.1007/s11096-014-0008-9. Epub 2014 Sep 14.
Economic evaluation of a randomized controlled trial of pharmacist-supervized patient self-testing of warfarin therapy. **Gallagher J**, Mc Carthy S, Woods N, Ryan F, O' Shea S, Byrne S.	J Clin Pharm Ther. 2015 Feb;40(1):14-9.
Structured pharmacist review of medication in older hospitalised patients: A cost-effectiveness analysis **Gallagher J**, O'Sullivan D, McCarthy S, Gillespie P, Woods N, O'Mahony D, Byrne S.	Drugs Aging. 2016 Feb 9. [Epub ahead of print]

Papers under review

Title and author	Reference
Clinical and economic benefits of a community pharmacy vaccination strategy **Gallagher J,** Byrne S, O'Dwyer S, Reilly P, Mc Carthy S.	Int J Clin Pharm. (Under review).

10.1.2 Published papers as a named author

Title and authors	Publication
Prevention of Adverse Drug Reactions in Hospitalised Older Patients Using a Software-Supported Structured Pharmacist Intervention: A Cluster Randomised Controlled Trial. O'Sullivan D, O'Mahony D, O'Connor MN, Gallagher P, **Gallagher J**, Cullinan S, O'Sullivan R, Eustace J, Byrne S.	**Drugs Aging.** 2016 Jan;33(1):63-73. doi: 10.1007/s40266-015-0329-y.
The impact of a structured pharmacist intervention on the appropriateness of prescribing in older hospitalized patients. O'Sullivan D1, O'Mahony D, O'Connor MN, Gallagher P, Cullinan S, O'Sullivan R, **Gallagher J**, Eustace J, Byrne S.	**Drugs Aging.** 2014 Jun;31(6):471-81. doi: 10.1007/s40266-014-0172-6.

10.1.3 Conference presentations – Oral

Year	Title	Conference
2015	Economic evaluation of a software-supported structured pharmacist medication review in hospitalised older patients	Health Services Research and Pharmacy Practice(HSRPP), 2015
2015	Economic evaluation of a randomized controlled trial of pharmacist-supervised patient self-testing of warfarin therapy	Health Services Research and Pharmacy Practice (HSRPP), 2015
2015	Economic evaluation of a randomized controlled trial of pharmacist-supervised patient self-testing of warfarin therapy	Dissemination of Health Research Board Funded Research: Community Drug Expenditure and Recent Cost Containment Measures
2014	Economic evaluations of clinical pharmacist interventions on hospital inpatients: 2008 – 2012	EuroDurg – Groningen, 2014
2014	Economic evaluation of a randomised controlled trial of supervised patient self-testing of warfarin therapy	HESG Glasgow Caledonian University 2014

10.1.4 Conference presentations – Poster

Year	Title	Conference
2015	A cost-effectiveness analysis of hospital pharmacist review in older patients.	ISPOR 18th Annual European Meeting, Milan.
2015	Economic evaluation of a randomized controlled trial of pharmacist-supervised patient self-testing of warfarin therapy	ISPOR 20th Annual International Meeting, Philadelphia
2013	Cost-outcome description of clinical pharmacist interventions in a university teaching hospital	ISPOR 16th Annual European Congress, Dublin
2013	Analysis of Interventions made by Clinical Pharmacists in an Irish Hospital Setting	FIP World Congress 2013, Dublin.
2013	Categorisation of Interventions made by Clinical Pharmacists in an Irish Hospital Setting	All Ireland Schools of Pharmacy Research Conference, Belfast.
2013	Categorisation of Interventions made by Clinical Pharmacists in an Irish Hospital Setting	Prescribing and research in medicines management (PRIMM), London.

10.1.5 Peer-reviewed conference abstract publications

Year	Title	Conference
2015	A cost-effectiveness analysis of hospital pharmacist review in older patients.	ISPOR Milan – Value in Health
2015	Economic evaluation of a randomized controlled trial of pharmacist-supervised patient self-testing of warfarin therapy	ISPOR Philadelphia – Value in Health
2015	Economic evaluation of a software-supported structured pharmacist medication review in hospitalised older patients	HSRPP – International Journal of Pharmacy Practice
2015	Economic evaluation of a randomized controlled trial of pharmacist-supervised patient self-testing of warfarin therapy	HSRPP – International Journal of Pharmacy Practice
2013	Cost-outcome description of clinical pharmacist interventions in a university teaching hospital	ISPOR Dublin – Value in Health
2013	Categorisation of Interventions made by Clinical Pharmacists in an Irish Hospital Setting	PRIMM – Pharmacoepidimiology and Drug Safety

10.1.6 Funding awards for doctoral training

Year	Award	Amount
2015	ISPOR Student Travel Bursary	€2000
2013	Roche Diagnostics	€10000
2013	Graduate School of the College of Medicine and Health, University College Cork travel bursary to attend health economics training course at .	€1000

10.2 Appendix 2: PHD Education and Training

10.2.1 UCC PhD Modules

Module title	Completed	Credits
PG6001 - Scientific Training for Enhanced Postgraduate Study	August 2013	5 credits
PG7016 - Systematic review for health service research	September 2013	5 credits
ST6013 - Statistics and Data Analysis for Postgraduate Research Students	July 2014	10 credits

10.2.2 Other short training courses

Course title	Institute / Body	Completed
Advanced cost-effectiveness analysis	University of York	July 2013
Discrete Event Simulation for Economic Analyses – Applications	ISPOR Amsterdam	November 2014
Pharmacoeconomic Modeling - Applications	ISPOR Amsterdam	November 2014
Introduction To Modeling	ISPOR Amsterdam	November 2014
Bayesian Analysis	ISPOR Philadelphia	May 2015

10.3 Appendix 3: Systematic review search strategy

Search strategy for systematic reviews

Title: Pharmacoeconomic studies of Clinical Pharmacy Intervention: Systematic review (2008 – 2012)

Time period: 01/01/2008 – 31/12/2012

Language: English (only)

Search completed: 25/04/2013

Pub Med strategy: Mesh terminology was employed.

(Drug Information Services OR Medication Therapy Management OR Drug toxicity OR Prescriptions OR Drug Therapy or Pharmacy Services, Hospital)

AND

(Cost and Cost Analysis or Economics, Pharmaceutical)

Academic Search Complete

((Pharmaceutical Services with following narrow terms ticked, Hospital Pharmacies, Medication Therapy management, Pharmacy – Information services, speciality Pharmacies) OR Drugs – Toxicology OR (Drug Therapy with following narrower items ticked, drug utilization, drugs – administration, drugs – prescribing, medication errors, polypharmacy, premedication.))

AND

Cost effectiveness

NHS Economic Evaluation Database:

Used strategy described for PubMed.

Cochrane Library:

Used strategy described for PubMed.

Embase

(Drug Information OR Medication Therapy Management OR Drug toxicity OR Prescription OR Drug Therapy or Pharmacy Services, Hospital)

AND

(Economic Evaluation or Pharmacoeconomics)

ECONLIT

Did not allow searching using Mesh terms and mapping was impractical. “Pharmacy” was only search term used.

SOCINDEX

(Pharmacy* or Pharmacist*) AND (Cost* or Hospital*)

10.4 Appendix 4: Data collection form for systematic review

Trial Name:	First author:
Year of Publication:	Journal Reference:
Intervention:	
Setting of study:	Sample size:
Study period:	Input costs:
Outcome measures:	
Results:	
Economic method:	Perspective:
Quality of study (Reason):	Type of study:
Comparator:	Characterising uncertainty:
Population demographics:	Discount rate:
Time Horizon:	Estimating resources and costs:
Currency price date and conversion rate:	Study parameters:
Incremental costs and outcomes:	
Eligible for Inclusion:	Reason for exclusion:

10.5 Appendix 5: CHEERS Checklist

CHEERS checklist—Items to include when reporting economic evaluations of health interventions.			
Section/item	**Item No**	**Recommendation**	**Reported on page No/ line No**
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	_____
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	_____
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	
		Present the study question and its relevance for health policy or practice decisions.	_____
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	_____
Setting and location	5	State relevant aspects of the system(s) in which the	_____

CHEERS checklist—Items to include when reporting economic evaluations of health interventions.			
Section/item	**Item No**	**Recommendation**	**Reported on page No/ line No**
		decision(s) need(s) to be made.	
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	_____
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	_____
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	_____
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	_____
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	_____
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	_____
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included	_____

CHEERS checklist—Items to include when reporting economic evaluations of health interventions.			
Section/item	**Item No**	**Recommendation**	**Reported on page No/ line No**
		studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	_____
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	_____
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	_____
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a	_____

CHEERS checklist—Items to include when reporting economic evaluations of health interventions.			
Section/item	**Item No**	**Recommendation**	**Reported on page No/ line No**
		common currency base and the exchange rate.	
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	_____
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	_____
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	_____
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input	_____

CHEERS checklist—Items to include when reporting economic evaluations of health interventions.			
Section/item	**Item No**	**Recommendation**	**Reported on page No/ line No**
		values is strongly recommended.	
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	_____
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	_____
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	_____
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in	_____

CHEERS checklist—Items to include when reporting economic evaluations of health interventions.			
Section/item	**Item No**	**Recommendation**	**Reported on page No/ line No**
		effects that are not reducible by more information.	
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	_____
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	_____
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	_____

* Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2013 Mar-Apr;16(2):e1-5. PubMed PMID: 23538200. Epub 2013/03/30. eng.

10.6 Appendix 6: Cheers checklist for SPRM in older hospitalized patients

Section	Item No	Recommendation	Completed
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared	Yes
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Yes
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Yes
Background and objectives		Present the study question and its relevance for health policy or practice decisions.	
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	No
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Yes
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Yes
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Yes
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Yes
Discount rate	9	Report the choice of discount rate(s) used for costs and	Yes

		outcomes and say why appropriate.	
Outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Yes
Measurement of effectiveness	11 a	*Single study-based estimates: D*escribe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Yes
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
Estimating resources and costs	13	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Yes
Currency, price, date and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Yes
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	N/A
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	N/A

Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Yes
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	No
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Yes
Characterising uncertainty	20	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Yes
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
Discussion			

Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Yes
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Yes
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Yes

10.7 Appendix 7: Economic impact of pharmacist interventions in University Hospital Waterford

Background

An analysis was conducted of the cost avoidance generated by clinical pharmacist interventions in University Hospital Waterford.

Methods

Interventions were documented by four pharmacists over a nine week period (13/10/2014 – 12/12/2014). The eClinical Pharmacy Suite was used to document the interventions. Interventions were assigned a rating, depending on the probability that an ADE would have occurred in the absence of the intervention. These ratings were then multiplied by the cost of an ADE in order to estimate cost avoidance.

Results

Cost avoidance of €407,958 was generated. Cost of service was found to be €49,129, resulting in a net cost-benefit of €358,829 and a cost-benefit ratio of 7.3:1. Interventions involving dose alterations, drug omissions and requests to review therapy were most common.

Cost Definition	**Value**
Cost Avoidance	€407,958
Cost of Service	€49,129
Net Cost-Benefit	€358,829
Cost-Benefit Ratio	7.3

Conclusion

In this study pharmacist interventions generated substantial cost avoidance. Clinical pharmacist interventions are seen as a valuable service which improves medication safety in hospitals and reduces the number of ADEs.

10.8 Appendix 8: Cost avoidance generated through pharmacist interventions in a paediatric hospital

Background

An analysis was conducted of the cost avoidance generated through clinical pharmacy interventions in terms of adverse drug event (ADE) avoidance.

Methods

Pharmacist intervention data was gathered from 01/01/13 to 31/12/13 from a paediatric hospital. A cost-descriptive analysis was carried out from the data gathered.

Results

A total of 688 interventions were documented. Interventions involving dosage adjustments (300) were the most common. The most common drugs involved in interventions during the study were gentamicin sulphate and ranitidine. The majority of the interventions were in the areas of respiratory (149) and cardiology (127) medicine. Total cost avoidance was found to be €116,488.11. A cost of service of €10,955.82 was calculated. The study resulted in a net cost-benefit of €105,492.29. A cost-benefit ratio of 9.6:1 was obtained.

Conclusions

Substantial cost-avoidance is generated through clinical pharmacy interventions in a paediatric hospital.

10.9 Appendix 9: Evaluation of anti-coagulation services in Cloyne Pharmacy and a cost analysis between primary and secondary care anti-coagulation clinics.

Aims

To evaluate anticoagulation management services in Cloyne Pharmacy and to conduct a cost analysis of primary and secondary care anticoagulation clinics.

Methods

A two year retrospective analysis of all INR results for patients attending the warfarin clinic at Cloyne Pharmacy between January 2012 and January 2014 was conducted. Mean percentage Therapeutic Time in Range(TTR) was calculated using the Rosendaal method. A cost analysis was conducted to compare patient and clinic cost between Cloyne Pharmacy warfarin clinic and Cork University Hospital. Patient knowledge, satisfaction and quality of life were assessed in Cloyne Pharmacy by a patient questionnaire.

Results

Mean percentage (TTR) was calculated for 61 patients and found to be 72.16%±15.76. Using the expert dosing system at Cloyne Pharmacy, RAID 'Express' CDSS, a mean % TTR was calculated to be 76.81% for 64 patients.

Table 1 Descriptive data from the patient questionnaire

	Cloyne	CUH
Mean distance travelled(km)	11.17	35.5
Time for travel and clinic(mins)	26.17	65.5
Retired (%)	86.4	86.4
Carer required (%)	33.3	33.3

Table 2 Clinic cost comparison between Cloyne Pharmacy and Cork University Hospital – Healthcare payer perspective

	Cloyne Pharmacy	**Cork University Hospital**
Pharmacist per 15 minutes (clinic)	€8	-
INR Test (Lancets and test strips)	€5	€2*
Mean number of tests in 6 months per patient	8.48	10.7*
Mean test cost in 6 months	€110.24	€21.40*
Salary costs	Included in pharmacist time	€145.98*
Total cost for managing a patients in 6 months	€110.24	€167.37

** - Costs calculated based on internal CUH data and expert guidance*

Table 3 Patient cost comparison between Cloyne Pharmacy and CUH – Societal perspective

	Cloyne	CUH
Mean TTR for 6 months	76.34%	59%
Mean costs per patient per visit	€33.68	€37.69
Cost per test	Included above	€2
Mean no of test per patient per 6 month	8.48	10.7
Total patient test cost per 6 months	€285.62	€424.68
Salary cost	-	€145.98
Total patient cost for 6 months	€285.62	€570.66

Conclusion

Cloyne Pharmacy is adhering to anticoagulation international standards and maybe cost-effective in comparison with hospital-based care.

10.10 Appendix 10: Ethical Approval

Ethics addendums were sought from and approved by the Clinical Research and Ethics Committee of the Cork Teaching Hospitals for chapter 3 – 5.

Full ethical approval for chapter 6 is detailed below.

UCC
Tel: + 353-21-490 1901
Fax: + 353-21-490 1919
Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee
Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Our ref: ECM 4 (oooo) 07/05/13

25th April 2013

Dr Stephen Byrne
Senior Lecturer
School of Pharmacy
Cavanagh Pharmacy Buidling
University College Cork
College Road
Cork

Re: Pharmacoeconomic study of influenza vaccination by pharmacists in Ireland.

Dear Dr Byrne

Expedited approval is granted to carry out the above study at:

- University College Cork.

The following document was approved:

- Application Form.

Please forward a data collection sheet for our files.

