

**The Role of Community Pharmacists in Disease Prevention:
A Study of the Delivery of Clinical Pharmacy Services in
Community Pharmacy in Ireland**

A thesis submitted for the degree of Doctor in Philosophy

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2018

Declaration

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August 2018

Acknowledgements

I wish to thank the following people for their support during my studies:

- My supervisor in Trinity College Dublin, Associate Professor Sheila Ryder, for her guidance and advice over the course of my studies; the time and effort dedicated to supporting me in my work is much appreciated
- The INCA research team in the Royal College of Surgeon's in Ireland, Clinical Research Centre, Beaumont hospital, in particular Professor Richard Costello and Elaine McHale for their guidance, instruction and for introducing the INCA study to me; thanks also to Garrett Greene, Fiona Boland and Breda Cushen for their support with elements of the statistical analysis
- The INCA research team in Trinity College Dublin for their support with technical aspects of the INCA device
- Vitalograph Ireland for supply of the INCA devices
- Glaxo Smith Kline, Ireland for the supply of Seretide Diskus inhalers
- Mary Rose Burke for her support in facilitating me to undertake this PhD and for her leadership and vision in relation to the development of the community pharmacy profession in Ireland
- My colleagues in Boots Ireland who have supported me over the last four years; my line managers Catriona Bradley, Liz Kerr, Steven Maxwell and Caoimhe McAuley; my Pharmacy Team colleagues Clare, Caroline and Dan and Gillian and the marketing team for supporting engagement with pharmacy services in Boots Ireland.
- A special thank you to my trusted colleague Mairead O'Grady for her collaboration on a number of clinical pharmacy services in Boots Ireland; her support and feedback through the years has been invaluable
- The pharmacists and pharmacy teams who deliver the clinical pharmacy services mentioned in this report and the patients who agree to participate in the research
- My family, especially my parents John and Mary for the opportunities and support they have provided to me and my husband Conor for his encouragement, support and patience.

The project is part funded by a research grant from the Health Research Board.

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Abbreviations

ABPM	Ambulatory Blood Pressure Monitoring
AF	Atrial Fibrillation
BP	Blood Pressure
CO	Carbon Monoxide
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CRF	Consultation Record Form
DBP	diastolic blood pressure
ECG	Electrocardiography
ESC	European Society of Cardiology
FTND	Fagerstrom Test for Nicotine Dependence
GP	General Practitioner
HBPM	Home Blood Pressure Monitoring
IPU	Irish Pharmacy Union
MTM	Medication Therapy Management
NRT	Nicotine Replacement Therapy
PSI	The Pharmaceutical Society of Ireland
SBP	Systolic Blood Pressure
SmPC	Summary of Product Characteristics
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
WCH	White Coat Hypertension
WHO	World Health Organisation

Summary

Aims

The overall aim of this research was to explore the role of the community pharmacist in disease prevention by evaluating the delivery of a number of clinical pharmacy services in the community pharmacy setting in Ireland.

Methods

A combination of qualitative and quantitative methodologies was used to explore the role of community pharmacists in disease prevention through the delivery of clinical pharmacy services. A literature review was carried out to identify work which had already been published in this area. An observational design was employed to review the delivery of a smoking cessation intervention and an ambulatory blood pressure monitoring service. The role of community pharmacists in supporting adherence to inhaler medication in patients with asthma and/or chronic obstructive pulmonary disease was assessed via a cluster randomised study design.

Results

The smoking cessation initiative was successful in supporting patients with a quit attempt and a 12-week carbon monoxide verified abstinence rate of 5.52% was observed. The ambulatory blood pressure monitoring service facilitated the detection of both hypertension and pulse patterns potentially indicative of atrial fibrillation with prevalence estimates observed broadly in line with previous estimates in primary care in Ireland. Significant differences in clinical and humanistic outcomes between intervention and usual care participants were observed in the inhaler adherence intervention as was a trend towards improved inhaler adherence, technique mastery and symptom control amongst intervention participants.

Conclusions

This research shows that delivery of clinical pharmacy services in the community pharmacy setting in Ireland is feasible. The interventions described facilitated health behaviour change to support primary disease prevention, detection of both hypertension and pulse patterns indicative of atrial fibrillation as a secondary prevention measure and improvements in medication usage in patients with respiratory disease to support tertiary disease prevention. The services described represent an expansion of the role of the community pharmacist within the Irish healthcare system.

Publications

O'Dwyer SM, Mac Hale E, Sulaiman I, Holmes M, Hughes C, D'Arcy S, Rapcan V, Taylor T, Boland F, Bosnic-Anticevich S, Reilly R, Ryder SA, Costello RW. The effect of providing feedback on inhaler technique and adherence from an electronic audio recording device, INCA™, in a community pharmacy setting: study protocol for a randomised, parallel-group, multi-centre controlled trial. *Trials*. 2016; 17: 226.

Sulaiman I, Sehult J, Mac Hale E, Boland F, O'Dwyer SM, Rapcan V, D'Arcy S, Cushen B, Mokoka M, Killane I, Ryder SA, Reilly RB, Costello RW. A Method to Calculate Adherence to Inhaled Therapy that Reflects the Changes in Clinical Features of Asthma. *Ann Am Thorac Soc*. 2016 Nov; 13(11):1894-1903.

O'Dwyer SM, MacHale E, Costello RW, Ryder SA. Use of a novel device to assess inhaler adherence in the primary care setting. Oral presentation: 7th All Ireland Pharmacy Healthcare Conference. Dundalk, Ireland; January 2015.

O'Dwyer, SM, Rossi K, O'Grady M, Henman MC, Ryder SA. Ambulatory Blood Pressure Monitoring as a Community Pharmacy Service. Poster presentation: Faculty of Health Sciences Research Day, Trinity College Dublin; September 2016.

O'Dwyer SM, O'Grady M, Ryder SA. Ambulatory Blood Pressure Monitoring as a Community Pharmacy Service. Accepted for oral presentation: 8th All Ireland Pharmacy Healthcare Conference. Dundalk, Ireland; October 2017.

Intended Publications

O'Dwyer SM, Mac Hale E, Matshediso MC, Greene G, Cushen B, Sulaiman I, Boland F, Bosnic-Anticevich S, Reilly RB, Taylor T, Ryder SA, Costello RW. Personalised biofeedback on inhaler adherence and technique by community pharmacists, a randomised clinical trial. *Submission process underway*.

O'Dwyer SM, O'Grady M, Ryder SA. Ambulatory blood pressure monitoring in the community pharmacy setting. *Paper for submission in draft stage*.

Chapter 1: Introduction to the thesis

1.1 INTRODUCTION

The traditional model of community pharmacy centres on the dispensing of medication to patients on foot of a written prescription from a doctor. Screening for and intercepting medication errors as well as providing information on the safe and efficacious use of medicines, both prescribed and supplied over the counter (without the need for a prescription), is the norm [1]. Increasingly pharmacists in the community setting are expanding their professional role beyond that of a supplier of medications to one which involves the provision of services for the benefit of patients and the health system as a whole [2]. They are taking a greater responsibility for improving outcomes associated with medicines use and are evolving their practice to provide a greater range of advanced clinical pharmacy services [3]. This is true of pharmacy both worldwide and in the Republic of Ireland. However varying levels of involvement with advanced pharmacy service provision have been reported in this jurisdiction [1, 4].

This thesis sets out to review the delivery of three clinical pharmacy services designed to improve patient outcomes in the areas of primary, secondary and tertiary disease prevention. This chapter clarifies what is meant by the terms disease prevention and clinical pharmacy services. It also provides some context as to the care setting in which the three pharmacy services are delivered; namely community pharmacy in the Republic of Ireland (which will be referred to as Ireland throughout).

1.2 BACKGROUND

1.2.1 Disease Prevention

Medicine is defined as the science of prevention, detection and treatment of disease [5]. Within the preventive strand, the goals of medicine and healthcare more generally can be broadly categorised into activities concerned with primary, secondary and tertiary prevention of disease. The aim of primary prevention is to reduce the incidence of a disease within the population and it involves interventions that are applied before there is any evidence of disease [6]. Examples include vaccination to offer protection against a disease agent and behavioural change interventions such as smoking cessation which aim to reduce exposure to risk factors that cause disease. Secondary prevention involves the early detection of disease in the asymptomatic stage to allow for interventions which can slow or stop progression [5]. Examples include screening for previously undetected disease and the administration of preventive drug therapies. Tertiary

prevention is concerned with slowing the progression of established disease, reducing the impact of complications [5]. Provision of cardiac rehabilitation post myocardial infarction and promotion of adherence to medications for chronic disease are examples of tertiary prevention initiatives.

In Ireland national health policy is focussed on keeping people well [7] and where illness occurs treating people in the most appropriate setting for their needs and as close to their home as possible [8]. Life expectancy in Ireland is increasing as is the prevalence of chronic disease and both of these trends will place significant burdens on the healthcare system into the future [9]. Healthy Ireland is a national framework for action on tackling common risk factors for disease at a population level in order to improve the health and wellbeing of all citizens [7]. It encourages cross sectoral participation and collaboration at national and local level focussed on increasing the proportion of people who are healthy at all stages of life [7]. Development of policies relating to the primary prevention aims of the Healthy Ireland framework are a core function of the Health and Wellbeing Division of the Health Service Executive (HSE) [10], the national body responsible for the provision of all of Ireland's public health services in hospitals and communities nationwide [11]. Priorities include increasing the level of physical activity Irish people engage in [12], encouraging uptake of healthier diets to reduce levels of obesity [13], reducing the level of alcohol [14] and tobacco use [15] and prevention of disease through vaccination [16].

Early detection of disease is supported through the work of the National Screening Service who provide screening for eligible persons (free at the point of access) as part of their national breast, cervical and colorectal cancer screening programmes [17]. It is also a key priority outlined in a number of the national disease specific strategies such as the National Cardiovascular Health Policy [18] and the National Cancer Strategy [19]. Effective management of chronic diseases such as asthma, chronic obstructive pulmonary disease (COPD) and heart failure, is being addressed via the development and implementation of a number of national clinical programmes [20]. The focus of these programmes, co-ordinated by the Clinical Strategy and Programmes Division of the HSE, is on developing standardised care pathways, clinical guidelines and models of care for the patient journey [21]. Doctors, nurses, allied health professionals and hospital managers with expertise in a particular clinical area work together to develop the individual programmes and work is now underway to re-structure the individual chronic disease programmes into an integrated care programme - "Prevention and Management of Chronic Disease" [22].

Within primary care it is envisaged that care will be delivered via a network of primary care teams comprising general practitioners, nurses, speech and language therapists, occupational therapists, physiotherapists, social workers, health care assistants, home helps, managers and administrative staff [23]. Such teams will be supported by a network of allied health care professionals as required. Pharmacists are mentioned as potential members of the primary care network in the Department of Health and Children's 2001 healthcare reform strategy [24] and again in the 2010 Joint Oireachtas Committee (on Health and Children)'s Report on Primary Medical Care in the Community [25]. However, their absence from the vision for primary care as outlined in the Department of Health's Future Health strategy of 2012 [23] is both notable and disappointing. It is the assertion of the author that community pharmacists, like other members of the healthcare team, have a valuable role to play in disease prevention and management and this thesis sets out to explore this role in more detail.