We note that the co-investigators involved in this study will be:

- James Gallagher and Liz Hoctor.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

10.11 Appendix 11: Thesis publications

10.11.1 Paper 1

Int J Clin Pharm
DOI 10.1007/s11096-014-0008-9

REVIEW ARTICLE

Economic evaluations of clinical pharmacist interventions on hospital inpatients: a systematic review of recent literature

James Gallagher · Suzanne McCarthy · Stephen Byrne

Received: 17 February 2014 / Accepted: 21 August 2014
© Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie 2014

Abstract *Background* Clinical and cost-effectiveness evidence are needed to justify the existence or extension of routine clinical pharmacy services in hospital settings. Previous reviews have indicated that clinical pharmacist interventions are likely to have a positive economic impact on hospital budgets but highlighted issues relating to the quality of studies. *Aim of the review* The primary aim of this review was to feature economic evaluations of clinical pharmacy services which targeted hospital inpatients. The review focused on the current cost-effectiveness status of different services, in addition to evaluating the quality of individual studies. Results of this systematic review were compared with cost-effectiveness and quality related findings of reviews which considered earlier time frames and alternative settings. *Methods* A systematic review of the literature included a review of the following databases: Academic Search Complete, Cochrane Library, EconLit, Embase Elsevier, NHS Economic Evaluation Database and PubMed. Only studies with an economic assessment of a clinical pharmacy service provided in a hospital setting were included. Data relating to the cost-effectiveness was extracted from eligible studies. Methodologies employed and overall quality of the studies was also reviewed. A grading system was applied to determine the quality of studies. Consolidated Health Economic Evaluation Reporting Standards statement was employed to determine which aspects of a high quality health economic study were employed. *Results* Twenty studies were deemed eligible for inclusion. Overall, pharmacist interventions had a positive impact on hospital budgets. Only three studies (15 %) were deemed to be "good-quality" studies. No 'novel' clinical pharmacist intervention was identified during the course of this review. *Conclusions* Clinical pharmacy interventions continue to provide cost savings. However, the standard of studies published has stagnated or even deteriorated in comparison with those included in previous reviews. Utilisation of published guidelines at initial stages of future studies may help improve the overall quality of studies.

Keywords Clinical pharmacy · Cost analysis · Cost-effectiveness · Economic evaluation · Hospital pharmacy · Pharmaceutical services · Quality assessment · Systematic reviews

Impact of findings on practice statements

- Clinically orientated researchers need to conform to health economic guidelines on the evaluation of health services in order to reduce uncertainty surrounding outcomes and improve the relevance of their research to healthcare decision makers.
- Clinical pharmacist interventions continue to have a positive impact on hospital budgets.
- Due to a lack of comparable outcomes measures, it is not possible to determine which clinical pharmacy interventions were most cost-effective in a hospital setting.
- There has been no economic evaluation of novel clinical pharmacy services published in English language academic journals during the period, 2008–2012. The increase in the number of studies originating from developing economies indicates that attempts are being

Electronic supplementary material The online version of this article (doi:10.1007/s11096-014-0008-9) contains supplementary material, which is available to authorized users.

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Published online: 14 September 2014

made to establish clinical pharmacy services. Moreover, the reduction in studies from developed countries may suggest that clinical pharmacy services are recognised as beneficial in these jurisdictions.

Introduction

The pharmacy profession has transformed from a dispensary-based role to one centred on the provision of clinical services. While still ensuring that medicines are sourced and dispensed to a high standard, hospital pharmacists have expanded their scope of practice [1], and pharmacy interventions include integral components of the enhanced role which pharmacists offer [2–4].

A pharmacist intervention is defined as the following "any action taken by a pharmacist that aims to change patient management or therapy'' [5]. Clinical pharmacy services employ the pharmacotherapeutic expertise of the pharmacist to ensure optimal patient outcomes [6, 7] and can improve the quality, safety and efficiency of care. Various pharmacist interventions including interaction with other healthcare teams, patient interviews, medication reconciliation and patient discharge counselling demonstrated improvements in patient outcomes [1].

In addition to clinical benefits, clinical pharmacist intervention have also demonstrated positive outcomes when measured using health-related quality of life assessments (HRQoL) [8]. This involves a multidimensional assessment of a patient's physical, functional, emotional and social well-being. Pharmacist interventions targeting specific conditions including asthma, hypertension and chronic heart failure have tended to show noticeable improvements in HRQoL [8].

However, there is an omnipresent danger that previous gains made by pharmacists will be eroded due to increased pressure on healthcare resources [9]. In order to vindicate the provision of additional pharmacy services, it is no longer sufficient to provide a justification exclusively based on clinical benefits. Cost-effectiveness data is also required [10].

Previous review articles have broadly reached the same conclusion, the operation of additional clinical pharmacy services results in cost savings to the healthcare payer [10–14]. However, many published studies have been of poor quality [12, 14], limiting the strength of any conclusions presented in previous reviews. Due to the previously highlighted quality concerns, it was decided to conduct a quality assessment of economic evaluations.

Aim of the review

This systematic review will examine economic evaluations of clinical pharmacy interventions made on hospital inpatients published between 2008 and 2012. The review will focus on assessing the economic outcomes of eligible studies. Additionally, it aims to provide a description of the quality of included studies. There has been no previously published systematic review which has exclusively focused on services specifically targeted to hospital inpatients covering the stated time period. This systematic review will provide evidence to healthcare decision makers regarding the cost-effectiveness of various services. Additionally, it will highlight to academics and clinical practitioners study areas which have been poorly designed and could be improved upon in the future.

Method

Search strategy

This review of the literature was undertaken in April 2013. Searches were conducted of the following databases: Academic Search Complete, Cochrane Library, EconLit, Embase Elsevier, NHS Economic Evaluation Database and PubMed. The publication dates of articles included in search strategy ranged from January 2008 to December 2012. All authors were involved in the development of PubMed search strategy and appropriate Medical Subject Headings (MeSH) terminology was utilised. The following MeSH terms were employed: "drug information services", "medication therapy management", "drug toxicity", "prescriptions'', "drug therapy'', "pharmacy services hospital'' combined with "cost and cost analysis'', "economics, pharmaceutical". Similar search strategies, with MeSH terms mapped to appropriate key words were used for additional databases. The full search strategy is available as supplementary electronic material. Search results from multiple databases were transferred to a reference manager, End Note X6. Due to the broad remit of the search strategy, a 'title review' stage was conducted to remove obviously non-pertinent studies. This was conducted by the primary author. Studies were removed in a cautious manner. Abstract review was then performed. If study clearly did not meet inclusion criteria it was excluded. Studies which had not been excluded following abstract review stage underwent full-text review. Full-text review was performed by the primary author. Studies selected for inclusion in systematic review were reviewed by co-authors to ensure they met eligibility criteria.

Review criteria and data extraction

Studies were required to meet multiple criteria specified in Table 1.

Table 1 Inclusion and exclusion criteria for systematic review

Inclusion criteria	Exclusion criteria
Published peer reviewed full-text articles	Non-peer reviewed literature e.g. government documents, technical reports, newspaper articles, letters to the editor, media releases
Study assessed an intervention performed by a pharmacist or team of pharmacists	Studies based on modelling effect of an intervention
Intervention must conform to the unabridged American College of Clinical Pharmacists (ACCP) definition of a clinical pharmacy [15]	
Study must include an economic assessment (Measurement of costs to provide the service, outcomes expressed in monetary terms or both)	
Interventions must be conducted on inpatients in a hospital setting	Studies conducted in outpatient clinics, nursing homes, veteran's affairs clinics and any form of community level care
Study published in English language	

The references of eligible studies and previously published systematic reviews were systematically searched to ensure that they did not contain further relevant research. The heterogeneity of health economic studies prevented a meta-analysis being undertaken. Grey literature (e.g. government documents, technical reports etc.,) was excluded.

Studies which met inclusion criteria were analysed with the aid of a data collection form (see Electronic Supplementary Material). Information collected included details of authors, type of intervention, study setting, study sample size, economic method, study period, outcome measures and results and multiple quality assessment related data. Completed data collection forms were reviewed by all listed authors.

Quality assessment

An established quality assessment of the economic methods employed was conducted [12]. Assessment comprised of a simple three question assessment, (1) Was a comparator used? (2) Were program costs evaluated and described? (3) Were program outcomes evaluated and described? Studies were determined to be "good-quality" studies if they complied with all three criteria. Studies which lacked a comparator or had multiple flaws were labelled as "poor-quality". Studies which included a comparator but which did not evaluate either program costs or program outcomes were labelled as "fair-quality". This quality assessment was included as it provided a clear distinction on the standard of studies from a health economic perspective. Furthermore, it had been utilised in previous systematic reviews which enabled comparisons to be drawn with earlier time periods [12].

In addition to the previously described quality assessment, the authors decided it would be worthwhile to conduct a more comprehensive quality appraisal of included studies to provide an in depth analysis of study areas. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [16], was applied to eligible studies. CHEERS statement contains a checklist detailing aspects of health economic methodologies which should be considered for inclusion in a study (see Electronic Supplementary material). As CHEERS statement was designed for use across all types of health economic evaluations, only items on checklist relevant to studies under review will be examined in this review.

Descriptive statistics were used to summarise type of intervention, economic analysis, model, perspective and sensitivity analysis. A data collection form was initially completed by the primary author and then independently reviewed by another named author.

Results

Following elimination of duplicate titles, the search strategy yielded 6,815 titles for review. Reasons for exclusion are outlined in Fig. 1. Twenty-two texts were considered eligible for inclusion in the systematic review. Studies were conducted in Asia [8], USA [8], Europe [5] and South America [1]. All studies were published in health related journals. Appendix 1 contains a summary of studies which met inclusion criteria.

Clinical pharmacy interventions

Interventions were in following areas antimicrobial management [17–22], targeted drug programmes [23–26], multidimensional clinical pharmacy service [27–29], paediatric programmes [30, 31], renal specialist [32, 33], pharmacotherapeutic optimisation [34, 35], intensive care service [36, 37] and neurosurgery [38]. All intervention types have been identified in previous reviews of the literature [10–13].

Antimicrobial management

Six antimicrobial interventions were identified. Five of the studies included a comparator, either in the form of a randomised controlled trial [19] or a pre- and post-

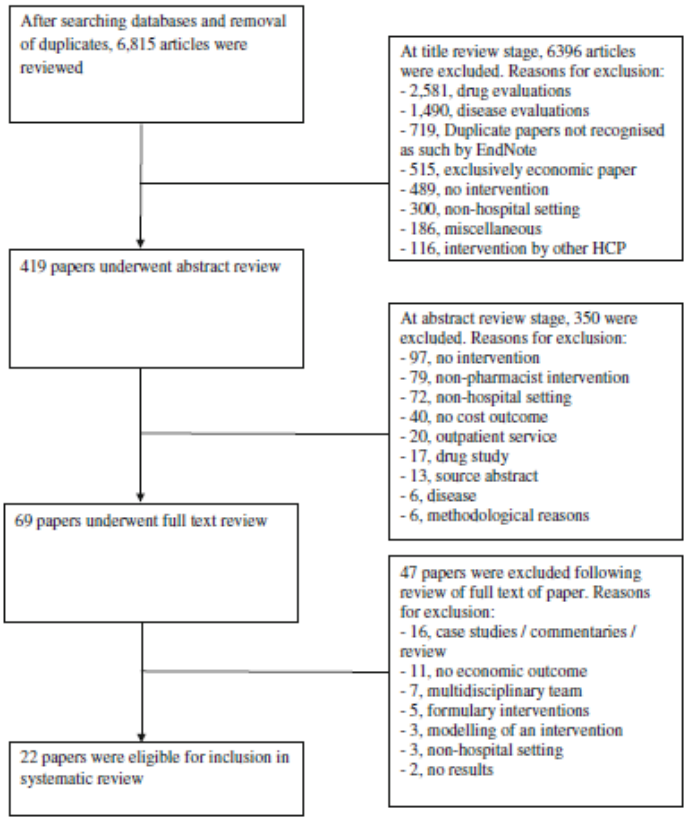


Fig. 1 Literature search method and screening results

intervention comparison [17, 18, 20, 22]. One study was a prospective audit [21]. Two studies evaluated antimicrobial stewardship programmes. A stewardship programme set in a Brazilian cardiology hospital, reported a reduction in mean antibiotic costs (Pharmacist present—US$9,623.73 vs. No pharmacist—US$18,034.89) when a pharmacist was included as part of a multidisciplinary team [17]. Study lacked information on the number of patients or interventions. An alternative antimicrobial stewardship programme was conducted in a US intensive care unit (ICU) [21]. On a sample of seventy patients, improved clinical outcomes were reported but associated antibiotic costs increased by US$192. An Irish study, attempted to reduce antibiotic costs through pharmacists highlighting interventions to switch from the intravenous (iv) to the oral (po)routes of administration [18]. Antimicrobial costs were reduced by €6.21 per patient. A study focusing on iv to po switching of levofloxacin in Taiwan, reported a reduction in total inpatient expenditure of US$2,446.9 [22]. Pharmacist provided antibiotic review services, showed overall cost savings in a US hospital but did not result in any significant reductions in cost per patient between control and intervention groups [20]. A similar programme in a Chinese hospital resulted in a reduction in total costs of hospitalization in the intervention group versus control group (US$1,442.3 ± 684.9 vs. US$1,729.6 ± 773.7) [19]. Antibiotic costs (US$832.0 ± 373.0 vs. US$943.9 ± 412.0) were also reduced. No study relating to antimicrobial management adequately assessed the costs of providing the service.

Targeted drug programmes

Four studies described cost outcomes associated with intervention on specific drugs or classes of drugs. Thirty-three interventions on biologic agents provided savings of US$15,922 in a US hospital [23]. Pharmacists simply rounded the dose of anticancer agents to reduce medication waste. Pharmacists discontinued unnecessary vitamin D supplements over a 1 year period, resulting in cost savings of US$111,282.40 [24]. A group of hospital pharmacists reviewed the appropriateness of prescribing iv esomeprazole resulting in savings of US$21,233 per month [25]. Pharmacists in Taiwan reviewing the appropriateness of activated protein C therapy in septic patients over a 2 year period, demonstrated a reduction in total direct medical costs [26]. Service costs were omitted in the above studies.

Multi-dimensional clinical pharmacy service

A multi-faceted pharmacist intervention programme incorporating medication reviews, patient counselling and discharge was reported as being unlikely to be cost-effective. This was based on a cost of €316243 per increase in quality adjusted life year (QALY) [27]. A similar study, also conducted in Sweden reported that the total cost of secondary care per patient was US$230 lower than in intervention group over a 12 month follow up period [28]. Significantly, both of these studies adequately described associated costs of providing a service.

A pharmacist led discharge programme, consisting of patient counselling, medicines reconciliation and overall medication support resulted in cost avoidance of $378,899 for a group of 229 patients [29]. Cost of service was not stated.

Paediatric programmes

Pharmacists review of medication appropriateness in a paediatric cardiac ICU resulted in cost savings of $12,482 from 131 patients [30]. However, the study lacked a comparator and didn't assess cost of service. Pharmacists participated in ward rounds in a Chinese paediatric hospital. Intervention and control group showed no significant differences in terms of cost of drugs or cost of hospitalisation [31].

Renal specialist

Pharmacist participation in renal team ward rounds resulted in cost savings of US$2,250 in comparison with control group [32]. The study size was 300 patients per group. Pharmacist recommendations on dosage adjustments for patients with renal impairment resulted in savings of $5,377 [33]. Savings were generated from 173 accepted interventions. Neither evaluation considered cost of providing the service.

Table 2 Quality assessment of eligible studies

Item from CHEERS checklist	% of studies included (n = 22)
Demographics	77 (n = 17)
Comparator	68 (n = 15)
Estimating resources and costs	36 (n = 8)
Study parameter	32 (n = 7)
Incremental cost-Effectiveness ratio	23 (n = 5)
Analysis of uncertainty	23 (n = 5)
Currency	18 (n = 4)
Perspective	9 (n = 2)
Horizon	4 (n = 1)
Discount	4 (n = 1)

Pharmacotherapeutic optimisation

Pharmacy students identified 320 interventions, resulting in a cost avoidance of $23,000 due to the prevention of potential adverse drug events [34]. A study evaluating the participation of pharmacists in a Dutch ICU ward reported savings of $26–40 per monitored patient-day. Cost of providing the service was estimated [35].

Intensive care programme

A retrospective review of hospital databases indicated, presence of ICU specialist pharmacists resulted in improved clinical and economic outcomes in patients with thromboembolic events. Examining a total population of 141,079, patients who did not receive specific pharmacist care had additional Medicare costs of $215 million and drug charges of $26 million [36]. Implementation of antifungal practice guidelines by a clinical pharmacist member of an ICU team resulted in a 50 % cost reduction in expenditure on antifungal agents [37].

Neurosurgery

A dedicated clinical pharmacist integrated as part of a neurosurgery team, resulted in total savings of US$1,718,260 from 11,250 interventions implemented over the 2 year study period [38].

Quality appraisal

Three studies [27, 28, 35], achieved 'good-quality' ratings. Twelve studies were described as being of 'fair-quality' as

they did not include the cost of providing the service or intervention as part of the evaluation. Seven studies were considered to be of 'poor-quality'.

The relevant criteria identified from the CHEERS checklist are listed in Table 2; the number of studies which successfully addressed individual criteria is also detailed. Only one study accommodated all relevant criteria [27]. The most common items to be included in studies were details of patient demographics (77 %) and a comparator (68 %). Statements on discount rates (measure of reduction in value of future costs and outcomes), horizon (period over which costs and outcomes were evaluated) and the perspective of the study were excluded in almost every study.

Discussion

Current status

Based on the studies examined in this review, clinical pharmacist interventions remain economically beneficial. The majority of studies included in this review demonstrated some degree of cost savings; however the disparate nature of evaluated interventions and outcome measures makes it impossible to determine the most beneficial intervention type. Furthermore, the methods used to calculate and report outcomes do not facilitate inter-disciplinary comparison.

Significant savings were generated through the prevention of ADEs; this concurs with findings of previous reviews which estimated that ADE prevention resulted in the highest cost-benefit ratio [10]. However, cost avoidance based results should be interpreted with caution, as it is difficult to predict the extent to which they will be reflected in real practice [11].

High cost-environments

Clinical pharmacy services which targeted complex high cost environments such as ICUs, neurosurgery or biologic agents demonstrated promising results. While specialist training and experience is required, interventions conducted in these settings have potentially a greater financial impact in comparison with interventions implemented in general wards. Furthermore, interventions deliver immediate savings which can be easily presented to administrators. Demands for critical care services are expected to increase [39]. Pharmacy education programmes should adapt accordingly to ensure graduates are suitably qualified for employment in these areas [40].

Cost-utility analysis

Multiple health technology assessment bodies have tended to favour cost-utility based evaluations which include measurements such as QALYs [41]. QALYs measure health as a combination of HRQoL and the expected duration of a patient's life, facilitating comparison between interventions in diverse healthcare settings [42]. QALYs were only used as the primary outcome in one included study [27]. This made the comparison of outcomes between interventions impracticable. Other outcome measures which could be utilised to a greater extent are reductions in hospitalisations or mortality rates. These measures are more generalisable and facilitate inter disciplinary comparison.

Comparison with previous reviews

The established trend in systematic reviews of economic analyses is the identification of a low number of 'good quality' studies [12, 14]. This issue is replicated in this review. The quality of studies from a health economic perspective has deteriorated in comparison with previous reviews. Perez et al. review established that 27 % of studies were of good quality [12]. Only 13 % of studies included in this review were labelled as good quality studies. The majority of studies did not make any attempt to calculate input costs for the study. When input costs are not appropriately estimated, it is impossible to make an informed decision on the true value of a service. Savings or associated benefits can be overestimated. Quality issues seem to be particularly prevalent in hospital studies. A recent systematic review which included community pharmacy, noted an improvement in standards of economic evaluations of clinical pharmacy services [13].

CHEERS checklist

The application of the CHEERS checklist on eligible studies highlights the poor reporting standards from a health economic viewpoint. Basic components of a high quality economic evaluation such as estimation of resources and costs, uncertainty analysis and discount rates were absent from the majority of studies. The primary outcome of the majority of included studies was clinically orientated. This is reflected in the manner in which they were reported. Stating the perspective of the study, would be expected in a good quality health economic publication. However, this was only quoted in two studies. It is expected that health economic studies would account for the uncertainty surrounding evidence used and some methodological

assumptions [43]. The most basic way to address this issue is by conducting a sensitivity analysis. However, the issue of uncertainty was not considered in the vast majority of the studies.

The highest quality evaluation included in this study concluded that a composite clinical pharmacist intervention consisting of medication review, patient education and provision of a medication report, was unlikely to prove cost-effective. Wallerstedt et al. used the EQ-5D questionnaire which is a generic preference measure used to calculate QALYs [44]. For mild impairments, which most pharmacy interventions would be directed towards, condition specific preference measures have proven to be more sensitive [45]. Despite their widespread use, QALYs are far from the perfect outcome measure and may exclude important health consequences [46].

Novel interventions

There were no new types of clinical pharmacist interventions highlighted in this review. This is a worrying finding for the future of pharmacy. While the profession has evolved, a constant stream of novel services will ensure that the profession does not stagnate. The lack of developments in economic evaluations of clinical pharmacy services is not just confined to a hospital setting. A recent review which included community, ambulatory and long-term care facilities did not unearth any 'novel' clinical pharmacy intervention [13].

A surprising aspect of this review was the increase in the number of studies reporting data from Asian healthcare systems. A number of these studies cited an under utilisation of pharmacy services in their jurisdiction. Production of economic evidence to augment clinical evidence is an excellent strategy to precipitate a change in mind-set within these countries.

Limitations

There is an English language bias in this review. This is particularly important in health economic evaluations as the cost-effectiveness of a study is affected by the jurisdiction in which it is performed. The review may also be subject to a publication bias as grey literature was not evaluated.

As previously discussed, the lack of standardisation in reporting outcomes and poor quality of studies reduced the ability for comparisons between interventions.

Conclusion

Clinical pharmacy interventions continue to provide cost savings. However, the number of studies examining the subject has decreased and there is a dearth of good quality studies. There was no novel clinical pharmacy service included in this review. The standard of studies published has stagnated or even deteriorated in comparison with those included in previous reviews. A number of reasons have been proposed to account for this, including lack of interest from academic journals due to the decline in 'novel' clinical pharmacy services. Alternatively, judgement may have been reached that established clinical pharmacy services are in general cost-effective and further research into them is unlikely to be necessary. Pharmacist interventions in complex high-cost healthcare settings have been supported by multiple studies included in this review and are an area of care which pharmacy research and education could be directed towards in the future. Economic analysis was not the main outcome measure in majority of studies and was added almost as an afterthought to the primary results. In order to increase their relevance, future economic evaluations should at the very least present the cost of providing a service in addition to economic and clinical outcomes in comparison with an alternative option. Utilisation of a checklist like the CHEERS statement has the potential to improve quality of studies; however previous published guidelines have not had a lasting impact.

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Conflicts of interest The authors have no conflicts of interest to disclose.

Appendix 1

See Table 3.

Table 3 Description of studies eligible for inclusion in this review

First author (year)	Title	Pharmacist intervention	Setting	No. of patients/ interventions	Economic method	Period	Outcome measures	Results	Quality	Type of study
Wallerstedt et al. [27]	A cost-effectiveness analysis of an in-hospital clinical pharmacist service	Composite intervention of medication review, drug treatment discussion with the patient at discharge and medication report	Two internal medicine wards in University Hospital in Sweden	181 control patients and 164 intervention patients	Cost-utility analysis	2007-2008, 6 month follow up on patient	Effectiveness measured in quality gain in quality adjusted life years (QALY) as measured by EQ-5D	Unlikely to be cost effective. Cost per QALY of €316243. No significant difference in total healthcare costs between study groups	Good	Randomised controlled trial
Magedanz et al. [17]	Impact of the pharmacist on a multidisciplinary team in an anti-microbial stewardship program: a quasi-experimental study	Impact of a pharmacist on an antimicrobial stewardship program (ASP)	Cardiology hospital, Brazil	Not provided	Cost analysis	Pharmacy responsible for ASP: 19 months. ID Physician responsible for ASP: 21 months. Pre-implementation of ASP (Control): 30 months	Mean monthly antibiotic costs	The mean monthly antibiotic cost, during the control stage, was US$30,727.56, US$18,034.89 in the ID physician led ASP period, and US$9,623.73 in the pharmacist led ASP period of the study ($P<0.001$)	Fair (missing cost of service)	Quasi-experimental study
Dunn et al. [18]	Implementing a pharmacist led sequential anti-microbial therapy strategy: controlled before and after study	The intervention group consisted of application of stickers and implementation of criteria for switch to oral antimicrobial therapy. Control was routine pharmacist care	753 bed academic hospital in Ireland	72 patients in intervention group and 44 in control group	Cost analysis	Three data collection periods of 10 consecutive days	Direct cost savings were measured but it was not primary outcome	Antimicrobial costs reduced by a mean €641 per patient	Fair (missing cost of service)	Prospective, controlled, before-and-after study design
Shen et al. [19]	Pharmacist intervention on antibiotic use in inpatients with respiratory tract infections in a Chinese hospital	Pharmacist making recommendations to clinical team of nurses and physicians. Control was absence of pharmacist involvement	Respiratory wards in tertiary hospital in China	178 patients (control group), 176 patients(intervention group)	Cost analysis	July 2009–April 2010	Total costs of hospitalisation and cost of antibiotics	The total costs of hospitalization in the intervention group were significant lower compared to the control group ($1,442.3 ± 684.9 vs. $1,729.6 ± 773.7). Cost of antibiotics ($432.0 ± 373.0 vs. $943.9 ± 412.0)	Fair (missing cost of service)	Randomised controlled trial
Wagger et al. [23]	Cost savings from dose rounding of biologic anticancer agents in adults	Cost savings from dose rounding of biologic agents	US	33 dose adjustments	Cost description	January 1–March 1 2005	Direct cost savings	$15,922, direct cost savings	Poor (no comparator, missing cost of service)	Retrospective database review

Table 3 continued

First author (year)	Title	Pharmacist intervention	Setting	No. of patients/ interventions	Economic method	Period	Outcome measures	Results	Quality	Type of study
Steinberg et al. [20]	Impact of Pharmacy Generated Recommendations on Antibiotic Therapy in Community Hospital	Pharmacist initiated antibiotic review service	550 bed community hospital. Only undertaken in selected wards. USA	122 patients.	Cost analysis	10 weeks. Dec 2005 to Feb 2006	Total money saved based on interventions generated. Total antibiotic cost per patient	Overall savings of $112.3 (132. No significant difference in cost per patient between control and intervention groups	Fair (missing cost of service)	Pre and post intervention
Moffett et al. [30]	Medication dosing and renal insufficiency in a paediatric cardiac intensive care unit: Impact of pharmacist consultation	Pharmacist made recommendation to renal team regarding appropriateness of medication	Paediatric cardiac ICU, Houston, Texas. USA	131 patients admitted during study period. 37 patient admissions required adjustment	Cost description	January through March 2006 3 months	Monetary impact of pharmacist intervention was determined by calculating the number of doses that were saved by decreasing doses or schedules	Cost savings of $12,482.54.	Poor (no comparator, missing cost of service)	Retrospective analysis
Gillespie et al. [28]	A comprehensive pharmacist intervention to reduce morbidity in patients 80 years or older	Compilation of list of meds on admission. Drug review. Patient education and discharge counselling. Contacted primary care physician. Standard pharmaceutical care was the control	2 acute medicine wards University Hospital of Uppsala, Sweden	199 patients in intervention group. 201 patients in control group	Cost analysis	October 1 2005- June 30 2006 (9 months)	Secondary outcome was cost of hospital care	Total direct cost of secondary care during follow up year was $490 per patient in the intervention group vs the control group, $210 per patient overall cost savings	Good	Randomized controlled trial
MacLaren et al. [36]	Effects of pharmacist participation in intensive care units on clinical and economic outcomes of critically ill patients with thromboembolic or infarction-related events	Direct patient care services provided by a pharmacist specifically devoted to an intensive care unit	Multiple US hospitals	141,079 Medicare patients who experienced a thromboembolic or infarction related event. 77,857 were in hospitals with critical pharmacist car	Cost analysis	Retrospective database review (01/01/04–31/ 08/05)	Medicare charges, drug charges and laboratory charges	Additional charges for control group in comparison with pharmacist group $215,397,354 in Medicare charges. $26,363,674 in drug charges, no difference in laboratory charges	Fair (missing cost of service)	Retrospective database review

Table 3 continued

First author (year)	Title	Pharmacist intervention	Setting	No of patients/ interventions	Economic method	Period	Outcome measures	Results	Quality	Type of study
Hassan et al. [32]	Impact of renal drug dosing service on dose adjustment in hospitalized patients with chronic kidney disease	Pre and post intervention period comparison. Pharmacist participation in nephrology team rounds. Only included impact of recommendations on dosing adjustment by pharmacist	35 bed nephrology unit, Penang General Hospital, Malaysia	Each phase had a random sample of 300 patients	Cost analysis	4 months. Beginning of Feb to end of May 2007	Drug cost savings of original physician regimen in comparison with pharmacist regimen	$2,250 US for study. For all patients admitted to unit over 1 year, 13,500 US$	Fair (missing cost of service)	Pre and post intervention
Campbell et al. [34]	Analysis of cost avoidance from pharmacy students' clinical intervention at a psychiatric hospital	Retrospective database review of interventions made by pharmacy students	Adult inpatient state psychiatric hospital, Missouri. 120 beds consisting of 2 adult acute care units, 1 adult intermediate care unit, child and adolescent unit, psychiatric emergency dept	320 interventions by 15 pharmacy students	Cost description	1 year. June 1, 2008–May 31, 2009	Estimated cost avoidance based on MedTrend values for adverse drug events and literature review	Cost avoidance of $23,000 (Literature calculation) or $4,000 (MedTrend calculation)	Poor (no comparator, missing cost of service)	Retrospective database review
Ijo et al. [28]	Pharmacy intervention on antimicrobial management of critically ill patients	Prospective pharmacy driven antimicrobial stewardship in the intensive care unit	31 bed medical-surgical and cardiac ICU. US	70 patients	Cost description	November 2009–February 2010 (3 months)	Financial outcomes from drug discontinuation, streamlining, iv-po conversion, dose optimization, addition and substitution	Service resulted in an additional cost of $192 to the pharmacy	Poor (no comparator, missing cost of service)	Prospective audit
Zhang et al. [31]	Clinical pharmacists on medical care of pediatric inpatients	Clinical pharmacist active participation in paediatric ward rounds. Control consisted of no clinical pharmacist participation	West China Second University Hospital	80 patients in each group	Cost analysis	4 Months. Dec 1 2010–March 31, 2011	Cost of drugs and cost of hospitalization. This was a secondary outcome	No statistical difference in costs of drugs and cost of hospitalization	Poor (multiple flaws)	Randomized controlled trial