1.2.2 Community Pharmacy practice

1.2.2.1 International Context

Community pharmacies represent a primary healthcare resource that is both accessible and convenient. A recent survey of 69 countries and territories reported over 1.5 million community pharmacies serving a population of 5,549 million (75% of the world's population) [26]. Globally the median number of citizens served by a community pharmacy is 4,182 but this varies widely with community pharmacies in lower income countries serving much larger populations and those in higher income countries typically serving between 2,000 and 8,000 persons [26]. The regulatory systems, health policies and remuneration systems vary between countries but commonalities in core functions of the community pharmacist can be observed. 85% of countries surveyed (n=63) state that community pharmacists are involved in medication dispensing and counselling, 81% (n=60) in pharmacovigilance and 80% (n=59) in compounding [26].

It has been suggested that despite accessibility, educational attainment, training and access to the community, pharmacists are a remarkably underutilised resource [27, 28]. In a joint statement on Good Pharmacy Practice (2) the World Health Organisation (WHO) and the International Pharmaceutical Federation (FIP) have outlined a number of key areas where pharmacists can expand their role for the benefit of the patient and health service. These include "traditional" functions such as the supply of medications as well as newer roles such as

administration of vaccines, medication therapy management and engagement in preventive care activities that promote public health and prevent disease[3]. The profession has responded to this call for professional evolution and a number of national pharmacy organisations have outlined their vision for pharmacy practice development into the future [4, 27, 29-31].

1.2.2.2 Community pharmacy practice in the Republic of Ireland

The network of 1,843 [32] community pharmacies in Ireland services more than 10 million visits/consultations per annum [33]. With the average community pharmacy open 50% longer than General Practitioner (GP) clinics and with no appointments generally necessary to avail of a consultation, there are more visits to Irish community pharmacies on a monthly basis than any other element of the primary health care service [33]. As a consequence it is estimated that up to three quarters of the adult population use Irish community pharmacies at least once a month [33], although it must be acknowledged that some of these visits may not be health related.

Ireland has a higher number of pharmacies per 10,000 population (3.75) than other developed nations such as the UK (2.21/10,000), the USA (1.01/10,000) and Australia (2.31/10,000) [34]. Despite this there is a notably lower number of pharmacists per community pharmacy when comparing Ireland (2.9 pharmacists/pharmacy) to countries such as Australia (5.3 pharmacists /pharmacy) and the USA (4.3 pharmacists/pharmacy) [35].

A modern regulatory system for the profession was introduced with the Pharmacy Act of 2007 [36]. Standards for community pharmacies include the requirement for all pharmacies to be registered with the Pharmaceutical Society of Ireland (PSI) [37] and to meet legislative criteria relating to the sourcing and supply of medication, the certification of staff and the availability of consultation rooms for private patient counselling [38]. Community pharmacies in Ireland are subject to audit and inspection by the PSI and pharmacists operate in accordance with a statutory code of conduct, are held accountable for their practice under the PSI fitness to practice procedures and undertake mandatory continuing professional development [35].

The identification of the need for new services to meet patients' needs as well as planning for and implementing same is a core competency for pharmacists in Ireland [39]. The vision for an expanded role for the community pharmacist into the future is laid out in the PSI's 2016 report entitled "Future Pharmacy Practice in Ireland: Meeting Patients' Needs" [35].

1.2.3 Clinical pharmacy services

1.2.3.1 Definition of clinical pharmacy services

Many terms exist in the literature relating to advanced clinical pharmacy services. Terms such as professional pharmacy services [40-42], clinical pharmacy services [43, 44], medication therapy management [45, 46] and cognitive services [47-49] (defined as “*those services or functions which require professional knowledge and skills beyond the ones required for the dispensing of a prescription medication*”[50]) are commonplace.

Underpinning all such service provision is the concept of pharmaceutical care first described in the 1970s [51] and most commonly cited as the Hepler and Strand definition:

“The responsible provision of drug therapy for the purpose of achieving definite outcomes which improve the patient’s quality of life”[52].

This definition has been amended and updated by various authors [53, 54] and organisations[55-57] over the years with the Pharmaceutical Care Network Europe (PCNE) recently adopting a new definition:

“Pharmaceutical Care is the pharmacist’s contribution to the care of individuals in order to optimise medicines use and improve health outcomes” [58].

For the purposes of this thesis the term “advanced clinical pharmacy services” will be utilised to reflect the advancement of the scope of community pharmacy service provision beyond that of medication distribution to a more patient-centred model focussed on the improvement of clinical outcomes for individual patients and the population as a whole.

1.2.3.2 International Context

As community pharmacists expand their professional scope of practice a range of different clinical pharmacy services are starting to be provided worldwide. Examples include health promotion interventions such as smoking cessation programmes, screening services designed to support disease detection and medication management programmes that aim to identify drug related problems and support adherence to prescribed medication as appropriate. As different countries have different health system structures, different patient populations with different health needs and different systems for pharmacist education and regulation pharmacy services have developed differently across different jurisdictions [59].

Internationally, engagement with advanced services is increasing with more than half of countries recently surveyed (number of countries survey = 69) reporting involvement with services such as medication usage review and measuring of clinical parameters such as blood pressure, blood sugar and body mass index [26]. Strong integration of such services into the national health system has yet to be achieved with only 12% of community pharmacy services covered by public or private health insurance [26].

Evidence as to the arrangements for remuneration of clinical pharmacy services in a region can give insights into how well embedded clinical pharmacy services are in the health system. A 2014 systematic review of remunerated clinical pharmacy services identified sixty programmes across Australia, Canada, Europe, New Zealand and the United States [43]. This review found that the majority (73%) of services were funded by government agencies with the remainder funded by private insurance plans[43]. All but one third party funded programmes was provided by community pharmacists based in the United States [43].

1.2.3.3 Clinical pharmacy services in Irish community pharmacy

The development and delivery of advanced services in the community pharmacy setting in Ireland is a relatively recent phenomenon. Engagement with national health promotion initiatives, co-ordinated by the Irish Pharmacy Union (IPU) in partnership with the HSE and the Department of Health, and primarily involving the display of posters and the circulation of information leaflets, is a common phenomenon. Some recent campaigns include the “Save Your Breath” COPD awareness campaign [60] and the “Ask your pharmacist about sexual health advice” campaign [61].

Provision of screening services such as blood pressure assessment is more ad hoc with little national co-ordination and services typically being provided on a more informal basis. The PSI conducted a baseline survey of the services available in community pharmacy and found that 47.5% of pharmacies had blood pressure screening facilities with 56.8% reporting that they had weight/height/Body Mass Index (BMI) facilities on site. However, these data were collected in 2011 and are likely to be somewhat out of date. Examples of community pharmacist involvement in anticoagulation management, cholesterol measurement, 24-hour blood pressure monitoring and medicines use reviews have been reported [62] and there has been strong engagement with the national seasonal influenza campaign whereby pharmacist have been facilitated, by way of national legislation [63], to administer seasonal influenza vaccinations in

the community pharmacy setting. This initiative has proven very successful with pharmacist administered flu vaccination now accounting for 10% of total influenza immunisation nationally [35]. Strong patient satisfaction with community pharmacist led clinical services has been reported [62, 64, 65] and community pharmacies are seen as a good place to make more health services available [66].

In Ireland, there is no system of universal access to health care which is free at the point of delivery. Free healthcare is provided by means of a “Medical Card” to a proportion of the population based on financial need, age (under 6 or over 70) or because of certain unique circumstances (*e.g.* children under 18 with a cancer diagnosis or people who contracted Hepatitis C or human immunodeficiency virus (HIV) from the use of human immunoglobulin-anti D blood products) [67]. Some patients with specified long term medical conditions (*e.g.* cerebral palsy, diabetes mellitus, epilepsy) are entitled to get drugs, medicines, and medical and surgical appliances directly related to the treatment of their illness, free of charge under a scheme known as the Long Term Illness scheme [68].

1.66m people (34.9% of the Irish population; 1.66m/4.76m) were in possession of a valid medical card in March 2017 with an additional 0.48m (10.1% of the population) having an entitlement to free GP care (“GP Visit Card”) but having to pay for the remainder of their medical expenses such as medication costs [69]. 0.14m people (2.9% of the population) have an entitlement to free medication under the Long-Term Illness scheme [70]. Over half of the population thus have no access to subsidised healthcare and any such expenses are covered privately. Some people take out private health insurance to fund future potential costs and as of December 2016 this number stood at 2.15m (45% of the population). With the bulk of insurance cover focussed on secondary care costs such as hospital stays and consultant fees very few provisions have been made for primary care. As a result, the structure of funding for clinical pharmacy services is different to other international models such as the American model of health insurance funding or the British model of funding through the National Health Service, with the majority of services initially introduced as privately funded services whereby the pharmacies delivering the service either absorb the cost of the service or charge a fee to patients when they avail of the service.

Some progress has been made towards a model of public funding for pharmacist delivered clinical services outside of those classed as core services (dispensing, screening for medication errors and the provision of advice on the safe and rational use of medicines either prescribed or bought over the counter). Irish pharmacists have been funded for the provision of a methadone

substitution service in the community since 1998 with the introduction of the Methadone Treatment Protocol. This protocol has expanded in recent years to also allow for a variety of structured supervision programmes for opioid dependent patients to be delivered in the community pharmacy setting under the Opioid Treatment Protocol [71]. Pharmacists are also funded for the provision of needle exchange services in certain locations throughout Ireland as part of the Pharmacy Needle Exchange Programme [72]. Since 2011 pharmacists have been involved in the national seasonal influenza programme [73] and immunisation pharmacists are currently being provided with free flu vaccines for the vaccination of eligible at-risk patients as well as being paid a fee of €15 for each seasonal influenza vaccine administered to an at-risk patient with medical card eligibility [74]. Most recently community pharmacists have been approved for funding of an emergency contraception service which is free at the point of access to women with medical card eligibility [75]. Emergency contraception services in community pharmacy have been provided on a private payment basis since 2011 [76] .

1.3 AIMS AND OBJECTIVES

Whilst the international evidence base is growing there is little or no published data on the implementation or delivery of advanced clinical pharmacy services in Ireland; hence the need for the current research. The aim of this thesis was to evaluate the delivery of a number of clinical pharmacy services in the community pharmacy setting. The effects of the interventions on relevant patient outcomes were the primary focus of the research.

The following objectives were identified:

- To explore current clinical pharmacy service provision in the community pharmacy setting;
- To describe the types of clinical pharmacy services being delivered;
- To review the delivery of three discrete clinical pharmacy services provided in a chain of community pharmacies in Ireland;
- To identify any recommendations for future service delivery within community pharmacy.