Table 3 continued

First author (year)	Title	Pharmacist intervention	Setting	No of patients/ interventions	Economic method	Period	Outcome measures	Results	Quality	Type of study
Wilkinson et al. [29]	Impacting readmission rates and patient satisfaction: Results of a discharge pharmacist pilot program	Pharmacist driven discharge program for high risk patients. No control	University of Kansas Hospital. 525 bed& average daily census	229 patients received pharmacist evaluation	Cost description	3 month study period beginning in Sept 2009	Cost avoidance calculated using Veterans affairs model	Total cost avoidance $378,899	Poor (no comparator, missing cost of service)	Prospective, cohort, non-randomized trial
Jing et al. [24]	The impact of pharmacist intervention on the use of activated Vitamin D in a tertiary referral hospital in Malaysia	Retrospective review of activated Vitamin D use. Pharmacists discontinued unnecessary use	University Malaya Medical Centre	557 patients	Cost analysis	1 year prior to intervention and 1 year post intervention	Cost of Vit D in pre and post intervention periods	Decrease of RM400616.80(US$111,282.40) annually. $P = 0.002$	Fair (missing cost of service)	Pre and post intervention
Nasser et al. [25]	Cost reduction associated with restriction policy on dispensing intravenous esomeprazole in Lebanon	Impact of pharmacist intervention on cost following implementation of restriction on esomeprazole iv dispensing. Physicians fill a form and pharmacists review prior to approval	Inpatients of a Lebanese hospital	Not given	Cost analysis	12 months pre restriction and 12 months post restriction	Measured reduction in IV vials dispensed, and calculated associated cost	Reduction of $21,233 per month	Fair (missing cost of service)	Pre and post intervention
Hou et al. [33]	Retrospective evaluation of the outcomes of applying the renal dosing monitoring system in a medical center	Computerized dosing system modifies dosing for patients with renal impairment. Pharmacist then decides whether to make recommendations. Retrospective analysis of outcomes	Inpatients in a Taiwanese hospital	12,057 cases reviewed. Pharmacists made recommendation in 202 cases and 173 suggestions were accepted	Cost description	April 2007–March 2008	Cost savings due to dosage adjustments	US$5,377	Poor (no comparator, missing cost of service)	Retrospective evaluation
Klopotowska et al. [35]	On-ward participation of a hospital pharmacist in a Dutch ICU reduces prescribing errors and related patient harm: an intervention study	ICU hospital pharmacist reviewed medications for ICU patients and noted issues for discussion with ICU physician. If consensus reached issues were scored as prescribing errors	Adult medical and surgical ICU in a 1,002 bed tertiary care academic hospital in Amsterdam	All patients admitted to ICU during study period	Cost analysis	8 months (intervention period). 3 weeks. (Baseline period). 3rd Oct 2005 and 30th June 2006	Estimate of cost avoidance. Secondary outcome	Cost savings of €26–40 per patient per day	Good	A prospective baseline vs intervention period study

Table 3 continued

First author (year)	Title	Pharmacist intervention	Setting	No of patients/ interventions	Economic method	Period	Outcome measures	Results	Quality	Type of study
Chan et al. [26]	Pharmacist intervention in activated protein C therapy for severe sepsis: influence on health and economic outcomes	Clinical pharmacists determine the appropriateness of prescribing activated protein C to a patient	Taiwanese hospital. Inpatients. No further info given	19 patients in each group	Cost analysis	2 years pre intervention. 2 years post intervention. Jan 2003 to Dec 2007	Total direct medical costs for both groups	Intervention group US$20,632.3 versus control group US$24,785.8. Converted to US dollars from taiwanese currency but no conversion date give	Fair (missing cost of service)	Retrospective comparison
Yen et al. [22]	Clinical and economic impact of a pharmacist-managed iv to po conversion service for levofloxacin in Taiwan	Pharmacist managed iv to po conversion programme for levofloxacin	Inpatients in a Taiwanese hospital. Tertiary hospital with 732 beds	37 patients in each group	Cost analysis	Pre intervention 1/07/08–31/08/08 (2 months). Intervention period 01/10/08-31/12/08 (3 months)	Two cost outcomes, total inpatient expenditure and cost of antibiotics for both groups	Antibiotics: Pre- intervention US$568.9 versus 449.0. Total inpatient expenditure: Pre-intervention US$6,096.5 versus 3,649.6. Converted to US Dollars but no conversion date	Fair (missing cost of service)	Retrospective comparison pre and post intervention
Swoboda et al. [37]	Implementation of Practice Guidelines for Antifungal Therapy in a Surgical Intensive Care Unit and Its Impact on Use and Costs	Implementation of practice guidelines for antifungal therapy by a clinical pharmacist	Surgical intensive care unit of the University Hospital of Heidelberg, Germany	372 patients in control period. 379 patients in intervention period	Cost analysis	Control period January 2005 – June 2006 (18 months). Intervention period July 2006–December 2007 (18 months)	Costs for antifungal agents during a period of 18 months before and after implementation	Total of €557110 was spent on antifungal agents during the control period. Total of €258306 was spent on antifungal agents during the intervention period	Fair (missing cost of service)	Pre and post intervention
Weant et al. [38]	Cost effectiveness of a clinical pharmacist on a neurosurgical team	Monitoring and evaluating patients, participating in team rounds	Neurosurgical service in a US hospital	1077 patients in control group. 1079 patients in intervention group	Cost analysis	2 years pre implementation period and 2 years post implementation period	Average pharmacy and intravenous cost of therapy per patient	The average pharmacy and intravenous therapy cost per patient between the pre- and post implementation groups decreased from $4,833 to $3,239	Fair (missing cost of service)	Pre and post intervention

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10.11.2 Paper 2

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Cost-outcome description of clinical pharmacist interventions in a university teaching hospital

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Abstract

Background: Pharmacist interventions are one of the pivotal parts of a clinical pharmacy service within a hospital. This study estimates the cost avoidance generated by pharmacist interventions due to the prevention of adverse drug events (ADE). The types of interventions identified are also analysed.

Methods: Interventions recorded by a team of hospital pharmacists over a one year time period were included in the study. Interventions were assigned a rating score, determined by the probability that an ADE would have occurred in the absence of an intervention. These scores were then used to calculate cost avoidance. Net cost benefit and cost benefit ratio were the primary outcomes. Categories of interventions were also analysed.

Results: A total cost avoidance of €708,221 was generated. Input costs were calculated at €81,942. This resulted in a net cost benefit of €626,279 and a cost benefit ratio of 8.64: 1. The most common type of intervention was the identification of medication omissions, followed by dosage adjustments and requests to review therapies.

Conclusion: This study provides further evidence that pharmacist interventions provide substantial cost avoidance to the healthcare payer. There is a serious issue of patient's regular medication being omitted on transfer to an inpatient setting in Irish hospitals.

Keywords: Hospital pharmacy, Adverse drug events, Health care economics, Ireland, Clinical pharmacy services, Cost avoidance

Background

The traditional role of a pharmacist predominantly involved the dispensing of medications in both hospital and community settings; consequently the pharmacist was quite detached from other healthcare professionals. The profession has since evolved to become recognised as an essential part of the healthcare team [1]. While still ensuring that medicines are sourced and dispensed to the highest possible standards, pharmacists have diversified into alternative areas of care in hospital practice [2]. Interventions are integral components of the new enhanced role which pharmacists offer in a clinical setting [3-8].

A pharmacist intervention is defined as any action taken by a pharmacist that aims to change patient management or therapy [9]. A pharmacist's expertise in pharmacology, pharmacotherapy and pharmaceutics ensures they have the requisite capabilities to offer suggestions to other healthcare staff on possible alterations to a patient's therapy [10,11]. This helps to ensure optimal patient outcomes, which has the potential to have an add-on economic benefit to the healthcare institution.

A myriad of studies have described the high rate of potential inappropriate prescribing and potential adverse drug events (ADE) in multiple healthcare systems [12-16]. An ADE is defined by the International Conference for Harmonisation as "any untoward medical occurrence in a patient administered a medicinal product which does not necessarily have to have a causal relationship with treatment". These issues cause repercussions in the form of increased resource utilisation [17]. Evidence of the clinical benefit and reduction in ADEs associated with enhanced roles for pharmacists in a hospital setting, are documented in the literature [2,5,18,19].

Healthcare systems worldwide are coming under increasing pressure due to a combination of aging populations and the proliferation of new expensive technologies

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[20]. All healthcare services need to show that they provide value for money for the investment made in their provision [21]. Despite early scepticism, health economic evaluations are required for the establishment and continued provision of services and technologies [20].

The provision of a clinical pharmacy service in a hospital setting is an investment which utilises costs which could be used elsewhere in the health system. Economic evaluations of clinical pharmacy services will help policy makers make informed decisions on whether they are a worthwhile investment. Studies in other jurisdictions have indicated that they are cost-effective, however these findings are not generalisable [22,23].

This paper will analyse the interventions made by a team of pharmacists in a university teaching hospital and evaluate the cost avoidance achieved through the prevention of an ADE. For the purposes of this study, cost avoidance refers to an intervention that reduces or eliminates additional expenditure that otherwise may have been incurred in the absence of the intervention [24]. It is a different measure to cost saving interventions, which refer to reductions in current spending due to changes in the expenditure on a patients treatment [25]. Cost avoidance interventions contain and control costs and over a longer period of time they can result in cost savings.

The study was based in an Irish university teaching hospital/tertiary referral centre setting over a period of one year. Similar studies have been performed, examining shorter time periods or focusing on specific interventions [3-7,25]. However, information which helps to evaluate the economic impact of pharmacist interventions over a longer period of time and covering an entire hospital domain is lacking. The authors have been unable to find a study where cost avoidance generated by a full department of clinical pharmacists in a full calendar year has been calculated.

Methods

Setting

This was a retrospective study based on a 1 year time period from 01/01/2012 to 31/12/2012 inclusive. Cork University Hospital (CUH) and the Cork University Maternity Hospital is a combined 850-bed hospital site. The hospital serves a population of over 620,000. In addition, it is a tertiary referral centre for over 1 million people, in the southern region of the Republic of Ireland. Approximately 32,000 inpatient admissions were recorded for 2012. All patients who were in receipt of a pharmacist intervention on their drug therapy were included in this study. There were no additional exclusion criteria. The Pharmacy Department consists of 15.8 whole time equivalent (WTE) pharmacists. As two WTEs are employed in managerial and administrative capacities, 13.8 WTE are available to document interventions as part of the daily pharmaceutical service. Interventions performed in all areas of the hospital, including the maternity unit, were included in this study.

Intervention analysis

Clinical pharmacist interventions are provided by many basic and senior grade pharmacists at CUH. Clinical pharmacist interventions are carried out at patient admission, during pharmacist led patient chart review or at the request of another healthcare professional. As previously discussed, the primary goal of a clinical pharmacist intervention is to ameliorate patient therapy.

Interventions made by pharmacists were recorded on a duplicate paper form. One form is kept by the pharmacist and one is passed on to the attending physician who has the final decision on whether to accept or reject the intervention.

In addition to producing a paper record of the intervention, the pharmacist retrospectively enters the proposed intervention into the 'eClinical Pharmacy Suite'. The 'eClinical Pharmacy Suite' is a browser-based application, aimed at supporting clinical pharmacists to record, grade and report medication related interventions or errors. Interventions were assigned by the clinical pharmacist to the most appropriate category in the application. Due to time constraints, not all recorded intervention had been entered on the computerised database. The primary researcher inputted any outstanding interventions and verified data which had been previously entered by hospital pharmacists. Intervention categories were developed based on the recommendations of an advisory group of clinical pharmacists from Ireland.

Cost analysis

The cost of providing this service was calculated based on the average time it took to carry out an intervention and the hourly cost of employing a hospital pharmacist. The average time of an intervention was based on a previously published study, which showed that the majority of pharmacist interventions in a university hospital setting took between 15 – 30 minutes to complete [7]. The hourly rate of employing a pharmacist at the mid-point of the salary scale was calculated based on an annual salary of €49,425 (Point 6 of 2010 salary scale) [26]. This underwent upward revision to account for employer related costs and hospital overheads based on guidance for conducting an economic analysis within the Irish healthcare system [27-29]. Base case scenario was calculated using the hourly cost of employing a basic level pharmacist at the mid-point of the salary scale and an average intervention time of 22.5 minutes.

Cost avoidance was calculated based on the probability that an ADE would have occurred in the absence of the proposed pharmacist intervention [18]. Interventions were

analysed by the primary author and a score was assigned based on the probability of a patient experiencing harm directly or indirectly from their prescribed/administered medicines, and also the potential of omission of regular medication, sub-therapeutic dosing or an ill-advised choice of therapy. Determination of the probability that a patient would experience harm in the absence of an action by a pharmacist was based on the methodology described by Nesbit et al. [25] (Table 1). The cost avoidance for each individual intervention was determined and total cost avoidance was accordingly calculated through summation of the individual interventions. A random sample of the interventions (n = 100) were reviewed by two academic pharmacists with hospital pharmacy experience and inter-rater reliability was calculated for the sample.

The authors were unable to find an estimated cost of an ADE, calculated based on data from the Irish healthcare system. The additional cost of treating an inpatient that experienced an ADE was taken from a recent study which utilised a micro-costing approach based on data from German hospitals [30]. This study also included a range of previously published ADE estimates (€934 – 5783). The majority of previously published studies which calculate cost avoidance used a cost of ADE determined by Bates et al. [5,7,24,25]. Rottenkolber ADE valuation was deemed to be more appropriate for this study as it was published in 2012 while Bates study was published in 1997 using US data [31]. This removed the need to account for currency differentials and inflation. Purchasing power parities between Germany and Ireland were used to further minimise differentials between the two countries. Cost of an ADE used in base case scenario was €1057.

A micro-costing approach, assigns a valuation to each individual unit of resource consumed and is considered the most robust costing method [32]. Diagnosis related group (DRG) costs for toxic side effects of drugs based on Irish hospital data were available but were not chosen as the cost of an ADE. The DRG estimate exclusively measured toxic side effects of drugs [33], furthermore DRG costs are generally less accurate in comparison to micro-costing estimates [32]. DRG costs for toxic side effects for drugs (€887) were included in sensitivity analysis calculations.

Following estimation of the cost of carrying out the pharmacist interventions and the resulting cost avoidance, net cost benefit and cost benefit ratio for providing the service were calculated. Analysis was calculated from the perspective of the healthcare institution. Discounting was excluded as events were all considered to have taken place in a 1 year time period.

Sensitivity analysis

One way deterministic sensitivity analysis was performed. Published ranges and confidence intervals where available determined the extent of the parameters. Sensitivity analysis was also performed using alternative published costs of an ADE [31], Irish DRG data and with various intervention acceptance rates.

Data analysis

Reports generated from the eClinical Pharmacy Suite database were in Microsoft Excel™ format. Summary statistics were calculated through Microsoft Excel 2010 (Microsoft Corp., Redmond, Washington). All other advanced analysis was conducted through IBM SPSS Statistics Version 18.

Ethical approval

Approval was obtained from the Clinical Research Ethics Committee of the Cork Teaching Hospitals, University College Cork, Ireland.

Results

A total of 4,257 interventions were documented on 2,147 individual patients (Table 2). The majority of the interventions were judged to have prevented potential

Table 1 Nesbit method for calculating indirect cost benefit [25]

Equation 1: Cost avoidance for individual intervention	***Probability of an ADE occurring X cost of an ADE [30] OR (0 or 0.01 or 0.1 or 0.4 or 0.6) X €1057***	
Probability of an ADE occurring	**Probability score**	**Example**
No harm expected	0.00	Pharmacist suggests changing patient from esomeprazole to omeprazole exclusively for economic reasons.
Very low	0.01	Patient regularly takes a bisphosphonate, but medication omitted from hospital kardex
Low	0.10	Patient takes an antibiotic twice daily, when recommended dose would be three times daily.
Medium	0.40	Metformin dose not reduced despite patient demonstrating renal impairment
High	0.60	Patient prescribed amiodarone while currently taking digoxin without any reduction in digoxin dose.

Source Nesbit, T.W. et al.: Implementation and pharmacoeconomic analysis of a clinical staff pharmacist practice model. American journal of health-system pharmacy 58(9), 784-790 (2001).

Table 2 Intervention analysis

	Number of interventions
Total number of patients who received intervention	2147 patients
Total number of interventions	4257
Mean number of interventions per patient (St. dev.)	1.98 (1.60)
Median number of interventions per patient (95% CI)	1 (0.06)
Range of interventions per patient	1 - 18
Interventions accepted by physicians (%)	1275 (29.92)
Interventions rejected by physicians (%)	61 (1.43)
Interventions with unknown acceptance outcome (%)	2921 (68.81)

ADEs (n = 3,417). The remaining interventions had no discemible impact on therapy or patient outcomes, based on the judgement of the primary author. Additional interventions required entry under multiple categories on the database, but were only evaluated once for potential prevention of an ADE.

Recorded acceptance rate by physicians was 29.92% (n = 1275). Only 1.43% (n = 61) interventions were recorded as being rejected by a physician. However, the rate of interventions with an unknown acceptance outcome was high, 68.81% (n = 2921).

Substantial cost avoidance of €710,000 was generated over a 1 year period from the perspective of the health care provider. Mean cost avoidance of €166 per intervention was generated. The cost of providing these interventions was €82,000. Substantial net cost benefits of €626,279 and a cost benefit ratio of 8.64 were generated based on this evaluation of pharmacist interventions (Table 3).