1.4 STRUCTURE OF THE THESIS

This research aims to evaluate a number of clinical pharmacy services. Services which impact on all stages of a patient’s health journey from health promotion through screening, diagnosis, medication management and administration will be reviewed with the objective of expanding the evidence base for such service provision in the community pharmacy setting. Considering that disease prevention can be broken down into three main areas, namely primary, secondary and tertiary disease prevention, the themes of the research will focus on the analysis of services in each of these three areas. An overview of the thesis structure is provided in Figure 1.1.

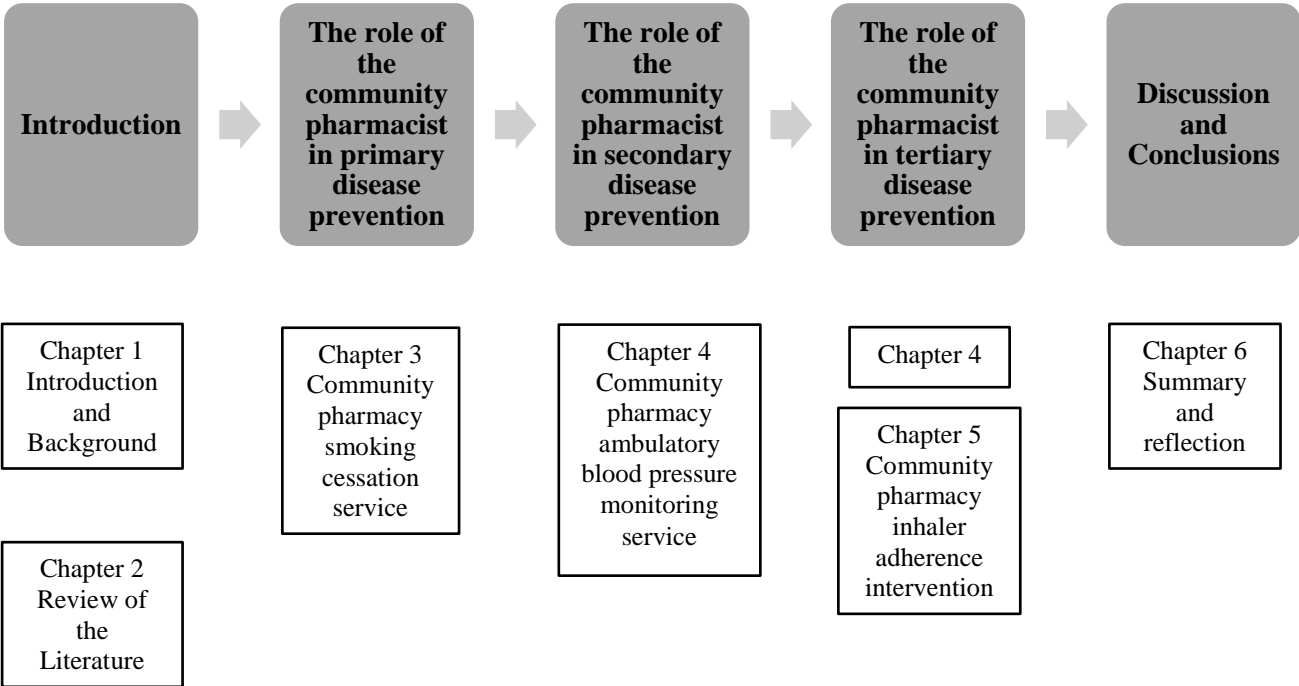


Figure 1-1: Structure of the thesis

Chapter 2: Review of the Literature

2.1 INTRODUCTION TO THE CHAPTER

Community pharmacy is in a state of flux, with pharmacists working to expand their scope of activity beyond traditional dispensing activities [77]. Much of this expanded scope of practice has been defined by the term “pharmaceutical care” [52]. Other terminology used to describe the types of expanded services delivered by community pharmacists include “clinical pharmacy services” [43, 44], “professional pharmacy services” [40-42] and “cognitive services” [48-50, 78].

Clinical pharmacy has been defined as “*a health science discipline in which pharmacists provide patient care that optimizes medication therapy and promotes health, wellness, and disease prevention*”. It embraces the philosophy of pharmaceutical care and is concerned with ensuring optimal patient outcomes [79, 80]. Pharmaceutical care practitioners are responsible for achieving definite outcomes that improve a patient’s quality of life [52] and clinical pharmacists have a responsibility to generate new knowledge that advances health and quality of life [80].

This chapter describes a literature review conducted to identify services provided in the community pharmacy setting that could be categorised as advanced clinical pharmacy services (*i.e.* services other than traditional medication dispensing, supply and counselling) and that report on relevant health outcomes for patients accessing those services.

2.2 OBJECTIVES

2.2.1 Primary objective

The aim of this review was to identify studies reporting on services that were described as advanced clinical pharmacy services and that identify patient outcomes resulting from the delivery of such advanced services in the community pharmacy setting.

2.2.2 Secondary objectives

The secondary objectives were as follows:

- To categorise the studies according to the type of intervention delivered;
- To describe the patient outcomes reported.

2.3 METHODS

2.3.1 Criteria for considering studies

2.3.1.1 Types of studies

In line with the Cochrane Effective Practice and Organisation of Care (EPOC) group recommendations [81] the following study types were included: randomised controlled trials, cluster randomised trials, non-randomised controlled trials, controlled before-after (CBA) studies and interrupted time series (ITS) studies. A decision was made to also include uncontrolled before-after studies and cross sectional studies even though this is outside of the recommendations of the EPOC group [81]. As the area of clinical pharmacy services in the community pharmacy setting is relatively new it was expected that a significant number of studies may be reported as uncontrolled before-after studies or cross-sectional studies. Additionally, the focus of the literature review was to identify the types of clinical pharmacy services delivered in the community pharmacy setting and not necessarily to report on their quality. Publication status of the study (i.e. whether available as a paper or abstract) was not a barrier to inclusion.

2.3.1.2 Types of participants

Participants were defined as any person/group of persons who received a clinical pharmacy service in the community pharmacy setting. Studies including participants who received a clinical pharmacy service in another setting (e.g. hospital, out-patient clinic, ambulatory care setting, in their own home) were excluded. Where studies had mixed settings, they were only included if the community pharmacy subset was analysed independently.

2.3.1.3 Types of interventions

Studies were included if they described the provision of a clinical pharmacy service which went beyond the scope of the traditional pharmacy service, namely the sale, supply and provision of counselling on medicines. Clinical pharmacy services were considered to be structured services, provided to an individual or group of individuals with the aim of maintaining or improving their health. They could be delivered by a pharmacist or another member of the pharmacy team (e.g. pharmacy intern, technician, health care advisor) provided they were a regular member of the pharmacy team working under the direct supervision of the pharmacist. Interventions delivered in the community pharmacy setting by other health care professionals such as nurses or dieticians were excluded as were interventions that did not involve active interaction between pharmacy staff and their patients such as the display of posters/leaflets in the pharmacy.

Interventions designed to optimise the use of medication and provided in a structured way (as opposed to standard counselling at the time of dispensing/supply) were included provided they were delivered to the patient prescribed/taking the medication. As a result, interventions targeted at other health care professionals such as general practitioners and nurses were excluded. Studies reporting the design and development of a service but not reporting on health outcomes for patients accessing the service were excluded, as were those which only focussed on assessing the views of patients, pharmacists or other health care professionals on the service in question. Economic analyses were included if they reported on specific health outcomes. Systematic reviews were excluded.

2.3.2 Literature search

The search strategy was purposely designed to be broad in scope in order to identify the various different types of expanded services conducted in community pharmacy setting. Whilst I am familiar with a number of different advanced clinical pharmacy services being provided in this setting, the intent of the search was to understand what studies would be retrieved when searching for interventions described as advanced clinical pharmacy services

An objective of the review was to classify community pharmacy services into those relating to primary, secondary or tertiary disease prevention activities, a preliminary review of the literature identified that these terms were not commonly used to describe such services. As such a decision was made to conduct a broad search excluding these terms and to classify retrieved articles thereafter.

The following databases were electronically searched for primary studies:

- EMBASE (via OVID), 1967- Dec 15th 2016
- International Pharmaceutical Abstracts, 1970 - Dec 15th 2016
- Web of Science (Core Collection), 1945 - Dec 15th 2016

A draft search strategy was created and tested by screening selected citations for relevance. Studies were limited to the English language.

The final search strategy comprised search terms related to:

a) The setting

(community NEAR/4 pharmac*):ab,ti OR (retail NEAR/4 pharmac*):ab,ti OR 'community pharmacy/exp' OR 'community pharmacy'

b) The intervention

'professional' NEAR/4 service* OR 'pharmacy' NEAR/4 service* OR cognitive NEAR/4 service* OR clinical NEAR/4 service* OR pharmaceutical NEAR/4 service* OR 'pharmaceutical care'/exp' OR 'pharmaceutical care'

c) The study design

'randomized controlled trial' (topic)' OR 'randomized controlled trial' (topic)' OR random\$:ab,ti OR ['controlled study'/exp OR 'controlled study'] OR ['cluster analysis'/exp OR 'cluster analysis'] OR ['controlled study'/exp/mj OR 'controlled study'/mj] OR ['cluster analysis'/exp/mj OR 'cluster analysis'/mj] OR [pre AND test OR pretest OR post AND test OR posttest] OR [pre:ab,ti AND test:ab,ti OR pretest:ab,ti OR post:ab,ti AND test:ab,ti OR posttest:ab,ti] OR 'time series analysis'/mj OR ['time series analysis'/exp OR 'time series analysis'] OR (controlled NEAR/4 trial):ab,ti OR (observational NEAR/4 trial):ab,ti OR ['observational study'/exp OR 'observational study'] OR ['observational study'/exp/mj OR 'observational study'/mj] OR 'intervention study':ab,ti OR ['intervention study'/exp OR 'intervention study'] OR ['intervention study'/exp/mj OR 'intervention study'/mj]

Appendix 1 details the full search strategy.

2.3.3 Data collection and analysis

The results of each study were imported into the EndNote reference management software (EndNote X7.5, Thomson Reuters, 2016). Duplicates were removed and the titles and abstracts were screened for relevance. Where a decision on inclusion could not be made on the basis of the abstract the full text was obtained and the citation was forwarded for a more comprehensive

review in a second round of screening. For any study excluded, reasons were recorded. Relevant data from included studies were extracted into a table that included the following items: citation, title, year of publication, country, study design, intervention type, disease state, participant numbers and summary of main outcomes. Where full text articles could not be retrieved from available databases efforts were made to contact authors to obtain the full text.

2.4 RESULTS

2.4.1 Study selection

Of 1,114 potentially relevant records initially retrieved, 876 remained after duplicates were removed. 603 were excluded after screening title/abstract and a further 143 were excluded after full text analysis. 130 articles were therefore included. A flow diagram of the search process is included in Figure 2.1.