The number of interventions that potentially avoided ADEs were as follows: 119 (2.8% of all interventions) of the interventions were associated with a probability score of 0.6 (high likelihood of preventing an adverse event), 1101 interventions (25.86%) were associated with a probability score of 0.4 (medium), 1514 interventions (35.56%) were associated with a probability score of 0.1 (low), 683 interventions (16.04%) were associated with a probability score of 0.01 (very low) and 840 interventions (19.73%) were associated with a probability score of 0 (no harm expected).

The most prevalent type of intervention was the identification of omissions of patient's regular pre-admission medication, followed by requests to change the dose of medications and requests for the physician to consider whether it was appropriate to continue with a medication (Table 4). The most common categories of medications to require interventions were proton pump inhibitors (n = 259), statins (n = 208), beta-blockers (n = 165), corticosteroids (n = 161) and penicillins (n = 157).

Inter rater reliability indicated an acceptable level of agreement, based on a random sample of 100 interventions. Average agreement between 3 raters was 0.744. Individual pairwise agreement was over the significant level of 0.7 for all 3 comparisons: Primary Rater (PR) – Academic Pharmacist (AP) 1 = 0.763, PR – AP 2 = 0.761, AP 1 – AP 2 = 0.709.

In all scenarios examined, the cost-benefit ratio remained positive (Table 5). All known variables underwent a one-way sensitivity analysis based on known ranges or using variations used in previously published sensitivity analysis on the topic. Nesbit et al. conducted a sensitivity analysis where the ADE probability underwent an each way variation of 50%, an identical variation was undertaken in this paper [25]. The greatest variance in cost-benefit ratio was displayed in the cost assigned to an ADE.

Two additional ADE cost estimates were investigated during the course of sensitivity analysis (Table 6). The estimated cost of an ADE calculated by Bates and adjusted due to change in setting and year resulted in a considerable increase in the cost benefit ratio.

Table 3 Cost analysis of pharmacist interventions

		Base case (Range)
1.	Cost avoidance	**€708221** (625808–3874783)
2.	**Cost of Service** - Pharmacist Wages	**€81942** (2.2402 – 110389)
[a]**3 = (1–2)**	Net Cost Benefit	**€626279** (567173–3764394)
[b]**4 = (1/2)**	Cost Benefit Ratio $\frac{\text{Net Cost Benefit}}{\text{Cost of Service}}$	**8.64**

[a](Cost avoidance – Cost of Pharmacy Services).
[b](Net Cost Benefit ÷ Cost of Service).

Table 4 Intervention categorisation

Category of intervention	N (%)
Drug	2759 (64.81%)
- *Drug, Omissions*	1820 (65.93% of Drug Category)
- *Drug, Review Therapy*	421 (15.24% of Drug Category)
- *Drug, Interaction*	124 (4.56% of Drug Category)
- *Drug, Other*	394 (14.27% of Drug Category)
Doses	920 (21.61%)
Frequencies	354 (8.32%)
Routes	125 (2.94%)
Duration	47 (1.10%)
Other	27 (0.63%)
Date/Time	20 (0.47%)
Rates	5 (0.12%)

Table 5 Sensitivity analysis for cost-benefit ratios

Variable	Lower limit *(Cost Benefit Ratio)*	Upper limit *(Cost Benefit Ratio)*
Time	**30 minutes per intervention** 6.48	**15 minutes per intervention** 12.96
ADE Probability	**−50% Probability score** 4.32	**+50% Probability score** 12.96
Salary	**Highest point on senior pharmacist scale** 6.42	**Lowest point on basic pharmacist scale** 12.07
ADE Cost[A]	**Lowest point on range** 7.63	**Highest point on range** 47.28
Intervention acceptance	**50% Acceptance** 4.32	**Known Acceptance (29.92%)** 2.59

[A]ADE range taken from a review of selected international studies regarding the economic consequences of ADEs which reported additional mean costs in the range of €934 to €5783 per case [34].

Discussion

Substantial cost avoidance was demonstrated in this study. Cost benefit ratio and net cost benefit remained positive under all conditions examined. To the authors' knowledge, this study is the first that has attempted to estimate the cost avoidance achieved in a total hospital environment over such an extended period of time. Direct comparison of savings generated in this study with previously published studies is difficult. The generalizability of pharmacoeconomic analysis is uncertain [35]. Calculation of cost avoidance will have inter study variations in the cost assigned to an ADE, methodologies, healthcare settings, duration of study and number of pharmacists employed.

The original study which implemented the cost avoidance method used in this paper generated a net benefit of $392,660 [25]. This was over a similar 12 month period but only included 3 WTE pharmacists operating on three specific hospital wards. Study location was in a US hospital. These pharmacists had undergone specialist training and were to a large extent exclusively performing interventions during their participation in the study. Cost benefit ratio of 3.1:1 was considerably smaller in the Nesbit study. Cost-benefit ratio was influenced significantly by the method used to calculate the cost of the service. The complete pharmacist salary was used to calculate the cost of providing the intervention rather than apportioning part of the salary based on the time pharmacist spent enacting the interventions.

A study by Olson et al. conducted in a 360 bed US hospital has the greatest methodological agreement with this paper [7]. This was conducted over a 3 month period and estimated the cost benefit ratio to be 1.2. Only 5 pharmacists provided interventions in this study. Although, substantial savings ($84,631) was generated from a small number of interventions, the cost-benefit ratio was lower than expected. As with the Nesbit study, cost-benefit ratio was reduced as full pharmacist salary was used to calculate the cost of providing the service. The results in this study provides evidence that the positive cost benefit ratio of clinical pharmacists' interventions is maintained over a longer period of time, with additional pharmacists and in a wider hospital setting.

Table 6 Sensitivity analysis using alternative ADE estimates

Alternative ADE estimate	Cost benefit ratio
DRG Toxic Side Effects [33]	7.25
Bates ADE Costing [31]	49.49

Cost avoidances are impacted significantly if they are focused in specific departments. Cost avoidance per intervention generated in our study was decidedly lower in comparison to a study conducted in an intensive care unit. The addition of a single critical care pharmacist to a 16 bed intensive care unit produced an average cost avoidance of $1596.27 - $1615.67 per intervention [5]. Input costs were omitted in this study so further comparison was not feasible.

While the cost-benefit ratio in this study was positive, it needs to be reiterated that this ratio was based on estimates of time and avoidance of cost rather than hard economic data. Therefore, the ratio could potentially be an overestimate. Furthermore, an evaluation of a clinical pharmacy service is strengthened when it also includes an assessment of the clinical and humanistic outcomes involved [36].

This high degree of omissions of patient's regular pre-admission medications (43% of all interventions) highlights the need for a dedicated system of medicines reconciliation at a tertiary healthcare level in Ireland. A pilot study of pharmacist-led medication reconciliation in two university teaching hospitals, elsewhere in Ireland, also identified omission of a pre-admission medication as the most common discrepancy [37]. These findings are replicated in other healthcare settings [38]. Medication omissions can have potentially serious consequences for patients depending on the nature of the drug omitted [39].

An argument could be presented not to include medication omissions as an ADE, based on a strict interpretation of the definition, as the patient did not receive the drug [40]. However, the decision was taken to include them in this study. Similar studies in the past have included the identification of medication omissions as a potential ADE [7,41]. The probability of a patient incurring harm is increased if they do not receive their regular medication, resulting in a related increase in hospital resource utilisation [42].

Medium and low scores were the most frequent probabilities assigned to the interventions. This reflects findings obtained in the majority of previous studies which implemented the same method of calculating cost avoidance [5,25,41]. The frequency of these scores were influenced by the number of medication omissions (39% of omissions were assigned a medium probability score and 37% assigned a low probability score.) Interventions designated with a high probability of preventing an ADE were largely composed of omissions of essential medications (e.g. anti-epileptic drugs) or known serious drug interactions.

The most common medication classifications requiring intervention were unsurprising. Proton pump inhibitors (PPI) were the medication classification requiring the most frequent intervention. Interventions on PPIs were largely suggestions to change to lower cost equivalents, highlighting therapeutic duplication, excess of therapy or suggestion for switching from intravenous to oral administration. The majority of these interventions resulted in cost savings to the healthcare provider. Inappropriate prescribing of PPIs is a significant issue in the Irish healthcare system and a significant drain on resources [43,44]. This demonstrates the pivotal role can play as cost containers in the healthcare system.

Another method of increasing the number of interventions would be the provision of further training for clinical pharmacists which would enable them to become specialists in various areas of patient care. This practice is common in other countries and has been shown to provide substantial monetary savings from interventions enacted by specialist pharmacists [5]. Specialised anti-microbial pharmacists have been shown to be of value and are now established in many hospitals in Ireland [45,46].

A significant level of agreement was found between three of the listed authors. Assignment of probabilities is subjective; therefore a high level of agreement is unlikely. On review of samples, almost all were within 1 score of each other, further indicating that probabilities were assigned by the primary author in a manner consistent with fellow professionals. Although, inter rater reliability was not examined for all interventions, the clinical background of the primary rater and the significant agreement level demonstrated in the sample indicate the ADE probabilities were assigned in an appropriate and consistent manner.

There was a high rate of interventions where the outcome was unknown at time of analysis. However, review of interventions where status was determined indicated that only a small minority of pharmacist interventions were rejected. This indicates that other healthcare professionals are receptive to pharmacist interventions on patient medication. The high level of unknown outcomes was most likely due to time constraints on the pharmacist. Following acceptance or rejection, system requires manual updating. It is understandable that an administrative task such as this may be neglected.

The importance of an accurate estimation of ADE cost was emphasized from the dramatic increase in cost benefit ratio if Bates et al. estimate of ADE was used. As previously stated, there is an absence of data on ADE costs in Ireland. The validity of estimated cost avoidance would be improved through application of local data on excess costs associated with ADE. Until this issue has been addressed, imperfect data is the only viable option. Sensitivity analysis undertaken in this study was deterministic in nature; performing probability sensitivity analysis would have been a more accurate robust method to determine whether pharmacist interventions would have maintained a positive cost benefit ratio.

The primary limitation was the limited availability of additional patient information (medical record, medical history, outcome of intervention etc.) when assigning adverse drug event probabilities. As this study contained a large number of patient interventions, it was not feasible to retrospectively retrieve this information from medical notes.

Another major limitation was the exclusion of some potential input costs. In order to conduct an intervention, problems must be located which takes up pharmacist time and therefore has an associated cost. Screening of a patient's medication may not be exclusively for the purpose of discovering interventions but it is one possible outcome from it. Additionally, other healthcare professionals are required to spend time reviewing suggested pharmacist interventions. This was also excluded from analysis.

Utilisation of a scoring system which also accounts for the severity of the potential ADE would significantly enhance this study. Such scoring systems exist but they do not assign a cost with the scoring outcome generated. There is no ideal system for assigning probabilities to adverse events but the widespread adaptation of one system would add to the ability to compare studies across jurisdictions. The classification of interventions is subjective. Generation of local guidelines on the classification of interventions would help reduce this variation.

While the interventions included in the study represented the majority of work conducted by clinical pharmacists, it is possible that some interventions were not inputted on to the eClinical System. Therefore, the current data may under-represent the cost avoidance produced.

The interventions were assigned scores by an individual rater. While sample of interventions examined for inter-rater reliability indicated that the primary author was assigning probability scores in a manner consistent with other pharmacists, review of complete dataset by additional pharmacists and other medical professionals would have enhanced the study.

Conclusion

Previous reviews have indicated that pharmacist interventions generate significant cost avoidance when measured under certain criteria and conditions [18]. This study has confirmed previous opinions and supplemented the body of evidence that the provision of clinical pharmacy services in an entire hospital provides value for money to the healthcare payer. An excessive amount of omissions of regular medications has been highlighted by this study. The estimation of cost avoidance would be improved by the development of a method which incorporated the potential severity of an ADE into the evaluation and an evaluation of excess costs associated with ADEs in an Irish healthcare setting.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JG performed analysis on data and was the primary author of the manuscript. SB devised the concept for the manuscript, performed analysis on sample data and revised drafts of the manuscript. NW provided advice on appropriate methods for calculating costs and revised drafts of the manuscript. DL revised drafts of the manuscript. SMcC participated in data collection, performed analysis on sample data and revised drafts of the manuscript. All authors read and approved the final manuscript.

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Economic evaluation of a randomized controlled trial of pharmacist-supervized patient self-testing of warfarin therapy

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SUMMARY

What is known and objective: **The increase in numbers of patients requiring oral anti-coagulation testing in outpatient clinics has focused attention on alternative flexible systems of anti-coagulation management. One option is pharmacist led patient self-testing (PST) of international normalised ratio (INR) levels. PST has demonstrated improvements in anti-coagulation control, but its cost-effectiveness is inconclusive. This study reports the first cost-effectiveness evaluation of a randomized controlled trial of an automated direct-to-patient expert system, enabling remote and effective management of patients on oral anti-coagulation therapy.**

Methods: **We conducted an economic evaluation alongside a randomised controlled trial investigating a pharmacist led PST method. The primary outcome was to determine the cost effectiveness of PST in comparison with usual care (management in a hospital based anti-coagulation clinic). Long term anti-coagulation patients were recruited to a 6 month cross over study between PST and routine care in an anti-coagulation clinic. Economic evaluation was from the healthcare payer perspective.**

Results and discussion: **On a per patient basis over a 6 month period, PST resulted in an incremental cost of €59·08 in comparison with routine care. Patients achieved a significantly higher time in therapeutic range (TTR) during the PST arm in comparison with routine care, (72 ± 19·7% vs. 59 ± 13·5%). Overall cost of managing a patient through pharmacist supervised PST for a 6 month period is €226·45. Additional analysis of strategies from a societal perspective indicated that PST was the dominant strategy.**

What is new and conclusion: **Pharmacist led patient self-testing is a viable method of management. It provides significant increases in anti-coagulation control for a minimal increase in cost.**

WHAT IS KNOWN AND OBJECTIVE

Despite the development of new oral anti-coagulant agents (NOACs), warfarin remains an integral option in anti-coagulation management strategies. In Ireland in 2010, 57 000 patients were in receipt of a prescription for warfarin.[1] This constitutes 1·7% of the population. The majority of patients (55%) required warfarin for treatment of atrial fibrillation.[1]

Warfarin is a well-established medication with a relatively low cost. However, unusually for an oral medication, it has significant expenses associated with the monitoring and management stage of the therapy. Warfarin is a medication with a narrow therapeutic index, requiring close management, and regular dosage adjustments can be necessary. Currently in Ireland, the majority of management is provided by dedicated hospital-based anti-coagulation clinics.[1]

There are documented limitations to hospital-based clinics, especially from a patient's perspective, which include the requirement to make regular and frequently time-consuming visits to the clinic.[2] Furthermore, previous studies have shown that alternative management strategies can improve anti-coagulation control in comparison with hospital-based anti-coagulation clinics.[3] The development of NOACs will decrease the overall proportion of patients dependent on warfarin as a long-term anti-coagulant; however, some patients will remain on warfarin therapy and therefore require an anti-coagulation management service.[4]

Patient self-testing (PST) of warfarin therapy is a concept which allows the management of warfarin therapy to move away from already overburdened hospital-based clinics to management at a primary care level. The PST model involves the patient measuring their international normalized ratio (INR) levels using a portable point-of-care (POC) device. There are clinical benefits associated with the application of PST over usual care in anti-coagulation management. Evidence ranging from randomized controlled trials (RCT), meta-analysis and full systematic reviews indicates that PST is associated with improved outcomes.[5–10] PST of oral anti-coagulation has been proven to be a safe option in all age groups.[11]

Input from healthcare professionals is still a fundamental requirement for the success of any PST strategy. Ryan *et al.*[9] demonstrated that a single pharmacist could favourably oversee the management of a group of patients managing their INR using a PST strategy. Pharmacists have a broad clinical and therapeutic knowledge and are using these skills to diversify into new areas of patient care.[12] With additional training in the area of anti-coagulation management and accreditation of required standards, pharmacists have shown they are capable of providing an anti-coagulation management service.[13]

The method by which results are communicated to the responsible professional is another crucial part of warfarin PST. Telephone-based communication has been proven as a viable method and is widely utilized in the United States.[14] However,

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availing of technological developments can reduce the cost, time and risk of errors associated with verbal communication.[15] 'Expert' software systems have been developed to assist in patient management and data recording. The RCT examined in this evaluation utilizes the CoagCare™ system (ZyCare Inc. Chapel Hill, NC, USA). CoagCare™ combines a direct-to-patient expert system accessed via the internet with PST to provide a novel model of pharmacist-supervized telehealth.[9]

This study is the first cost-effectiveness evaluation of an internet-based, direct-to-patient expert system in anti-coagulation management. The direct-to-patient expert system employs a rule-based algorithm to inform patients how to adjust warfarin therapy based on INR data which has been recorded and inputted by the patient.[9] Previous cost-effectiveness analysis has been inconclusive as to whether similar systems offer 'value for money' to the healthcare payer.[16]

In this study, a cost-effectiveness analysis was undertaken based on the outcomes and resource utilization from a RCT of pharmacist-supervized PST of warfarin therapy using an internet-based system.[9] The primary aim of this study was to determine the incremental cost-effectiveness of PST in comparison with usual care.

METHODS

Trial protocol

This cost-effectiveness analysis was based on data from an RCT which is documented elsewhere.[9] In summary, the trial was a prospective, randomized controlled crossover study. Patients were initially assigned to either 6 months of routine care or 6 months of PST. At the end of the 6-month period, the patient was transferred to the alternative arm. The crossover design of the study eliminated the potential for covariate disparities. The primary outcome was the difference in the time in therapeutic range (TTR) between the two arms. Overall TTR for each arm was calculated using the Rosendaal method.[17] For the purposes of this trial, TTR was defined as the time spent within 0·5 units of the targeted INR value.[9] Patients were required to have been on warfarin therapy for at least 2 months prior to the start of the study and expected to have a requirement for warfarin for the duration of the 12-month study. Patients were excluded from the trial if they were unable to use a POC device, if they missed attending more than two clinic appointments in a 6-month period prior to recruitment screening or if the patient was taking an additional anti-coagulant other than warfarin. Furthermore, patients were excluded if they had experienced a haemorrhagic complication in the preceding 6 months or if they were unable to attend the hospital clinic at short notice. Following recruitment, patients received comprehensive training from the research pharmacist.

Initially, INR levels were measured in the PST arm twice weekly. Following stabilization of INR levels, intervals between tests were increased to a maximum of once every 2 weeks. Management of deviations from the targeted INR value or other patient issues was the responsibility of the research pharmacist, assisted by the CoagCare™ system. During the course of routine care, patients attended the anti-coagulation management service (AMS) for INR measurement every 4-6 weeks. Any necessary dosage adjustments were calculated by a doctor or nurse associated with the clinic.

RCT information

Patient recruitment and provision of routine care were provided at the AMS of Cork University Hospital (CUH). Currently, the AMS has approximately 850 regular patients. Additionally, the clinic is responsible for short-term anti-coagulation patients and the processing of INR tests which are taken at other locations. In 2012, 120 000 INR tests were processed at the medical laboratory in CUH.

The total patient enrolment was 162 patients, 132 of whom completed both the AMS and PST arms of the trial. Only patients who completed both arms of trial were included in the final analysis. The mean age of the patients was 58·7 ± 14·3 years. Indications for oral anti-coagulation therapy consisted of prosthetic heart valve – 49 (37·1%), atrial fibrillation – 43 (32·6%), deep vein thrombosis (DVT)/pulmonary embolism (PE) – 29 (22%) and other – 11 (8·3%). Patients withdrew from the trial for the following reasons: warfarin therapy discontinued ($n = 8$), patient found PST stressful ($n = 5$), left the AMS ($n = 5$), issues with internet access ($n = 4$), poor correlation between PST meter and laboratory INR results ($n = 3$), non-anticoagulant-related death ($n = 2$) and difficulty obtaining sample of blood using lancet ($n = 1$).

Pharmacoeconomic analysis

The analysis has a time horizon of 6 months which is the duration of the intervention arm. Discounting of costs or outcomes was not required as the time horizon was <1 year. Base case analysis is from the narrower perspective of the healthcare payer. Base case analysis used mean values determined during the RCT. Resource utilization was over a 6-month time period. The effect measurement was TTR in both the routine care and intervention arms. The duration of the trial was unsuitable for the adequate measurement of patient-orientated outcomes such as death and non-fatal thromboembolic events. However, TTR is a documented marker for haemorrhagic and thrombotic complications.[18] Kaatz reasons that TTR should be the standard quality indicator for anti-coagulant control as there are pragmatic issues affecting the completeness and accuracy of adverse event gathering.[19]

Costs associated with the control and intervention groups are described in Table 1. The cost of processing an INR test at the CUH laboratory had previously been calculated as part of an internal CUH evaluation. Costs of staff were calculated based on expert guidance from staff of CUH, internal CUH data and published HSE salary scales.[20] Patients received a 90-min education and training session from the pharmacist. These were carried out in groups of one to three people; the pharmacist conducted 44 separate sessions.[9] Mean daily time required to manage a group of 80 patients was 23·2 min (±9·5 min standard deviation). Therefore, an estimated 20 h per month would be required for management of 132 patients. A cost of €30 per hour was applied to pharmacist time required for the study. The cost of the POC system was sourced from Roche Diagnostics, the manufacturer of the device used in the RCT.

The cost of warfarin therapy was excluded from both arms as significant differences in usage between groups were not anticipated; furthermore, warfarin is a relatively cheap medication. Referenced unit cost prices are from 2012. Value added tax (VAT) was excluded from study costs based on recommendations for conducting health technology assessments in Ireland.[21]

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Table 1. Costs associated with anticoagulation management

Anticoagulation management service[a]	€
Cost per laboratory INR test	2·00
Medical staff[b,c]	8·08
Nursing[b,d]	62·67
Clerical officer[b]	8·17
Senior medical scientist[b]	9·43
Phlebotomy [b]	52·51
Healthcare assistant[b]	5·11
Patient self-testing group	**€**
Cost per coaguchek strip	3·66
Lancets (200)	12·62
Pharmacist supervision[b]	27·27
Cost of education session per patient	15·00
Coaguchek® XS Meter (purchase cost)	588·00
CoagCare – 6-month license cost	25·00

[a]Mean cost per patient per 6-month period.
[b]Four senior house officer hours and three consultant haematologist hours per week.
[c]One whole time equivalent (WTE) clinical nurse specialist and 2·5 WTE's staff nurse.
[d]Costs calculated based on internal CUH data and expert guidance.

Sensitivity analysis

One-way sensitivity analysis was conducted on all known variables. Standard deviations and confidence intervals were employed where possible. In the absence of any indication of variability, a ±50% variation was applied. Additional evaluations which were inclusive of societal benefits such as travel costs and patient time foregone through attendance at AMS were also included in a supplementary evaluation. An argument for evaluation from a societal perspective can be made as significant costs can be accrued due to patients' requirement to attend an anti-coagulation clinic. Societal benefits were calculated using resource consumption and patient data obtained in the RCT.[9] Cost per kilometre travelled by car was calculated using recommended Irish reimbursement rate for a mid-sized car.[22] Working time sacrificed due to attendance at anti-coagulation clinic was calculated using national average wage per hour (Q3 2013).[23] Leisure time lost through attendance at clinic was valued at 35% of the local average gross wage. This methodology had been used in previously published attempts to calculate cost of attending an anti-coagulation clinic.[2] The cost to the HSE for provision of POC devices to patients was also investigated. Machine costs were spread over a 5-year period using a straight-line depreciation method. This was deemed acceptable as 5 years is recognized as the minimum lifespan of these machines.[24] The year one purchase cost of a CoagChek XS meter was included in this scenario.

RESULTS

Patients achieved a significantly higher TTR during the PST arm in comparison with routine care, (72 ± 19·7% vs. 59 ± 13·5%). Increases in TTR were achieved for both patients who were initially randomized to PST group (16·6%) and AMS group (12·3%). The effect of order of management was non-significant ($P = 0·412$).

There was a substantial difference in the frequency of testing between the trial groups. The PST group tested their INR almost four times more frequently than the AMS group over a 6-month period (Table 2). The mean frequency of testing days for PST was 4·6 days, which was a considerably shorter time period than the 19·6 days between each test in the control group.

The base case cost-effectiveness analysis indicated that on a per patient basis, PST was slightly more expensive than AMS (Table 2). On a per patient basis over a 6-month period, PST resulted in an incremental cost of €59·08 in comparison with routine care. The overall cost of managing a patient through pharmacist-supervized PST for a 6-month period was €226·45. Difference in overall cost was minimal, and PST was the dominant strategy in some scenarios examined during sensitivity analysis, specifically if analysis was conducted from a societal perspective or at the maximum estimate of the cost of AMS staff, as demonstrated in Table 3. Unsurprisingly, the most expensive scenario evaluated was if the full cost of the POC meter was reimbursed by healthcare payer.

DISCUSSION

Based on the results of this study, on a per test basis, PST is marginally more expensive in comparison with centralized laboratory testing. This is similar to the established trend of previous publications.[2,5] However, it does offer additional benefits to the healthcare payer in exchange for this extra cost. It is speculative to determine whether this strategy is cost-effective, as no threshold has previously been suggested for an increase in TTR. However, the relatively small value of the incremental cost increases the probability that a healthcare payer would surmize that it is a worthwhile strategy to finance. The fact that multiple scenarios examined in the sensitivity analysis, including an evaluation from a societal perspective, concluded that PST was the dominant strategy, gives further credence to this prospect.

The cost-effectiveness of PST is dependent on the method of evaluation used, choice of comparator and the setting. As far as the authors are aware, this is the first economic evaluation of a pharmacist-supervized direct-to-patient system. Furthermore, this is the first evaluation of PST that has been undertaken in an Irish population. The strategy evaluated in this paper is favourable on a cost per patient basis in comparison to a number of other PST strategies which have undergone economic evaluation. Claes *et al.* evaluated a similar method which involved a CoaguChek device,

Table 2. Cost-effectiveness of 6 months of patient self-testing (PST) vs. anticoagulation management service (AMS) (usual care)

	Patient self-testing	Anticoagulation management service
Mean % TTR (95% CI)	72 (±2·32%)	59 (±3·36%)
Median % TTR (IQR)	74 (64·6–81)	58·6 (45·5–73·1)
Mean INR tests/ patient ± SD (Range)	41·7 ± 6·6 (24–60)	10·7 ± 5·2 (5–35)
Cost of 6 months of patient management	€226·45	€167·38
Incremental cost of 6 months of PST therapy vs. AMS	€59·08	

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Table 3. One-way sensitivity analysis on incremental cost of 6 months of patient self-testing (PST) therapy vs. anticoagulation management service (AMS)

	€
Testing frequency	
Minimum value 95% CI	34·92
Maximum value 95% CI	88·23
Point of care device reimbursement	
5 year straight-line depreciation	176·68
AMS staff[a]	
Minimum value (15% of workload)	−13·91 (Dominant)[b]
Maximum value (5% of workload)	132·07
Societal perspective	−13·44 (Dominant)[b]
Excluding pharmacist training	44·08

[a]Based on expert guidance, sensitivity analysis of ±50% was applied.
[b]This scenario was both less costly and more effective in comparison with management at AMS. Therefore, PST is dominant over usual care.

dosing software and GP management in Belgian GP practices; however, this method was more expensive and achieved an inferior TTR level to our study. Perhaps the most comprehensive evaluation of PST strategies was a health technology assessment conducted in Canada. This concluded that PST was not cost-effective based on a threshold of €50 000 (CAN) per quality-adjusted life year (QALY). However, when calculated from a societal perspective, PST was determined to be cost saving.[26] Although QALYs attempt to give an overall measurement of the impact of a therapy or intervention on a patient, they can lack sensitivity when used in the comparison of two similar treatment strategies, as is the case with PST and AMS.

Time in therapeutic range is a reliable indicator of the performance of any method of anti-coagulation management and therefore is a suitable effect measurement for this cost-effectiveness analysis. The current study showed a difference of 13% between the means of both groups and a 15·4% difference between the two median values. The Stroke Prevention Using Oral thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III and SPORTIF V studies suggest that the incidence of death, major bleeding and stroke may be halved by a 15% improvement in TTR.[27] Similar increases were obtained during the course of this study.

Significantly, the TTR levels associated with this study were greater than the 70% range which would be considered a good level of control. A retrospective review of 6108 patients with non-valvular atrial fibrillation showed that patients with INR control of 70% of time in range had a significantly reduced risk of stroke.[28]

The cost of managing a patient using PST based on our trial data was determined to be €226 for a 6-month period. In comparison, the net ingredient cost of 6 months of therapy of either of the two NOACs currently licensed for the prophylaxis of thromboembolic events in Ireland is between €456·06 (Dabigatran 150 mg × 60 capsules per month) and €384·66 (Rivaroxaban 20 mg × 28 tablets per month).[29] Previous studies indicate that these are cost-effective in comparison with conventional warfarin management.[30] However, the comparator used in both of these trials was conventional warfarin management, which is associated with reduced TTR levels and overall poorer patient outcomes. No significant effect has been shown between patients treated with dabigatran and those who are treated with warfarin and have TTR levels >65·5%.[31] The management strategy evaluated in this paper has an overall TTR of 72%. Improvements in warfarin control may force a reappraisal of the cost-effectiveness of NOACs.

Although, the increase in testing frequency has been hypothesized as the reason for the observed benefits of PST,[32] it does not offer a comprehensive explanation. Similar testing frequencies in control and intervention groups resulted in better outcomes in the groups using POC monitoring.[33,34]

Patient self-testing is not a suitable strategy for all patients. This is reflected in the reasons given by patients for dropping out of the trial. Thirteen patients did not complete the trial for reasons which could be attributed to difficulties with PST management. Future research should attempt to investigate which patient groups would benefit most from self-testing or self-monitoring strategies. Some studies have suggested focusing on those with mechanical heart valves or those under 55 years of age; however, conclusive evidence is lacking.[35]

Limitations

The limited duration of the RCT restricts the utility of the data as initial costs such as patient training and purchase costs of the POC devices are loaded into a 6-month time period, even though they will have a longer term benefit to the patient who is not captured during this study. The duration and sample size did not allow for a significant level of haemorrhagic and thromboembolic complications to be detected. Optimal management of warfarin therapy in the form of PST has a long-term benefit to the patient in terms of reduced thromboembolic events and deaths.[5] The benefit is not one that is conclusively detectable after 6 months of data collection.

Some of the costs calculated were based on expert guidance and internal hospital data. Workload of AMS staff was based on expert guidance from senior staff in the anti-coagulation clinic at CUH; however, variation of this estimate had the greatest effect on outcome. Wide variations were employed to any assumptions based on expert guidance during sensitivity analysis. Analysis based on microcosting techniques would considerably reduce uncertainty around outcomes. Additionally, there was a self-selective nature to patient recruitment. Therefore, the group studied may not be representative of the actual population. The estimated percentage of patients who are prescribed warfarin for atrial fibrillation was lower in this study compared with national levels.

As with all economic evaluations based on a single RCT, there are considerable issues associated with the generalizability of the results reported. However, this has been partially addressed through the application of a sensitivity analysis.

WHAT IS NEW AND CONCLUSION

PST provides a significant increase in anti-coagulation control for a modest increase in expenditure. This is maintained in all situations evaluated in sensitivity analysis. The associated increase in INR control for a modest increase in expenditure demonstrated in this study provides further evidence that optimally managed warfarin therapy remains a viable strategy for anti-coagulation management. Therefore, pharmacist-supervized patient self-testing should be considered as an alternative to NOACs which are both more expensive and not established.