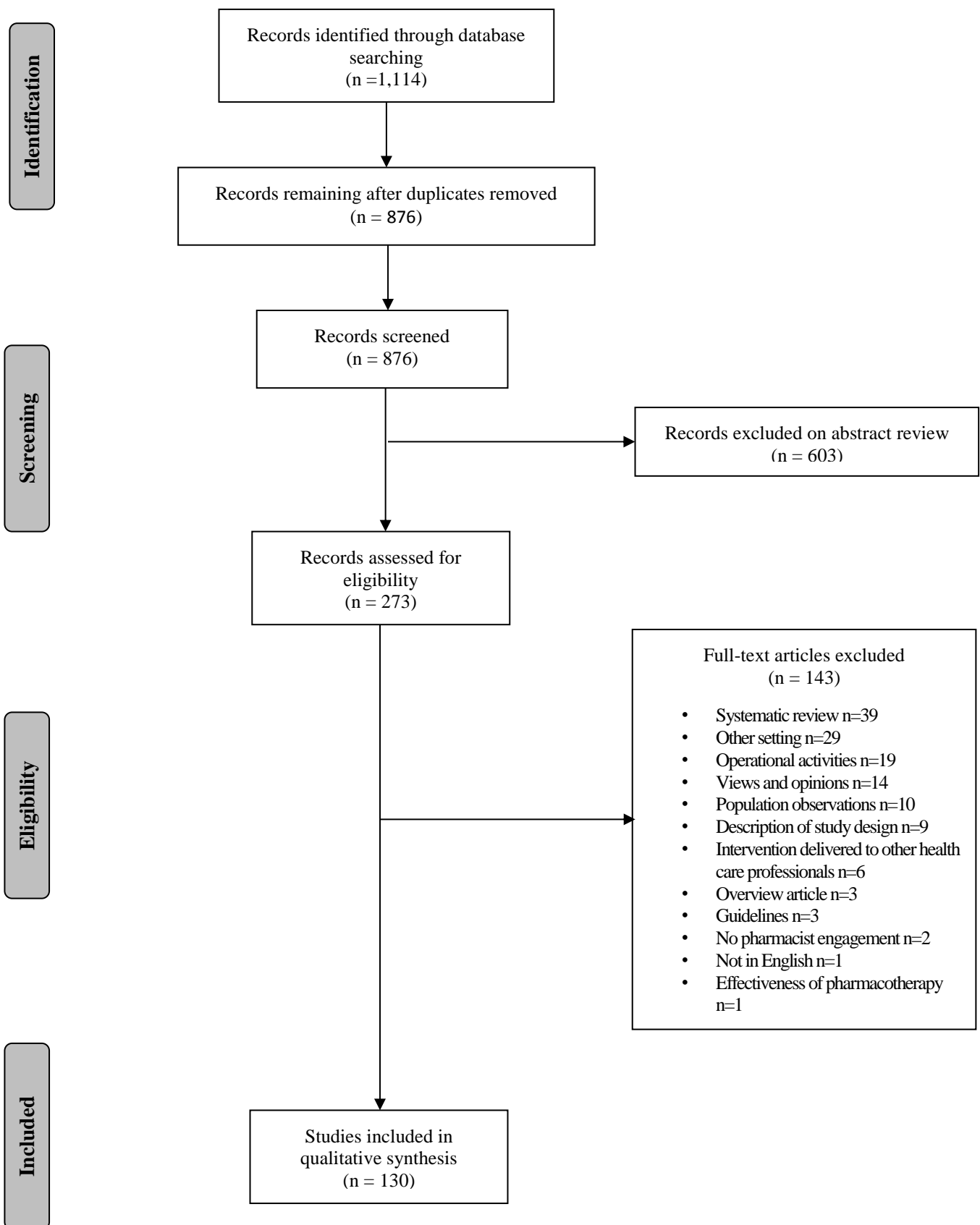


Figure 2-1: Flow diagram depicting the screening process of retrieved articles

2.4.2 Studies included in qualitative synthesis

The retrieved articles (n=130) included in qualitative synthesis are outlined in Table 2.1.

Table 2-1: Overview of studies included in qualitative synthesis

(Note: table extends over 67 pages)

Author(s) Year Country	Disease state	Study design	Sample Size	Intervention				Main outcomes	Record Type
				Type	Description	Disease Prevention Classification	Delivered By		
Abreu et al 2013 Portugal [82]	CVD	Randomised controlled trial	23	Medication Management	Two groups - one intervention (n=13), one control (n=10). Intervention = Medication follow-up service (systematic assessment of the patient's medication profile with aim of identifying medication negative clinical outcomes and providing intervention targeted at addressing same). Control= usual care.	Tertiary	Pharmacist	No differences between the two groups with regards to basal cardiovascular risk (CVR) biomarkers (body mass, smoking habit, fasting glucose, systolic blood pressure (SBP) & diastolic blood pressure (DBP). No differences existed in a pre-post comparison for any of the components of the CVR in the control group (McNemar p>0.05) The only component with a pre-post difference in the intervention group was the SBP (McNemar p=0.028). When components were combined into an overall risk score (SCORE), a significant difference appeared in the pre-post analysis in the intervention groups (McNemar p=0.046) whereas no difference existed in the control (McNemar p = 1.000). Significant difference in CVR was found between intervention and control groups at the end of the study (Mann-Whitney p = 0.041).	Abstract
Aguiar et al 2012 Brasil [83]	CVD	Uncontrolled before after study	51	Medication Management	One group (n=51). Intervention = pharmaceutical care service focussed on health education and monitoring of drug-	Tertiary	Pharmacist	The rate of blood pressure (BP) control increased significantly from 0% to 57.2% of elderly (P = 0.000). The mean reduction from baseline was 26.6 mm Hg for SBP (P < 0.0001), 10.4 mm Hg for DBP (P < 0.0001), and 15.7 mm Hg for pulse pressure (P < 0.0001).	Full text article

Author(s)	Disease	Study design	Sample	Intervention			Main	Record	
					related problems (DRPs).			Adherence increased from 17.1% to 68.6% (p<0.001)	
Aguwa et al 2008 Nigeria [84]	CVD	Uncontrolled before after study	40	Medication Management	One group (n=40). Intervention = structured pharmaceutical care to identify drug related problems, design and implement a therapeutic monitoring plan and provide patients with education and counselling to support medication management.	Tertiary	Pharmacist	SBP decreased by 14.3 mmHg (p<0.001), DBP decreased by 10.8 mmHg (p<0.001), BMI decreased by 0.5 (p=0.18) and drug adherence improved by 0.17 (p<0.001). Forty two percent (42%) of the subjects were referred back to their physician in order to optimise their drug therapy. Quality of Life (QoL) (measured using the WHOQOL-BREF) showed significant differences in the physical health (p<0.001), social relationship (p=0.002) and environment (p<0.001) domains. Participants reported reduction in smoking in 100% of smokers n=7 (p=0.5), increase of 0.46 in proportion exercising (p=0.001), increase of 0.37 in proportion who reduced salt intake (p=0.004), increase of 0.33 in proportion who reduced alcohol intake (p=0.008), and increase of 0.46 in proportion self-measuring their BP (p=0.001)	Full text article
Ahrens et al 2003 USA [85]	Risk Factor - weight management	Randomised controlled trial	88	Risk factor management	Two groups - intervention a (n=45) =meal replacement plan; intervention b (n=43) =reduced calorie diet. Patients in both groups visited the pharmacist every 3 weeks for a total of 13 visits. Active weight loss phase = 3 months. Weight maintenance phase = 10 weeks.	Primary	Pharmacist	During the active weight loss phase, the Meal Replacement (MR) (n = 45) and Reduced Calorie Diet (RCD) (n = 43) groups lost a significant amount of weight, although no significant difference was found between the groups (mean standard error = 4.90 +/- 0.30 kg MR versus 4.30 +/- 0.30 kg RCD; P=16). In the weight maintenance phase, the MR group lost 0.70 +/- 0.40 kg and the RCD group lost 0.90 +/- 0.40 kg (P =0.60). Significant improvements were observed in waist circumference, systolic and diastolic blood pressure, and triglyceride levels (no p values reported) No significant changes were seen in high-density lipoprotein cholesterol or low-density lipoprotein cholesterol levels in either group	Abstract

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
Alehyan et al 2011 Spain [86]	Multiple	Controlled before after study	not stated	Medication Management	Two groups – one intervention (n= not stated), one control (n= not stated). Intervention = pharmaceutical care service designed to detect and solve negative outcomes associated with medication. Control= care not defined.	Tertiary	Pharmacist	59% of detected negative outcomes were solved and 89% were classified as avoidable. Around 18% of negative outcomes were related to drug neediness, and 39% and 43% related to drug effectiveness and drug safety, respectively. Around 15% suspicions of negative outcomes were not accepted by the doctor. A 4.2% decrease of the total number of drugs per patient was observed.	Abstract
Ali et al 2012 England [87]	Diabetes (type 2)	Randomised controlled trial	48	Medication Management	Two groups – one intervention (n=23), one control (n=23). Intervention= pharmaceutical care (education about diabetes, its treatment and associated cardiovascular risk factors). Patients were seen for monitoring/counselling by a community pharmacist on six occasions over a 12-month period).	Tertiary	Pharmacist	A significant reduction was found in SBP (P = 0.012), blood glucose (P < 0.001) and HbA1c (P < 0.001) in the intervention group as compared with the control group after 12 months. BMI (p= 0.057), diastolic blood pressure (p=0.748) were non-significantly lower in the intervention group as compared with the control group. Greater changes in total cholesterol in the intervention group at 12 months (p< 0.001) but total cholesterol was higher in the intervention group at baseline (p=0.016)	Full text article
Amariles et al 2012 Spain [88]	CVD	Randomised controlled trial	714	Medication Management + Disease Management	Two groups - one control (n=358), one intervention (n=356). Control = usual care	Tertiary	Pharmacist	After 8 months of follow-up, there were statistically significant differences in favour of the intervention group in the proportions of patients who achieved therapeutic goals for: BP (52.5% vs 43%, p=0.011),	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					(routine dispensing) plus verbal and written counselling regarding CVD prevention. I Intervention = pharmaceutical care service involving a structured, systematic consultation aimed at identifying and addressing actual or potential negative outcomes associated with medication taking along with verbal and written counselling regarding CVD prevention.			SBP (54.5% vs 45.5%, p=0.017), Total cholesterol (TC) control (56.5% vs. 44.1%, p=0.001), BP/TC control (37.1% vs. 21.8%, p<0.001).	
Amruso et al 2004 USA [89]	CVD	Observational study	50	Medication management	One group (n=50). Intervention= pharmacy based anticoagulation monitoring, dosage adjustment and patient education	Tertiary	Pharmacist	During the 6 months of initial therapy with warfarin, 243 of 435 (56%) INRs were in desired therapeutic ranges. A total of 15 bleeding episodes were reported, of which 10 were minor and 5 were significant. No thromboembolic events were reported.	Abstract
Armour et al 2004 Australia [90]	Diabetes (type 2)	Non-randomised controlled study	188	Disease Management	Two groups - one intervention (n=106), one control (n=82). Intervention = pharmacist led type 2 diabetes clinic with blood glucose monitoring, goal setting and disease management support.	Tertiary	Pharmacist	Pharmacists delivered 1,459 interventions and blood glucose levels were significantly reduced in the intervention group (no p value reported). No change in the proportion of patients with A1C values greater than 7% in control group. In intervention group this proportion was significantly reduced, from 72% at baseline to 53% after 9 months (no p-value reported). Well-being and the risk of nonadherence were significantly improved in intervention patients (no p values reported).	Abstract

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
Bajorek et al 2016 Australia [91]	CVD	Cluster randomised study	38	Medication Management	<p>Three groups - one control (n=11), one short intervention (n=17), one intervention (n=10).</p> <p>Intervention= service comprising screening and monitoring of BP, as well as addressing poor BP control through therapeutic adjustment and adherence strategies with follow up over 12 months (3 months in short intervention group).</p>	Tertiary	Pharmacist	<p>All groups saw a decrease in BP over time but overall, between-group comparisons showed that there were no significant differences in the 3-month SBP (P>0.5) or DBP (P>0.5) between any of the three groups.</p> <p>In the short intervention group a significant decrease from baseline BP was noted in both SBP and DBP at month 3 (P<0.01 and P=<0.01, respectively).</p> <p>No significant differences between control and intervention groups in regard to the 12-month SBP (P>0.5) or DBP (P>0.5).</p> <p>In terms of the absolute mean differences in SBPs recorded within each group from the time of the baseline measurement to the final visit the largest change was observed within short intervention group (decrease of 25mmHg; P<0.01), followed by the control (22mmHg; P<0.01) and intervention (21mmHg; P<0.01) groups</p> <p>No significant difference in adherence between groups over time.</p>	Full text article
Balisa-Rocha et al 2012 Brasil [92]	Diabetes (type 2)	Uncontrolled before after study	34	Medication Management	<p>One group (n=34).</p> <p>Intervention = medication therapy management comprised of monthly visits (40-60min) scheduled over 10 months to identify drug related problems, design and implement a plan to address identified problems, provide counselling to</p>	Tertiary	Pharmacist	<p>Patients' baseline and final evaluation measures for glycosylated hemoglobin, capillary blood glucose, blood pressure, and waist circumference were significantly different (p < 0.05).</p> <p>Patients' mean HbA1c decreased 2.0%, p<0.001; capillary glucose decreased from 230.9 (±103.3) to 176.4 (±76.5), p=0.005; SBP decreased from 148.5 (±19.7) to 128.9 (±14.7), p<0.001; DBP decreased from 83.1 (±12.1) to 76.1 (±9.8),p<0.001; no significant decrease in BMI.</p> <p>There were significant improvements in domains of QoL as measured by SF-36®- functional capacity (p=0.022),</p>	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					support lifestyle modification and education to aid medication management.			physical aspects (p=0.003), pain (p=0.003) , general state of health (p= 0.026), vitality (p<0.001), and mental health (p<0.001). For the domains of social and emotional aspects, mean scores increased but the difference was not statistically significant.	
Beaucage et al 2006 USA [93]	Infectious disease	Randomised controlled trial	255	Medication Management	Two groups - one intervention (n=126), one control (n= 129). Intervention = medication therapy management in form of pharmacist telephone follow up on day 3 of antibiotic treatment to identify drug related problems and encourage adherence to therapy.	Tertiary	Pharmacist	No significant differences observed between groups in terms of adherence, number of infectious symptoms or infection severity.	Full text article
Beaunoye r et al 2014 Canada [94]	Chronic kidney disease	Cluster randomised study	168	Medication Management	Two groups - one intervention (n=117), one control (n=51). Intervention = pharmacists who were trained to detect and manage drug related problems in patients with chronic kidney disease(CKD) had access to patients' clinical summaries as well as facilitated access to the CKD clinic. Control = usual care	Tertiary	Pharmacist	There was an additional decrease of -9.8 mm Hg (95% CI: - 15.8 to -3.7) in systolic blood pressure in the intervention group (n = 117) compared to the patients receiving usual care (n = 51). In diabetic patients (n = 100), an incremental reduction in the glycosylated haemoglobin concentration of 0.4% (95% CI: -0.9 to -0.1) was observed in the intervention group. In the dyslipidemic patients (n = 96), the changes in the LDL cholesterol levels were similar in both groups. The changes in the glomerular filtration rate were similar in both groups.	Full text article
Benrimoj et al	Multiple	Uncontrolled before after	168	Medication Management	Two groups (n=168) received two different	Tertiary	Pharmacist	Comparisons made within groups only.	Abstract

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
2003 Australia [95]		study			<p>interventions.</p> <p>Intervention a (n not reported) = patient medication management service (PMMS)- medication review designed to assist the patient in managing their medication with follow up support.</p> <p>Intervention b = patient medication concordance service (PMCS) - an initial long consultation with the pharmacist, two shorter follow-up consultations, and further short consultations when required - written and verbal information on all medicines was provided as was a medication card listing all current medications, doses, dosage times and any special instructions.</p>			<p>PMMS -16.6% of the patients experienced an improvement in symptoms that was attributed to the pharmacist's advice. In addition, 3.6% experienced an improvement in side effects and adverse drug reactions (no p values reported).</p> <p>PMCS - the proportion of medications described as causing side effects was 17.6% and, at the final follow-up, this had been reduced to 2.7%, (p<0.034).</p>	
Bereznicki et al 2012 Australia [96]	Asthma	Cluster randomised study	1201	Medication Management + Disease Management	<p>Three groups - control (n=434), intervention a (n=414), intervention b (n=353).</p> <p>Intervention a = mail - eligible patients were sent a personalized letter encouraging them</p>	Tertiary	Pharmacist	<p>There were significant improvements in the preventer-to-reliever ratio after the intervention period in the per protocol (PP) analysis (p<0.0001 for all groups) and the intention to treat analysis (ITT) (p<0.0001 for control and intervention a and p=0.006 in intervention b group).</p> <p>Daily short acting beta agonist (SABA) usage decreased in all three groups (p<0.0001) in both PP and ITT analyses.</p>	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					<p>to see their GP for an asthma management review, an information letter to hand to their GP and an educational brochure containing information on asthma, respiratory medication, general management, monitoring and first aid.</p> <p>Intervention b = face to face - the patients received the materials directly from the pharmacist and had the option for a pharmacist discussion if requested.</p> <p>Control = usual care.</p>			<p>The magnitude of improvement in the face-to-face intervention group was greater than in the mailed intervention group, which was greater than in the control group.</p>	
Bernsten et al 2001 Multiple European [97]	Multiple	Randomised controlled trial	2454	Medication Management	<p>Two groups - one control (n=1164), one intervention (n=1290).</p> <p>Intervention = structured pharmaceutical care to identify actual and potential drug-related problems and where necessary formulate an intervention and monitoring plan.</p> <p>Control=usual care.</p>	Tertiary	Pharmacist	<p>QoL -In the pooled data, there were no significant differences between the control and intervention patients in any of the 8 dimensions of QoL as measured by the SF-36 over time (AUC summary measure analysed; independent t-test, $p > 0.05$). A number of significant differences in some domains were evident in the individual country analyses.</p> <p>Hospitalisation - data of acceptable quality were available from 4 countries); during the 18-month study, a lower proportion of intervention patients reported one or more hospitalisations compared with control patients (35.6 and 40.4%, respectively); however, this difference was not statistically significant (Chi-squared test, $p > 0.05$).</p> <p>In the pooled data, there were no significant differences between the control and intervention patients at any assessment point with regard to knowledge of medicines,</p>	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
								contact with GPs or prescription and non-prescription drug use.	
Black et al 2008 UK [98]	Sexual Health	Observational study	133	Provision of EHC + Counselling	Two groups - one accessing an emergency contraception service in a pharmacy (n=50), one accessing an emergency contraception service in a clinic (n=83).	Other	Pharmacist	<p>Pharmacy patients got medication more quickly -Seventy percent of women who went to a pharmacy and 43.9% who went to a clinical service obtained EHC within 24 h (p=.004).</p> <p>A greater proportion of women attending a clinical service felt at least quite comfortable asking for EHC, compared to those who went to a pharmacy 91.5% versus 74.0% (p=.007).</p> <p>Those who obtained EHC from a clinic also felt significantly better informed about both EHC 95% v 82% (p=.015) and their future contraceptive options 90.4% v 28.0% (p<0.001), compared to the women who attended a pharmacy.</p>	Full text article
Blenkinso pp et al 2000 UK [99]	CVD	Randomised controlled trial	180	Medication Management	<p>Two groups - one intervention (n=101), one control (n=79).</p> <p>Intervention= adherence support in the form of a structured consultation to identify patients' medication adherence-related problems and information needs. Advice, information and referral to the general practitioner (GP) were provided by the pharmacist as required.</p> <p>Control = usual care.</p>	Tertiary	Pharmacist	<p>Self-reported adherence better in intervention group versus control 62.9% v 50% (p<0.05).</p> <p>Patients whose blood pressure was uncontrolled prior to the study were more likely to become controlled in the intervention group (P<0.05).</p>	Full text article
Bluml et al 2000	CVD	Observational study	574	Medication Management + Chronic	One group (n=574). Intervention = structured disease	Tertiary	Pharmacist	Significant improvement in cholesterol (TC, triglycerides (TG), high density lipoprotein (HDL), low density lipoprotein (LDL)) between baseline and end point 2yrs	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
USA [100]				Disease Management	management to help patient understand health status, cholesterol levels and goals, their treatment plan and importance of compliance to medication.			later (p<0.0001). Of the 345 patients started on medication, 323 continued with drug therapy, for a resultant patient medication persistence rate of 93.6%. Of 2,817 documented visits for patients on medications, 2,539 occurrences of compliance (i.e. within 5 days of expected refills) were reported, for a resulting per-visit medication compliance rate of 90.1%.	
Bond et al 2007 UK [101]	CVD	Randomised controlled trial	1493	Medication Management	Two groups - one intervention (n=980), one control (n=513). Intervention = medication therapy management in the form of consultations that assessed therapy, compliance, lifestyle and social support with recommendations to support care sent to GP. Control = usual care.	Tertiary	Pharmacist	No statistically significant differences between intervention and control groups were shown at follow-up for any of the outcome measures: <ul style="list-style-type: none"> • proportion of patients on target for a) receiving secondary prevention treatment (aspirin) for CHD in accordance with the National Service Framework; b) lipid management; c) blood pressure management; d) risk factor (smoking, alcohol, diet, physical activity, BMI) management; • cumulative score summarizing 'appropriate treatment' and advice, • QoL as measured by SF-36. 	Full text article
Bouvy et al 2003 Holland [102]	CVD	Randomised controlled trial	152	Medication Management	Two groups; one control (n=78), one intervention (n=74). Intervention =structured consultations (monthly over six months) to identify medication compliance issues and support with improvement.	Tertiary	Pharmacist	Over the 6-month study period, patients in the intervention group had 140/7656 days without use of loop diuretics compared to 337/6196 days in the usual care group (relative risk 0.33 [CI 95% 0.24-0-38]). Two consecutive days of non-dosing occurred on 18/7656 days in the intervention group compared to 46/6196 days in the usual care group (relative risk 0.32 [CI 95% 0.19-0-551]). There were no significant differences in re-hospitalisations and mortality.	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					Control = usual care.				
Boyle et al 2004 USA [103]	Multiple	Observational study	382	Screening	One group (n=382). Intervention= pharmacy based screening for a variety of untreated or uncontrolled health risks in men using the Men's Health Risk Assessment Tool.	Secondary	Pharmacist	Of 382 men identified by the Men's Health Risk Assessment Tool (MHRAT) as being at risk for 1,194 significant health conditions (mean, 3.1 conditions per patient), 69% had not received a physical examination from a physician for a period ranging from more than 1 year to 22.6 years. Of men who were recommended to make an appointment, 64% were seen by a physician or were waiting on a scheduled appointment at the end of the study.	Abstract
Brook et al 2003 Holland [104]	Depression	Randomised controlled trial	147	Medication Management	Two groups - one intervention (n=69), one control (n=78). Intervention = structured pharmaceutical care in the form of 3 x coaching session over 6 months to encourage adherence to medication. Control= usual care.	Tertiary	Pharmacist	In a PP analysis at the 6-month follow-up intervention patients were less depressed (p=0.001) and less anxious (p=0.003) than the controls. The intervention patients improved significantly more on obsessive-compulsive symptoms (P=0.003), interpersonal sensitivity (P=0.024) and somatization (p=0.021). In an ITT analysis using the last observation carried forward method at the 6-month follow-up intervention patients were less depressed (p=0.027) and less anxious (p=0.042) than the controls. ITT analysis using the group mean imputed method showed no significant differences between groups at 6 months.	Full text article
Bryant et al 2011 New Zealand [105]	Multiple	Randomised controlled trial	498	Medication Management	Two groups - one intervention (n=269), one control (n=229). Intervention = Comprehensive Pharmaceutical Care (CPC)- clinical medication review followed by meeting with patients GP to discuss recommendations about possible medicine	Tertiary	Pharmacist	There was no significant difference for any of the SF-36 domains (QoL) between baseline and 6months for the intervention group. Significant differences were observed between the intervention and control group, favouring the control group, for emotional role (P = 0.024) and social functioning (P = 0.019). Medication appropriateness index (MAI) improved significantly from baseline to six month in the intervention group (p< 0.001), and not in the control group. The difference in 6-month scores between the intervention and	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					changes delivered over 12 months. Control = usual care for 6 months and CPC for six months.			control groups was also significant (P = 0.003). For the control group in the second 6 months, after the CPC medication review, the MAI significantly improved (p=0.002). Significantly more medicines were started in the control group than the intervention group (P < 0.0001) and there were significantly more dosage reductions and medicine switches in the intervention group than the control group (p=0.037).	
Bunting et al 2008 USA [106]	CVD	Uncontrolled before after study	565	Medication Management + Disease Management	One group (n=565). Intervention = medication therapy management service where treatment goals were reviewed, therapy assessed and recommendations for changes made to doctor.	Tertiary	Pharmacist	Significant reductions were observed in SBP at year 1,2,3,4,5,6 (all p<0.001) and DBP at year 1 (p<0.005) and years 2-6 (p<0.001). LDL, TC and TGs were all significantly lower than baseline at yr1-6 (p<0.05), HDL significantly worse in year 5. The risk of having a cardiovascular event in the study was decreased by 53%, compared with the historical time point (OR 0.4691 [0.328–0.671]) (non-significant). Patient use of emergency departments (Eds) and need for hospitalization significantly decreased during the study, by 54% overall compared to the historical time period (OR 0.461 [0.349–0.611]. P <0.0001).	Full text article
Burke et al 2012 Ireland [107]	CVD	Observational study	1,645	Screening	One group (n=1,645). Intervention = pharmacy-based screening for cardiovascular disease (lifestyle assessment and measurements of blood pressure, waist circumference, body mass index, random glucose levels and	Secondary	Pharmacist	One quarter (24.2%) of participants were assessed as at moderate to high risk of cardiovascular disease over the next 10 years. Measurements demonstrated that 66.5% of patients surveyed had a body mass index above normal, with 23.6% having a body mass index in the obese range. One in six participants stated that they took no exercise (16.9%) while a similar proportion were current smokers (16.8%) and 7.6% indicated that they consumed in excess of the recommended weekly alcohol limits in Ireland.	Abstract