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J Gallagher was responsible for analysing data from randomized controlled trial and drafted manuscript. S Mc Carthy, N Woods and S Byrne were responsible for designing the research strategy. F Ryan, S O'Shea and S Byrne designed the randomized controlled trial on which economic evaluation was based. F Ryan was responsible for patient management and data collection during original RCT. All authors revised the manuscript and approved the final version of the manuscript. The authors would like to thank staff at the Warfarin Clinic, Directorate of Medicine and Haematology department at CUH for their time and support.

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ORIGINAL RESEARCH ARTICLE

Structured Pharmacist Review of Medication in Older Hospitalised Patients: A Cost-Effectiveness Analysis

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Abstract

Background A recent cluster randomised controlled trial (RCT) conducted in an Irish hospital evaluating a structured pharmacist review of medication (SPRM), supported by computerised clinical decision support software (CDSS), demonstrated positive outcomes in terms of reduction of adverse drug reactions (ADR).

Objective The aim of this study was to examine the cost effectiveness of pharmacists applying an SPRM in conjunction with CDSS to older hospitalised patients compared with usual pharmaceutical care.

Method Cost-effectiveness analysis alongside a cluster RCT. The trial was conducted in a tertiary hospital in the south of Ireland. Patients in the intervention arm ($n = 361$) received a multifactorial intervention consisting of medicines reconciliation, deployment of CDSS and generation of a pharmaceutical care plan. Patients in the control arm ($n = 376$) received usual care from the hospital pharmacy team. Incremental cost effectiveness was examined in terms of costs to the healthcare system and an outcome measure of ADRs during an inpatient hospital stay. Uncertainty in the analysis was explored using a cost-effectiveness acceptability curve (CEAC).

Results On average, the intervention arm was the dominant strategy in terms of cost effectiveness. Compared with usual care (control), the intervention was associated with a decrease of €807 [95 % confidence interval (CI) −3443 to 1829; $p = 0.548$) in mean healthcare cost, and a decrease in the mean number of ADR events per patient of −0.064 (95 % CI −0.135 to 0.008; $p = 0.081$). The probability of the intervention being cost effective at respective threshold values of €0, €250, €500, €750, €1000 and €5000 was 0.707, 0.713, 0.716, 0.718, 0.722 and 0.784, respectively.

Conclusions Based on the evidence presented, SPRM/CDSS is likely to be determined to be cost effective compared with usual pharmaceutical care. However, neither incremental costs nor effects demonstrated a statistically significant difference, therefore the results of this single-site study should be interpreted with caution.

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Key Points

The structured pharmacist review of medication/clinical decision support software (SPRM/CDSS) intervention results in improved clinical outcomes and a reduction in healthcare expenditure on the management of older hospitalised patients.

The SPRM/CDSS intervention is likely to be cost effective compared with usual care, even if the healthcare payer was unwilling to pay any money to prevent an adverse drug reaction.

Addition or realignment of pharmacy staff to implement this programme could have significant clinical and economic benefits to the healthcare system.

1 Introduction

Interventions targeting medication optimisation in older persons have the potential to significantly improve patient outcomes and reduce unnecessary expenditure [1, 2]; therefore, any potential improvements in prescribing and medication use in this expanding group could have a substantial positive impact on resource consumption.

Multiple approaches have been proposed to minimise the prevalence of inappropriate prescribing and preventable adverse events in older patients, including prescriber education initiatives, use of screening tools to highlight inappropriate medications, medication review by health professionals and structured protocols for medication review [3]. A recent clinical trial that incorporated a number of these elements into a structured medication review programme has demonstrated promising clinical outcomes [4].

Medication review in a hospital setting is generally conducted on an ad hoc basis and can vary depending on the experience and ability of the professional conducting the review [5]. The structured medication review implemented by O'Sullivan et al. was designed with the aim of reducing inappropriate prescribing and adverse events in a geriatric population [4]. It is based on the application of a computerised clinical decision support software (CDSS), which incorporates patient data from multiple sources and clinical guidelines [6]. Application of CDSS in a hospital setting is associated with fewer patient complications, lower mortality rates and lower costs [7]; however, a review of the evidence highlighted that CDSS does not appear to reliably prevent adverse drug events (ADEs), and in some instances can have a negative influence on work practices [8].

The evidence-based guidelines included in our unique CDSS system include the widely used STOPP/START (Screening Tool of Older Person's Prescriptions/Screening Tool to Alert doctors to Right Treatment) criteria (version 1) [9]. STOPP/START attempts to optimise pharmacotherapy in older patients by identifying medications that may be inappropriate to use (STOPP) and suggesting medications that patients should be receiving according to current available evidence (START) [10]. A recent cluster randomised controlled trial (RCT) sought to apply a structured pharmacist review of medication (SPRM) that was supported by CDSS. The intervention has demonstrated improvements in terms of adverse drug reactions (ADR) [4] and medication appropriateness measures [11].

Uncertainty still remains around the cost-effectiveness status of medication reviews [12, 13]. Research examining net ingredient costs within health systems is simple to measure and often quoted. These studies simply provide a summary of the overall cost of drugs based on their list prices; however, they do not offer an accurate reflection of changes in patient outcomes. The cost of prescribing, dispensing and monitoring must also be taken into consideration [14]. There is also the potential that the outcome of a medication review will have negative consequences for a patient. Effectiveness of medication reviews can be difficult to evaluate due to the overlapping effects of polypharmacy and the highly complex and transient health status of patients.

Prior to recommending a general adoption of any intervention, investigation of the economic and budgetary impact of this method is a prerequisite. Despite some promising evidence [4, 11], a comprehensive economic evaluation of the implementation of the programme has not yet been conducted. The aim of this study was to perform a cost-effectiveness evaluation of the SPRM/CDSS program based on its application in an RCT in an older population in order to reduce in-hospital ADRs. This is the first economic evaluation of a programme which is based on the application of STOPP/START.

2 Methods

2.1 Structured Pharmacist Review of Medication/Clinical Decision Support Software (SPRM/CDSS) Intervention

Comprehensive details of this trial have been published elsewhere [4]. In summary, the RCT was conducted in an 810-bed teaching hospital in Ireland between June 2011 and June 2012. This trial was cluster-randomised, with

Table 1 Baseline characteristics of patients enrolled in the randomised controlled trial

Variable	Intervention ($n = 361$)	Control ($n = 376$)
Age [years; median (IQR)]	77 (71–83)	78 (72–84)
Male [n (%)]	180 (49.9)	190 (50.5)
Female [n (%)]	181 (50.1)	186 (49.5)
Length of hospital stay [days; median (IQR)]	8 (5–13.5)	9 (5–16)
Hospital mortality rate [n (%)]	17 (4.7)	17 (4.5)

IQR interquartile range

consultants from each speciality represented in each trial arm. Patients were randomised into either an intervention or control group based on the consultant with primary responsibility for their care during their hospital stay. The intervention arm consisted of 361 patients. Patients in the control arm of this study received usual pharmaceutical care ($n = 376$), which consisted of ad hoc pharmaceutical review from a hospital pharmacist employed at the study site. This involved hospital pharmacists performing an unstructured pharmaceutical review with communication of any suggested interventions to the attending medical team via handwritten notes attached to the patient's hospital Kardex. In some cases, medicines reconciliation was also performed. The baseline characteristics of the recruited patients are presented in Table 1. No significant differences existed between the groups in terms of age, sex, functional status, cognitive function or number of medications at entry to the study.

The SPRM/CDSS intervention consisted of four elements, the first of which was direct contact with the patient's community pharmacy and or general practitioner in order to reconcile the patient's medication history from available medical and pharmacy records.

The second element was deployment of the CDSS to review the patient's list of medications in order to identify any drug related problems, such as incorrect drug omission, dosage, frequency and formulation. The CDSS also identified problems with drug appropriateness, non-indication, drug–drug interactions (DDIs), excessive doses for the level of renal or hepatic impairment, potential prescribing omissions as defined by the START criteria [15] and potentially inappropriate prescribing (PIP) as defined by the STOPP [15], Beers [16] and PRISCUS criteria [17]. Potential DDIs in the CDSS were informed using the British National Formulary 61 [18]. The CDSS allowed standardisation of the data collection, medication review and ADR detection process.

Third, the intervention pharmacist then reviewed CDSS output and interpreted which potential interventions were clinically relevant. Clinical relevance was informed by accounting for clinical status, number of prescription drugs and the likely risk:benefit ratio of each recommendation. Finally, a written pharmaceutical care plan was presented to the attending medical team, which decided whether suggested alterations would be implemented.

SPRM/CDSS was applied to patient profiles within 48 h of admission. All patients aged ≥65 years admitted under the care of the medical or surgical services through the emergency department were eligible for inclusion. Additional exclusion criteria included (1) admission to psychiatric services, intensive care unit, and specialist geriatric or clinical pharmacology services; (2) anticipated length of stay (LOS) <48 h; and (3) elective admission.

2.2 Economic Evaluation

This economic evaluation consisted of a trial-based analysis conducted alongside the RCT. The perspective of the healthcare provider [Health Service Executive (HSE)] was adopted with respect to trial-related costs and outcomes. Evidence on resource use and patient health outcomes was collected by the intervention pharmacist during the course of the study and retrospective review of patient medical records. The time horizon for this evaluation was confined to patient discharge or 10-day follow-up, whichever came first; this was informed by average LOS for elderly patients in the Irish hospital system [20]. The average LOS for patients aged 65–74 years is 7.9 days, and 10.4 days for patients aged 75–84 years. The study was not designed to measure the medium/long-term impact of this intervention, and discounting of costs or outcomes was not required due to the limited follow-up period. Statistical analysis was conducted on an intention-to-treat (ITT) basis, in accordance with guidelines for conducting cost-effectiveness analysis alongside cluster RCTs [21]. Missing data were not an issue in this evaluation as follow-up was facilitated by a unique hospital number identifier and confined to a single centre over a short time period.

2.3 Cost Analysis

Multiple cost components were included in the analysis and are described in Table 2 (costs are expressed in Euros (€) using 2012 prices, unless otherwise stated). The primary component was the cost of employing and training a

Table 2 Costs associated with care of patients

Cost component	Unit cost (€)	Description	References
Pharmacist	40.00	Per application of SPRM/CDSS	HSE salary scales [23]
Non-consultant hospital doctor	5.06	Per review of pharmaceutical care plan	HSE salary scales [23]
Senior staff nurse	3.55	Per review of pharmaceutical care plan	HSE salary scales [23]
Inpatient day	850.00	Cost of care per hospital inpatient day	HSE inpatient ready reckoner [24]
Software costs	1000.00	One-off installation of software programme	Investigator estimate
Training costs	2000.00	Training costs of trial pharmacist	Investigator estimate

SPRM structured pharmacist review of medication, *CDSS* clinical decision support software, *HSE* Health Service Executive

pharmacist to implement the programme. We took the mid-point of the HSE pharmacist scale (new entrant) and adjusted according to guidelines for conducting economic evaluation in Ireland [22, 23]. Salary was adjusted for employers' insurance cost, pension payments and general overheads. Based on discussion with the intervention pharmacist, it was agreed that 1 h was an appropriate duration to assign for pharmacist time spent implementing the intervention.

The second component consisted of the associated follow-up time for other healthcare professionals to implement the suggested interventions. Costs associated with physician and nurse review of the pharmaceutical care plan were included. Expert guidance dictated that it would take approximately 5 min for both physicians and nurses to review written communication and approve or reject suggested interventions. The mid-point on the specialist registrar scale was used in cost-analysis, and nursing salary was based on the cost of a senior staff nurse.

The third major component was the cost of a hospital inpatient stay; this cost was obtained from aggregated national data [24]. In general, micro-costing estimates of patient estimates are preferable; however, in the context of this piece of research, a broader cost, such as the diagnosis-related group cost, is a justifiable choice as patients are admitted due to a diverse range of primary indications. The fourth component consisted of the support structures necessary to implement the intervention, including software and training required to implement SPRM/CDSS (accessed from internal trial data).

2.4 Effectiveness Analysis

The primary outcome measure of this RCT was the difference in the proportion of patients in the two groups who experienced a non-trivial ADR during the course of their hospital stay. ADRs were identified by a trained clinical pharmacist and verified by a physician. A comprehensive description of ADR identification and outcomes is provided elsewhere [4].

2.5 Cost-Effectiveness Analysis

Techniques were adopted to account for the effect of clustering and correlation of cost and effect data collected alongside cluster RCTs. Cost-effectiveness analysis was presented in the form of an incremental cost-effectiveness ratio (ICER). An ICER is an additional cost per unit effect; in the case of this study, the cost of preventing an additional non-trivial ADR in hospital. In an economic evaluation, one treatment or method is considered more cost effective than its comparator if it meets one of the following conditions [27]:

1. Less costly and more effective;
2. More costly but more effective, with an ICER that is considered acceptable by decision makers; and
3. less costly and less effective, but the additional cost per unit of effect of its comparator is not considered by decision makers to be worth paying.

While threshold ICER values exist for some generic measures of health [e.g. cost per quality-adjusted life-year (QALY)], acceptable values for cost per ADR prevented have not yet been proposed. In this paper, we examined a number of hypothetical thresholds.

Incremental analysis was undertaken using a multilevel mixed-effect regression model for both cost and effect data. The model was designed to control for treatment arm, age, sex, number of medications at admission and consultant (cluster group). This form of regression analysis is appropriate for normal and non-normal distributional forms of clustered data [28]. Regression for total costs was estimated using multilevel mixed-effects linear regression models, while regression for ADR events used mixed-effect logistic regression models.

The estimated treatment arm effects represent the difference in means for control patients compared with intervention patients, with 95 % confidence intervals (CIs) and p values reported to examine the statistical significance of these coefficients based on standard errors estimated using the mixed command in STATA 13.

Uncertainty in the analysis was addressed by estimating CIs and a cost-effectiveness acceptability curve (CEAC), which link the probability of a treatment being cost effective to a range of potential threshold values (λ) that the health system may be willing to pay for an additional unit of effect [29]. Non-parametric bootstrapping with 1000 replications was conducted on the difference in mean costs and mean ADR events to generate ICER replicates. The ICER replicates were used to generate a CEAC [30]. Analysis was performed using STATA (IBM SPSS Statistics 22; IBM Corporation, Armonk, NY, USA) and Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA). A scenario analysis was performed which varied the time required by all healthcare professionals to complete intervention by ±50 %.

2.6 Guidelines and Ethical Considerations

This manuscript followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines for reporting health economic evaluations [19]. Completed CHEERS checklist describes level of compliance of this manuscript with CHEERS guidelines [see electronic supplementary material (ESM) Table S1], and the original clinical cluster randomised trial conformed to Consolidated Standards of Reporting Trials (CONSORT) guidelines [21]. The Biomedical Ethics Committee (Institutional Review Board) of the University College Cork teaching hospital network approved the trial protocol and the trial was registered with the United States National Institutes of Health (NCT01467128; http://clinicaltrials.gov/show/NCT01467128). Written consent was sought and obtained from all participating patients prior to enrolment in the study.

3 Results

No significant demographic differences were noted between the two treatment arms, and 56 % of patients in usual care received some form of pharmacist review of medication. Demographic analysis is presented in the original RCT paper [4].

SPRM/CDSS strategy was dominant compared with usual pharmaceutical care, showing improved outcomes in terms of ADRs experienced, alongside a reduction in associated costs (see Table 3). The mean cost of caring for an intervention patient during a single admission was €13,250 [standard deviation (SD) €15,530], while the control group showed a mean cost of care of €15,465 (€19,310). Median costs also favoured the intervention arm (€8954) compared with usual care (€10,029). Following the application of a multilevel mixed-effects model in STATA, and accounting for baseline differences across groups, the adjusted incremental difference in costs of −€807 was non-significant.

Similarly, the effectiveness measures favoured the intervention strategy. The odds ratio for experiencing an ADR was 0.655 when comparing SPRM/CDSS with usual care, which related to an adjusted difference in mean number of ADRs of −0.064 (95 % CI −0.135 to 0.008; $p = 0.081$).