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					cholesterol levels).			In 54.8% of cases the pharmacist provided individualised advice to the patient on how they could decrease their risk of cardiovascular disease.	
Carr et al 2007 UK [108]	Eczema	Uncontrolled before after study	50	Medication Management	One group (n=50). Intervention= Structured consultation to assess management of eczema using emollients with training and education to support best use	Tertiary	Pharmacist	Increased numbers using cream effectively. There was a small, statistically significant reduction in itch following the intervention (mean reduction 1.43, SD 2.76, t=3.61, P=0.001), a small, statistically significant reduction in irritability (mean reduction 1.23, SD 2.84, t=2.86, P=0.006) but little reduction in sleep disturbance (mean reduction 0.34, p=0.44) or skin appearance (mean reduction 0.75, p=0.09).	Full text article
Cerulli et al 2004 USA [109]	Osteoporosis	Observational study	140	Screening	One group (n=140). Intervention= bone mineral density (BMD) screening using an ultrasound BMD analyzer, results reviewed with the participant during an education session and forwarded to primary care providers.	Secondary	Pharmacist	At 3 months, 11% of patients reported having improved exercise habits, and 30% had increased their calcium and vitamin D intake.	Abstract
Chabot et al 2003 Canada [110]	CVD	Cluster randomised study	100	Medication Management + Disease Management	Two groups; one control (n=59), one intervention (n=41). Intervention = structured disease and medication management (e.g. positive feedback and rewards, education to improve adherence, recommendation on life-style changes, and dosage of medication). Control = usual care.	Tertiary	Pharmacist	Results stratified into high and low-income patients. In intervention patients with high income, when compared with the control group, the pharmacy program resulted in: <ul style="list-style-type: none"> • significant SBP reduction (-7.8 vs. 0.5 mm Hg; p = 0.01) but not DBP • an increase in the proportion of patients with BP controlled with an SBP <140 mm Hg and a DBP <90 mm Hg (p=0.073) • a significantly greater proportion of patients reporting doing physical activity for at least 20 minutes ≥3 times a week (p=0.048) • a greater proportion of patients reporting being 	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
								<p>adherent to medication (p=0.067)</p> <p>No significant improvement in any measure for low-income participants versus control.</p> <p>The intervention group were more likely to be concerned about their health than those in the control group.</p>	
Chau et al 2016 Holland [111]	Multiple	Observational study	3807	Medication Management	<p>One group (n=3,807).</p> <p>Intervention = structured clinical medication review to assess the aim and use of the patients' medication, to identify any DRPs experienced or perceived by the patient and to recommend interventions to address such DRPs.</p>	Tertiary	Pharmacist	<p>A median of two DRPs (interquartile range 1–4; mean 3.0) was identified per patient.</p> <p>Overtreatment (25.5 %) and undertreatment (15.9 %) were the most common DRPs.</p> <p>Pharmacists proposed a variety of interventions (e.g. discontinuation of a drug (19.6 %), patient monitoring (18.4 %) e.g. BP monitoring) the majority of which (69.9 %) was either implemented or led to alternative interventions</p>	Full text article
Cocohoba et al 2012 [112]	HIV	Retrospective cohort study	15933	Medication Management	<p>Two groups; one control (n=11,679); one intervention (n=4,254).</p> <p>Intervention = medication therapy management (not clearly defined but pharmacists assess, counsel and manage patients living with HIV and related comorbidities).</p> <p>Control = usual care.</p>	Tertiary	Pharmacist	<p>Intervention group had significantly better regimen refill adherence as measured by median mMPR (Medication Possession Ratio) (90% vs. 77%, p < 0.0001).</p>	Full text article
Cordina et al	Asthma	Randomised controlled	152	Medication Management	<p>Two groups; one control (n=66); one</p>	Tertiary	Pharmacist	<p>Improvement in inhaler technique was significantly higher in the intervention group than in the control group</p>	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
2001 Malta [113]		trial		+ Disease Management	intervention (n=86). Intervention = pharmaceutical care (patient education and monitoring to support optimal use of medication and disease management). Control = usual care.			(p=0.021). Health related quality of life (HRQoL) of the intervention patients improved at 12 months (p=0.044); this was not the case for the control group. No significant between groups differences were observed. Peak expiratory flow rate (PEFR) significantly decreased (got worse) in control patients compared with intervention patients (p=0.009); change in PEFR from baseline to study conclusion was not significantly different between the two groups.	
Correr et al 2011 Brasil [114]	Diabetes (type 2)	Non randomised controlled study	96	Medication Management	Two groups; one control (n=46); one intervention (n=50). Intervention = structured review of medication and medical conditions to identify any negative clinical outcomes and to recommend interventions to address such negative outcomes; monthly visits over 12 months. Control = usual care.	Tertiary	Pharmacist	52.9% of pharmacist interventions involved referral to a physician and 68 % of such interventions were fully accepted by physicians. Relative to the control group, the intervention group exhibited greater glycosylated haemoglobin (HbA1) reduction (-2.2% [95% CI -2.8%:-1.6%] vs. -0.3 [95% CI - 0.8: 0.2]; P<0.001) and greater fasting capillary glycaemia reduction (-20.1 mg/dl [95% CI-31.9 mg/dl:-8.3 mg/dl] vs. 4.3 mg/dl [95% CI -13.4 mg/dl:22.2 mg/dl]; P = 0.022). These differences persisted after adjustment for baseline values. There were no significant differences in any other clinical measures between the groups.	Full text article *note that this is the same interven- -tion as that in [115] below but different outcome reported
Correr et al 2008 Brasil [115]	Diabetes (type 2)	Non- randomised controlled study	96	Medication Management	Two groups; one control (n=46); one intervention (n=50). Intervention = structured review of medication and medical	Tertiary	Pharmacist	After 12 months, all HRQoL indexes in the intervention group showed improvement. In the control group, on average, they remained unchanged or poorer. The intervention group showed a significant improvement in HRQoL (as measured by the DQOL-Brasil, validated in portugese) compared with the control group (0.08 vs -0.01,	Full text article *note that this is the same

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					conditions to identify any negative clinical outcomes and to recommend interventions to address such negative outcomes; monthly visits over 12 months. Control = usual care.			respectively; p=0.036) even after adjusting for gender, age and time of diabetes diagnosis (p = 0.047). Satisfaction and impact domains presented the most significant improvement (0.13 vs 0.00 [p=0.030] and 0.07 vs -0.04 [p=0.033], respectively)	intervention as that in [114] above but different outcome reported
Cranor et al 2003 USA [116]	Diabetes (type 2)	Uncontrolled before after study	187	Medication Management + Disease Management	One group (n=187). Intervention = pharmaceutical care (consultations to set and monitor treatment goals and to receive diabetes education, home glucose meter training, and information about adherence to medication)	Tertiary	Pharmacist	Patient were followed up every 6 months over 3.5years. HbA1c decreased at all follow-ups, with more than 50% of patients demonstrating improvements at each time. The number of patients with optimal A1c values (< 7 %) also increased at each follow-up. Significance difference from baseline to follow up was observed at year 1,2,3 follow up only. LDL-C and HDL-C concentrations, also improved but not significantly.	Full text article *note that this is the same intervention as that in [117] below but different outcome time-frame and sample size
Cranor et al (b) 2004 USA [117]	Diabetes (type 2)	Uncontrolled before after study	85	Medication Management + Disease Management	One group (n=85). Intervention = pharmaceutical care (education, self-monitored blood glucose (SMBG) meter training, clinical	Tertiary	Pharmacist	The proportion of patients with HbA1c values in the optimal range increased significantly (p=0.04) from 42% at baseline to 57% at follow-up. HbA1c improved significantly, from a mean ± SD of 7.5% ± 1.5% at baseline to 7.0% ± 1.3% at follow-up (P < .01). None of the other lab values (total cholesterol, HDL, LDL)	Full text article *note that this is the same interven

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					assessment, patient monitoring, follow-up, and referral)			showed significant differences	-tion as that in [116] above but different outcome time-frame and sample size
DiDonato et al 2013 USA [118]	CVD	Uncontrolled before after study	81	Disease Management	One group (n=81). Intervention = wellness coaching in pharmacy with pharmacist coach (monthly to quarterly consultations over 12 months providing personalised disease specific education, goal setting, and monitoring).	Tertiary	Pharmacist	Patients' TC (p=0.034), LDL (p=0.007), HDL (p=0.008), DBP (p<0.001) and fasting blood glucose (p<0.001) were reduced significantly. Mean changes in TG, SBP, weight, BMI and waist circumference were not statistically significant (p>0.05). No statistically significant differences were seen in the number of patients at goal level for each monitoring parameter or in patient's HRQoL scores.	Full text article
Doucette et al 2009 USA [119]	Diabetes (type 2)	Randomised controlled trial	78	Medication Management + Disease Management	Two groups; one control (n=42); one intervention (n=36). Intervention = disease and medication management (medication use review, treatment and disease management education and recommending medication changes to physicians when appropriate) over up to	Tertiary	Pharmacist	Compared with changes in the control group, patients who received interventions significantly increased the number of days per week that they engaged in a set of diet (p=0.001) and diabetes self-care (p=0.027) activities (1.25 and 0.73 more days/wk, respectively). The mean 12-month changes for A1C, LDL-C, and blood pressure were not significantly different between the 2 study groups.	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					4 quarterly visits. Control = usual care.				
Edmond Pistja et al 2015 Albania [120]	CVD	Randomised controlled trial	120	Medication Management	Two groups - one control (n=60), one intervention (n=60). Intervention = pharmacist led medication management consultations to support improved adherence and reduce blood pressure. Control = usual care	Tertiary	Pharmacist	Statistically significant decreased BP (p=0.005) from baseline to post intervention in the intervention group. Mediation adherence was higher in the intervention group at the end of the study (no p values reported).	Abstract
Elliott et al 2002 USA [121]	Osteoporosis	Observational study	133	Screening	One group (n=133). Intervention = screening for osteoporosis.	Secondary	Pharmacist	Of 133 women 20% had calcaneal osteoporosis, 30% met National Osteoporosis Foundation (NOF) treatment criteria and 75% of these were unaware of their low bone mass. Half of the women received <1200 mg/d of calcium, the recommended dose for osteoporosis prevention. Women who had discussed bone density test results with their physicians were more likely to receive central dual energy X-ray absorptiometry (DXA) measurements and/or start antiresorptive therapy than women who did not.	Abstract
Elliott et al (b) 2016 UK [122]	Multiple	Randomised controlled trial	504	Medication Management	Two groups - one control (n=253), one intervention (n=251). Intervention = New Medicines Service (NMS) which involved one consultation 7-14 days after presentation of prescription for a new medication	Tertiary	Pharmacist	In an unadjusted ITT analysis of 378 patients still taking the initial medicine at study completion, 115/190 (60.5%) and 133/188 (70.7%) (p=0.037) patients were adherent in the normal practice and NMS arms, respectively. In an adjusted (adjusted for recruiting pharmacy, disease, age, sex and medication count) intention-to-treat analysis, the odds ratios (OR) for increased adherence was 1.67 (95% CI 1.06 to 2.62; p=0.027) in favour of the NMS arm. When imputation of missing values was included in the	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					<p>followed by another 14–21 days thereafter to identify problems with treatment and provide support if needed.</p> <p>Control = usual care.</p>			<p>adjusted model the OR (95% CI) was 1.62 (1.04 to 2.53, p=0.032) in favour of NMS.</p>	
Emmertson et al 2003 New Zealand [123]	Asthma	Observational study	100	Medication Management	<p>One group (n=100).</p> <p>Intervention = structured pharmaceutical care (medication review, care planning, education, recommendations and referral where appropriate)</p>	Tertiary	Pharmacist	<p>On average, 4.3 medication-related problems were identified per patient.</p> <p>The most common interventions were revision of patients' asthma action plans, referral and medication counselling.</p> <p>Within 6 months of the initial consultation with the pharmacist, 70% of patients were estimated to have had between one-quarter and three-quarters of their medication-related problems resolved.</p> <p>Clinical outcomes included reduced bronchodilator use and improved symptom control in around two-thirds of patients (no p values reported). Modest improvement in daily PEFr in 2/3 patients but not significant.</p>	Full text article
Eussen et al 2010 Holland [124]	CVD	Randomised controlled trial	899	Medication Management	<p>Two groups; one control (n=460); one intervention (n=439).</p> <p>Intervention = pharmaceutical care to support adherence to cholesterol medication (monitoring of lipid levels and education to support adherence provided over 5 individual counselling sessions during a 1-year period).</p>	Tertiary	Pharmacist	<p>Significantly lower rate of discontinuation within 6 months after initiating therapy in intervention participants versus usual care (HR 0.66, 95% CI 0.46 to 0.96). No significant difference between groups was found in discontinuation at 12 months (HR 0.84, 95% CI 0.65 to 1.10).</p> <p>Median MPR was very high (>99%) in both groups and did not differ between groups.</p> <p>In intervention patients both mean total cholesterol and LDL-C levels declined significantly during the study (no p value reported), A higher percentage of adherent patients (MPR ≥90%) than nonadherent patients reached target LDL-C levels after 3 months (67% vs 45%, respectively; p = 0.01) and 6 months (74% vs 50%, respectively; p = 0.01).</p>	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					Control = usual care.				
Fera et al 2008 USA [125]	Diabetes (type 2)	Observational study	914	Disease Management	One group (n=914). Intervention = chronic disease management (scheduled consultations to assess disease knowledge, provide education, support with clinical goal setting and coaching to improve disease management).	Tertiary	Pharmacist	At initial visit compared with 1 year, mean A1C decreased from 7.6% to 7.2% (p<0.001), mean LDL cholesterol decreased from 96.3 to 93.3 mg/dL (p<0.001), and mean systolic blood pressure decreased from 131.3 to 128.7 mm Hg (p<0.001) and diastolic from 79.3 to 77.3 mmHg. Increases were seen for influenza vaccination rate (from 43% to 61%), eye examination rate (from 60% to 77%), and foot examination rate (from 38% to 68%) for the initial visit to the end of the analysis period (no p values for these measures)	Full text article
Fikri- Benbrahi et al 2013 Spain [126]	CVD	Non- randomised controlled study	176	Medication Management	Two groups; one control (n=89); one intervention (n=87). Intervention = Structured consultation with the pharmacist to receive education relating to hypertension and coaching to improve adherence to antihypertensive medication. Control = usual care.	Tertiary	Pharmacist	In the intervention group, the percentage of adherent patients increased from baseline to the endpoint (86.0% vs. 96.5%; p=0.022). No significant change in the control group (86.5% vs. 85.4%; p=0.928). The proportion of patient adherence at the end of the study was higher in the intervention group compared to the control group (96.5% vs. 85.4%; P = 0.011). The odds of adherence to antihypertensive drug therapy in the intervention group was 4.07 (95% CI: 1.04–15.95; p=0.044) times higher than the control group.	Full text article
Fornos et al 2006 Spain [127]	Diabetes (type 2)	Randomised controlled trial	112	Medication Management	Two groups; one control (n=56); one intervention (n=56). Intervention = structured consultation to identify and manage actual or potential drug related problems.	Tertiary	Pharmacist	There was a significant difference in changes from baseline between the intervention and the control group in: DRPs (1.7 ± 1.2 versus 3.1 ± 1.2, P<0.0001), knowledge (17.9 ± 3.7 versus 11.4 ± 6.7 points, P<0.0001), HbA1c (7.9 ± 1.7 versus 8.5 ± 1.9%, P<0.0001), Fasting blood glucose (154 ± 61.3 versus 168 ± 57.8 mg/dl, P=0.0004), total cholesterol (202 ± 41.5 versus 217 ± 43.5 mg/dl, P=0.0054),	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					Control = usual care.				
Garcao et al 2002 Portugal [128]	CVD	Randomised controlled trial	100	Medication Management	Two groups; one control (n=50), one intervention (n=50). Intervention= medication therapy management (monthly over 6 months) to prevent, detect, and resolve DRPs, monitoring of blood pressure, education and encouragement to support adherence and lifestyle modification to support disease management. Control = usual care.	Tertiary	Pharmacist	SBP (135 ±16.4 versus 150 ±19.9 mmHg P=0.0006). Prevalence of uncontrolled blood pressure decreased by 77.4% in the intervention group (P<.0001) and by 10.3% in the control group (P =0.48). SBP fell from a mean +/- standard deviation of 152 mm Hg +/- 23 mm Hg to 129 +/- 15 mm Hg in intervention patients and 148 +/- 16 mm Hg to 143 +/- 20 mm Hg in control patients (P<0.001). Twenty four of 29 (83%) detected actual DRPs were resolved. About 40% of potential DRPs were prevented.	Abstract
Gardner et al 2008 USA [129]	Sexual Health	Observational study	214	Prescribing	One group (n=214). Intervention = Pharmacist prescribing (conducted consultation, measured weight and blood pressure and prescribed hormonal contraceptives according to the protocol guidelines)	Other	Pharmacist	195 women (91%) were prescribed hormonal contraceptives by participating pharmacists. After 12 months, 70% of women responding to an interview reported continuing use of hormonal contraceptives.	Abstract
Geurts et al 2010 Holland [130]	Multiple	Randomised controlled trial	521	Medication Management	Two groups; one control (n=271); one intervention (n=250). Intervention = structured adherence support consultation (questionnaire to	Tertiary	Pharmacist	There was no significant difference found in adherence between intervention and control groups.	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					identify adherence related problems and consultation to discuss). Control = usual care.				
Geurts et al (b) 2016 Holland [131]	CVD	Randomised controlled trial	512	Medication Management	Two groups - one control (n=264), one intervention (n=248). Intervention = clinical medication review to identify actual and potential drug-related problems followed by the development and implementation of a pharmaceutical care plan in consultation with patient and their GP. Control = usual care.	Tertiary	Pharmacist	The study intervention (p<0.001) and the number of medicines used (p = 0.030) had a significant effect on the number of interventions proposed. Intervention patients had a significantly decreased DBP after 1-year follow-up (79.8–76.8 mmHg; p = 0.008). HDL-cholesterol showed a small but significant increase in two groups (intervention patients with intervention: 1.29–1.37 mmol/L; p = 0.021; control: 1.26–1.37 mmol/L; p = 0.039). LDL-cholesterol showed a small but significant decrease in the control group (2.61–2.58 mmol/L; p = 0.032). Other parameters showed no significant effect.	Full text article
Goode et al USA 2004 [132]	Osteoporosis	Observational study	532	Screening	One group (n=532). Intervention = pharmacy-based osteoporosis screening with referral and follow-up.	Secondary	Pharmacist	The stratification for risk of fracture (based on T-scores for the peripheral ultrasound densitometry device used in the screening) was 37%, high risk; 33%, moderate risk; and 30%, low risk. A total of 78% of patients indicated that they had no prior knowledge of their risk for future fracture. In the moderate- and high-risk categories, 37% of patients scheduled and completed a physician visit, 19% had a diagnostic scan, and 24% of those patients were initiated on osteoporosis therapy subsequent to the screening.	Full text article
Gorostiza et al 2011 Spain	HIV	Observational study	806	Screening	One group (n=806). Intervention = screening for HIV using a point of	Secondary	Pharmacist	The mean age of test users was 36.2 years (SD: 11.0; range: 16-82;71% men). 7 HIV test outcome were positive (0.85%; 95%CI: 0.34 to	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
[133]					care test in community pharmacy (rapid HIV antibody test on capillary blood).			1.75), 5 positive tests were in males. More than half of the users hadn't had a previous HIV test.	
Grainger-Rousseau et al 1996 Northern Ireland [134]	Asthma	Non-randomised controlled study	152	Medication Management + Disease Management	Four groups (no n reported for individual groups); one control group (usual care) and three treatment groups (asthma management service delivered as education alone; monitoring alone or education and monitoring).	Tertiary	Pharmacist	Inhaler technique improved significantly after education (no detail given on exact levels or p-value). HRQoL, pulmonary function tests, and subjective symptom scores did not change markedly over the study period. The majority (90%) of pharmacist recommendations for changes in drug therapy were implemented by general practitioners.	Abstract
Hammerlein et al 2011 Germany [135]	Asthma/CO PD	Uncontrolled before after study	757	Medication Management	One group (n=757). Intervention= assessment of inhaler technique followed by instruction to to improve technique where required; follow up after 4-6 weeks	Tertiary	Pharmacist	At baseline, 597 patients (78.9%) made at least one error in performing their inhalation. This number dropped to 214 (28.3%) from the first to the second appointment (P < 0.001). The average number of errors dropped from 2.5 to 0.5 per patient (P < 0.001).	Full text article
Hare et al 2008 USA [136]	Depression	Observational study	18	Screening	One group (n=18). Intervention = screening for depression using the 10-item Harvard Department of Psychiatry/National Depression Screening Day Scale (HANDS) tool.	Secondary	Pharmacist	The mean (+/- SD) total score on the 10-item Harvard Department of Psychiatry/National Depression Screening Day Scale (HANDS) tool was 5.8 +/- 5.0. Overall, of 18 total participants, 14 were unlikely to have symptoms of major depressive disorder (MDD), 3 had symptoms consistent with MDD (including 1 reporting recent suicidal thinking), and 1 had symptoms strongly consistent with MDD. Patients followed the pharmacist's referral recommendations in all cases	Abstract
Henderson et al	Hepatitis C	Observational study	1475	Medication Management	Two groups; one control (n=293), one	Tertiary	Pharmacist	A significantly greater proportion of patients were persistent to their 3-drug hepatitis C regimen containing	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
2014 USA [137]					intervention (n=1,182). Intervention= medication supply in speciality pharmacy (delivery of medication to location of patient's choice, refill reminders, regimen-specific education, administration training, and coping tips and scheduled telephone follow ups to ensure rapid resolution of any concerns or questions). Control = usual care.			telaprevir in intervention group, compared with control (56.0% vs. 39.9%, P < 0.001). After multivariate adjustment, patients in the intervention group had 1.89 times greater odds of being persistent to their regimen compared with patients in the control group (95% CI=1.44-2.48)	
Herborg et al 2001 Denmark [138]	Asthma	Non- randomised controlled study	500	Medication Management	Two groups - one control (n=264), one intervention (n=236). Intervention= structured pharmaceutical care to identify and try to resolve drug therapy problems, support improved adherence and patient knowledge and coaching to improve coping skills and patient empowerment. Control = usual care.	Tertiary	Pharmacist	Improvements in asthma symptom scores were seen in both groups from baseline to 12 months; intervention patients had a better symptom score than control patients at 12 months (1.52 versus 1.88; p=0.022). Inhalation technique improved in both groups and at 12 months intervention patients had better inhalation technique than control patients (0.17 errors per patient versus 0.75; p=0.001). HRQoL improved significantly more in intervention patients than in control patients (p=0.029), as did asthma related quality of life (p<0.001). Intervention patients visited GPs 1.4 times more than control patients (p=0.012). No significant differences were found for PEFr.	Full text article
Holdford et al	CVD	Non randomised	2,872	Medication Management	Two groups - one control (n=1899), one	Tertiary	Pharmacist	Adherence (as measured by proportion of days covered, PDC) in the intervention group ranged from 0.80 to 0.87	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
2013 USA [139]		controlled study			intervention (n=973). Intervention = appointment-based medication synchronization (consultation with pharmacist to identify and resolve drug related problems followed by synchronization of chronic medications to be refilled on a single day each month). Control = usual care.			versus a range of 0.58 to 0.63 in the control group and the difference was statistically significant across all drug classes (p<0.0001 for angiotensin-converting enzyme inhibitor ACEIs/ angiotensin receptor blockers ARBs, beta-blockers, dihydropyridine calcium channel blocker DCCBs and statins; p=0.001 for thiazide diuretics and metformin). Greater percentage of adherent patients in intervention group (range 66% to 79% versus 37% to 41% in control) which was statistically significant across all drug classes (p<0.0001 for angiotensin-converting enzyme inhibitor ACEIs/ angiotensin receptor blockers ARBs, beta-blockers, dihydropyridine calcium channel blocker DCCBs and statins; p=0.0017 for thiazide diuretics and p=0.0003 for metformin). Intervention patients had 3.4 to 6.1 times greater odds of adherence compared with control patients. Greater percentage of control patients became non-persistent within 1 year (67% to 74% versus 34% to 48%) and difference was significant across all drug classes (p<0.0001 for angiotensin-converting enzyme inhibitor ACEIs/ angiotensin receptor blockers ARBs, beta-blockers and statins; p=0.0003 for dihydropyridine calcium channel blocker DCCBs, p=0.0006 for thiazide diuretics and p=0.0013 for metformin).	
Hui-Callahan et al 2013 USA [140]	Diabetes (type 2)	Uncontrolled before after study	25	Disease Management	One group (n=25). Intervention= pharmacist counselling on healthy behaviours. Participants received a \$5 incentive for each weeklong behaviour log completed and reviewed with the pharmacist.	Tertiary	Pharmacist	Patients self-reported increased levels of BP and blood glucose monitoring. No differences in HbA1c level pre and post-intervention (at 12 weeks).	Abstract
Jódar-	Multiple	Cluster	1403	Medication	Two groups; one	Tertiary	Pharmacist	By the end of the follow-up, both groups had reduced the	Full text