As both mean health costs and outcomes scores favoured the intervention arm of the trial, it was unnecessary to calculate an ICER. It can be stated that SPRM/CDSS was dominant to usual care during the course of this RCT; however, as with all attempts to calculate the cost effectiveness of an intervention, there is a degree of uncertainty surrounding this outcome. Even if the healthcare payer was unwilling to pay any money for the prevention of an ADR, the intervention strategy is still likely to be cost effective (probability of being determined cost effective = 0.707). A scenario analysis demonstrated that if healthcare professional time associated with intervention was increased by 50 %, SPRM/CDSS remained the dominant strategy (see ESM Table S2).

A graphical representation of the probability of the intervention being cost effective is given in Fig. 1. The majority of entries are in the south-east quadrant, indicating that the intervention group is likely to be considered cost effective.

The overall cost of applying the intervention to a group of 361 patients was estimated to be approximately €20,000, or €55 per patient. The majority of the SPRM/CDSS intervention costs were associated with the cost of the trial pharmacist's time in conducting the intervention (€40 per patient). LOS in the hospital was responsible for the majority of the cost associated with management in both arms.

4 Discussion

Combining a CDSS with a medication review incorporating STOPP/START is likely to be cost-effective, which is predominantly based on the premise that even at a €0 threshold, the probability of the intervention being cost effective is 0.707. The probability of the intervention being cost-effective increases to 0.759 if a €3000 threshold is applied. The thresholds applied were arbitrary, but when one considers that the mean cost associated with a single ADR event has been estimated at €2250 [31], the threshold values presented in Table 3 are a reasonable measure of what could be considered value for money. Similar increases in the cost of care could be imputed from this study as patients who experienced a suspected ADR had their average LOS increased by 3 days [4].

Table 3 Incremental cost-effectiveness analysis

	Intervention ($n = 361$)	Control ($n = 376$)
Cost analysis		
Total cost (€)		
Mean (SD)	13,250 (15,530)	15,465 (19,310)
Median (IQR)	8954 (5618–14,515)	10,029 (5572–17,830)
Effectiveness analysis		
Total ADRs [*n* (%)]	50 (13.85)	78 (20.74)
ADRs per patient [*n* (%)]		
0	311 (86.15)	298 (79.26)
1	40 (11.08)	66 (17.55)
2	9 (2.49)	12 (3.19)
3	1 (0.28)	0 (0.00)
ADRs per patient [mean (SD)]	0.169 (0.456)	0.242 (0.503)
		Intervention vs. control
Incremental analysis		
Incremental cost		
Total cost		
Difference in mean		−807 (95 % CI −3443 to 1829); $p = 0.548$
Incremental effect		
ADR event		
Odds ratio		0.655 (95 % CI 0.431–0.994); $p = 0.047$
ADR events (*n*)		
Difference in mean		−0.064 (95 % CI −0.135 to 0.008); $p = 0.081$
Incremental cost-effectiveness analysis		
Threshold value (λ) per ADR averted (€)		Probability that intervention is cost effective
0		0.707
250		0.713
500		0.716
750		0.718
1000		0.722
3000		0.759
5000		0.784
10,000		0.833
20,000		0.878
25,000		0.898
50,000		0.918

Reported estimates for incremental differences in costs and effects adjusted to account for baseline differences between groups

Regression for total costs estimated using multilevel mixed-effects linear regression models and controlling for treatment arm, age, sex, number of medications at admission and clustering

Regression for ADR event estimated using mixed-effect logistic regression models and controlling for treatment arm, age, sex, number of medications at admission and clustering

Probabilities for cost effectiveness estimated parametrically using net benefit regression models for analysis at each threshold value

IQR interquartile range, *SD* standard deviation, *ADR* adverse drug reaction, *CI* confidence interval

ICER results are not presented in the regular form of cost per additional unit of health. Our results show that SPRM/CDSS is likely to result in reduced costs and improved health outcomes. If ICER was plotted on ICER plane, it would be located in the 'south-east' quadrant. It is possible to represent this in ICER traditional terms;

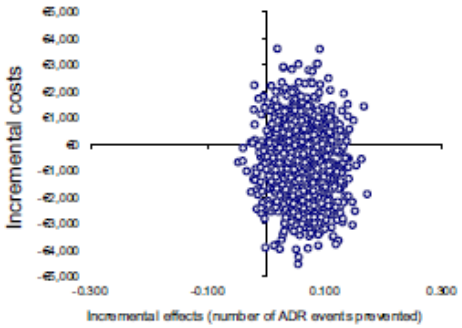


Fig. 1 Representation of the incremental cost-effectiveness ratio of structured pharmaceutical review of medication/clinical decision support system compared with usual care. *ADR* adverse drug reaction

however, it would be a 'negative ICER'. This is ambiguous as a 'negative ICER value' would also be possible with a method of care that would cost more but resulted in reduced health outcomes, i.e. was plotted in the 'north-west' quadrant. When a cost-effectiveness analysis finds that option A is associated with decreased costs and increased health outcomes compared with option B, it is considered more practical to state that option A is dominant compared with option B. Therefore, as stated in our Results section, SPRM/CDSS intervention was dominant compared with usual care in the context of this RCT.

This is the first study to evaluate the economic impact of a novel SPRM/CDSS-based intervention. The CDSS element of the intervention was highly influenced by the application of the STOPP/START criteria. We are unaware of any study that has included the practical application of the STOPP/START criteria as part of a comprehensive cost-effectiveness evaluation. Since their development in 2008, STOPP/ START criteria have become a widely used method of identifying and improving instances of PIP. This study provides further evidence for the adoption of STOPP/ START guidelines as a fundamental part of any healthcare review conducted by a healthcare professional in an older population.

The principal barrier to the application of SPRM/CDSS at a wider level is capacity. This RCT demonstrated that a single pharmacist could recruit three trial patients each day; however, it should be noted that the pharmacist in question was not employed on a full-time basis to apply SPRM/ CDSS interventions to patients. If all older hospitalised patients are to receive this method of care, increased pharmacy staff numbers will be required; however, we believe that this will be a worthwhile investment since healthcare payers will likely be rewarded in the form of substantial cost avoidance from a reduction in ADRs. Previous reviews have concluded that for every €1 invested in clinical pharmacy services, a saving of €4.80 is achieved [32]. Furthermore, a correlation exists between increased clinical pharmacy services/pharmacy staff numbers and reduced mortality [33].

The results of this study are aligned with previous evaluation of clinical pharmacist services. Pharmacist interventions are generally considered to be cost effective [34]; however, a recent Cochrane review declared that it is difficult to make a generalised conclusion on the efficacy of pharmacist interventions due to the heterogeneity in study comparison groups, outcomes and measures evaluated [35]. Moreover, a recent systematic review highlighted issues with the general quality of economic evaluations of pharmacist interventions from a health economic perspective [34]. The present study has implemented recommendations from the CHEERS statement to ensure that this manuscript presents a transparent, high-quality evaluation.

It has been established that conducting economic evaluation based on data from RCTs is a suitable methodology [25]. This approach has dual advantages. First, internal validity is maintained due to the comprehensive nature of data collection during the trial and, second, there is a modest marginal cost associated with collecting required data alongside a trial that is predominantly clinically orientated [25]. While a cost-utility analysis with a health-related outcome measure is recommended as the reference case in Ireland [22], it was not a realistic outcome measure for this study. The population under consideration has multiple comorbidities and often an initially poor health status; therefore, health-related quality of life (HRQoL) is inappropriate in this case [26].

A very similar assessment to our study recently evaluated the Lund Integrated Medicines Management Model (LIMM), an alternative structured protocol designed to optimise drug treatment [36]. A modelled economic evaluation estimating costs and utility loss from medication errors needing medical attention within a 3-month time period was determined to be dominant compared with usual care. Gillespie et al. evaluated a model of unstructured pharmaceutical care in older patients on a hospital ward [37], and reported that the total cost per patient in the intervention group was lower than the control group. Patient outcomes in terms of reduction in hospital visits and emergency department visits were also reported.

Conversely, a similar structured clinical pharmacy service in a Swedish hospital setting was labelled as unlikely to be cost effective [38]. The study generated an ICER of €316,243 per unadjusted QALY, highlighting the effect that a small increase in QALY values can have on the cost-effectiveness status of an intervention or therapy. Reasons hypothesised for the negative verdict on cost effectiveness included the previously mentioned lack of specificity

associated with generic outcome measures, the conduct of the study in a pharmacist-naïve environment with relatively inexperienced pharmacists, and non-attendance of medical rounds by the intervention pharmacist.

It is likely that the intervention acceptance rates in our study were negatively affected by non-attendance of medical rounds by the research pharmacist. Similar intervention methods that included a pharmacist as a member of a multidisciplinary team have demonstrated higher intervention acceptance rates [37, 39]. Other factors that have been proposed as having an influence on the acceptance rate of pharmacist interventions include ward type and pharmacist grade [40].

Methods used to investigate the economic evaluation were appropriate for the type of data available. Multilevel mixed-effect models are a suitable method for estimating the incremental net benefits for a clinical trial of this nature; clustered data can potentially lead to biased results [41]. Normal statistical analyses are generally unsuitable; however, the methods employed for our analysis overcome this issue [28]. These techniques account for both the clustering and correlation of cost and effect data.

There are several limitations to the present cost-effectiveness analysis, predominantly relating to the extrapolation of the findings to routine clinical practice. Training and software costs were not recorded at the time of the event and were solely informed by investigator estimate. It is likely that some costs associated with this intervention were overestimated. For example, the 1-h period allocated to conducting the intervention included the time required to obtain the patient's consent to participate in the intervention. Since minimal time would be required to obtain patient consent for a medication review (if indeed this was in fact considered necessary at all), the time spent with each patient is likely to be less in routine practice than was estimated for this analysis. A time-in-motion study which gathered data on healthcare professional time required to complete the intervention would have reduced uncertainty surrounding this input. In addition, as healthcare professionals become more familiar with the application of the SPRM/CDSS programme, they will be able to apply it more efficiently and come to quicker decisions regarding the relevance of a suggested intervention.

This study is based on the work of one pharmacist in a single centre. Aspects of the intervention that would be variable between settings include the ability of the pharmacist involved and the extent of the uptake of interventions by the associated medical team. The fact that the trial pharmacist was singularly responsible for determining whether an intervention is clinically relevant is a subjective decision. However, there are previous examples of medication optimisation due to the application of STOPP/START and other variations of SPRMs [10, 42].

Furthermore, the single-site nature of the study also increases the potential for crossover learning between healthcare professionals within the hospital environment. Ideally, this study would be conducted on a larger scale involving multiple hospital sites; however, this was not possible due to limited resources available to implement this RCT.

Zermansky and Silcock have suggested a gold-standard method for economic evaluation for medication review [14]. Ideally, from a health service perspective, evaluation should be conducted with a 1-year follow-up period. HRQoL should be the effectiveness measure of choice, facilitating comparison with established societal values. The ideal comprehensive evaluation would be a cost-benefit evaluation over a 5-year period from a societal perspective. It would be valuable to compare a number of alternative medication review strategies using these suggested methods.

5 Conclusions

Based on the information available from the corresponding RCT, a software-supported structured pharmacist intervention is likely to be cost effective even if the healthcare payer is unwilling to assign any additional finance for the prevention of ADRs. However, as the authors are unaware of decisions previously made based on the cost per ADR prevented, there is some degree of uncertainty regarding the cost-effectiveness status of the intervention from a policy perspective. In addition, the difference in incremental costs and effects on an individual basis did not demonstrate statistical significance. To date, medication reviews conducted by pharmacists have primarily received funding at a primary care level [5]. At a minimum, this study further adds to the growing body of evidence that a structured form of medication review and reconciliation incorporating STOPP/START criteria is superior to current medication review based on a pharmacist's individual clinical knowledge.

Author contributions James Gallagher, Stephen Byrne and Suzanne McCarthy wrote the manuscript; James Gallagher, Suzanne McCarthy, Paddy Gillespie and Noel Woods analysed the data; David O'Sullivan, Denis O'Mahony and Stephen Byrne designed the original research trial; and David O'Sullivan and James Gallagher performed the primary research.

Compliance with Ethical Standards

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Conflicts of interest All authors have completed the Unified Competing Interest form at https://www.icmje.org/coi_disclosure.pdf

(available on request from the corresponding author) and declare the following: David O'Sullivan was funded by a Health Research Board of Ireland grant to conduct this research using the STOPP/START criteria. Denis O'Mahony and Stephen Byrne were members of the development and validation team that created the STOPP/START criteria and are named on a patent of computer software that used these criteria. James Gallagher, Suzanne McCarthy, Paddy Gillespie and Noel Woods have no conflicts of interest relevant to the content of this study.

Ethical approval The trial protocol was approved by the Biomedical Ethics Committee (Institutional Review Board) of the University College Cork teaching hospital network.

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10.12 Appendix 12: Policy brief

Clinical Pharmacy Services in Ireland – A solution to our healthcare problems?

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Issue

Clinical pharmacy services have the potential to have a positive impact within the Irish healthcare system. However, due to budgetary constraints in recent years they have been the target of reduced expenditure rather than any . Healthcare systems in other countries have demonstrated greater use of the skills and knowledge of pharmacists.

Policy implications

The established network of community pharmacies and highly experienced and educated pharmacy workforce is a resource which can be utilised to greater effect. Pharmacists in the community pharmacy have the capacity to provide solutions to planned transfer of responsibility from hospitals to community settings.

However, any increase in service provision by pharmacist will likely require additional funding. Traditionally, pharmacy services at both community and hospital level have been an easy place to make savings in times of budgetary crisis.
In the short to medium term all healthcare groups are likely to seek additional funding. Facilitating new pharmacy staff at hospital level or additional clinical pharmacy services in the community will increase pressure coming from other groups of healthcare professional to accede to their requests.

Key findings

Recently, researchers at the School of Pharmacy, University College Cork have conducted a series of economic evaluation of clinical pharmacy services . This research provides a comprehensive analysis of the clinical and economic benefits associated with these services. It also provides an accurate description of the costs associated with the provision of the described services.

- Pharmacist interventions at a major university teaching hospital prevented €710,000 additional spending over a 1 year period. The cost of providing this service was €82,000.
- A pharmacist-led anticoagulation management service in the community provides a clinically significant increase in anticoagulant control for a minimal increase in cost. It will cost the state an additional €60 for six months care using the pharmacist-supervised method in comparison to nurse-led management in a hospital setting. Greater anticoagulation control results in a reduction in strokes and mortality. Implementation of this service would enable transfer of patient care from an outpatient hospital setting to a local community pharmacy.
- A structured pharmacist review of medication in older hospitalised patients was shown to result in better patient outcomes at a decreased cost to the state.
- Pharmacist vaccination services averted a total of 848 influenza cases across all age groups during the 2013/2014 influenza season. Due to receipt of vaccination in a pharmacy setting, 444 influenza-related GP visits were prevented. In terms of more serious influenza-associated events, 11 hospitalisations and five influenza-related deaths were averted. Costs averted were approximately €305,000.

Recommendations

Short term

- Employment of chief pharmacist who will become an integral part of the HSE senior leadership team.
- Engagement with HPAI / IPU representatives to development a 5 year framework agreement outlining plans for expenditure and service development. This will facilitate improved pharmacy service delivery and maximise patient health outcomes.
- Explore budgetary capacity to employ a number of pharmacy specialist positions at hospital level to facilitate medicines optimisation for targeted complex patient groups (e.g. geriatric patients).
- Increase funding of community pharmacy vaccination scheme to support additional at-risk groups for influenza vaccination.
- Support pilot schemes for pharmacist-led management of anti-coagulation in rural areas. Provide funding for scheme to run for 3 years in order for patient outcomes under this form of management to be adequately assessed.

Long term

- Working in conjunction with IPU and the Schools of Pharmacy and within framework agreements, transform community pharmacies from “retail” orientated to the established first line choice of medicine and health management in a community setting. This will be a long term goal and one likely to necessitate repeated framework agreements in order to establish, implement and revise clinical pharmacy services in the community.

Further reading

Gallagher J., Economic evaluations of clinical pharmacy services in Ireland, PhD Thesis. https://cora.ucc.ie/handle/10468/140