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
Sánchez et al 2015 Spain [141]		randomised study		Management	control (n=715), one intervention (n=688). Intervention= medication review to identify drug related problems and negative outcomes associated with medications with follow up over six months. Control = usual care.			mean number of prescribed medications they took, although this reduction was greater in the intervention group (0.28 ± 1.25 drugs; $p < 0.001$) than in the control group (0.07 ± 0.95 drugs; $p = 0.063$). Older adults in the intervention group demonstrated improved QoL ($+ 0.0528 \pm 0.20$ ($p < 0.001$)) and control participants experienced a slight reduction in their quality of life: 0.0022 ± 0.24 ($p = 0.815$). Both groups experienced a reduction in the percentage of older adults who at visited the A&E department once during the 6 months before and during the 6 months of the study, although this reduction was greater in the intervention group (27.9 vs. 14.2 %; difference 13.7 %; $p < 0.001$) than in the control group (29.1 vs. 24.9 %; difference 4.2 %; $p = 0.044$).	article
Johnson et al 2008 USA [142]	Osteoporosis	Observational study	159	Screening	One group (n=159). Intervention = pharmacy-based osteoporosis screening with referral for further testing/treatment where indicated.	Secondary	Pharmacist	Of the 159 women screened risk of fracture (based on T-score) was 8%, high risk; 45%, moderate risk; 47%, low risk. 53% at moderate/high risk were referred to their GP. 80% of patients responded to a follow up phone survey and 3 and 6 months with following insights: At 3 months 64% of respondents had discussed calcium supplementation with their pharmacist, 50% had increased calcium intake, 21% has increased weight bearing activity. 37% had spoken to GP at 3 months and doctor recommended increased calcium intake (13.5%), increased weight bearing exercise (9.6%) and ordered DXA scan (4.8%). At six months 44% of respondents indicated starting a calcium supplement since month 3 and 43.8% increased weight bearing exercise, a further 16.5% spoke to GP about screening results with 6.92% referred for a DXA scan.	Full text article
Kempen et al	Multiple	Observational study	4574	Medication Management	One group (n=4574).	Tertiary	Pharmacist	On average, 2.9 (0–26; SD 2.1) DRPs per review were recorded, of which, an average of 0.90 (0–18; SD 1.2) led	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
2014 Holland [143]					Intervention = clinical medication review to identify drug related problems and formulate intervention proposals.			<p>to a medication change.</p> <p>The most frequently identified DRPs were overtreatment (25 %), which includes duplicate therapy and no indication apparent, and suboptimal therapy (16 %). Wrong dosage—dose too low and dose too high combined—accounted for 10 % of all DRPs.</p> <p>Of all identified DRPs, 31 % resulted in a direct medication change. 29 % of all DRPs did not lead to an intervention.</p> <p>On average, the implementation rate for all proposals to change medication was 42 % (proposal to stop a drug had the highest implementation rate (47 %), and proposal to start a drug was least likely to be implemented (35 %)).</p> <p>Overall, the proposal to synchronise medications (to allow for simultaneous dispensing in the future) had the highest implementation rate (83%)’’Information provided’’ was the most frequently recorded intervention (25 %), followed by ‘‘Performed monitoring’’ (20 %).</p>	
Kennedy et al 2002 USA [144]	Risk factor - smoking cessation	Observational study	48	Smoking Cessation	<p>One group (n=48).</p> <p>Intervention= pharmacist delivered one on one smoking cessation counselling</p>	Primary	Pharmacist	<p>Of the 48 patients, 12 (25.0%) abstained from smoking cigarettes for 12 months or more beyond their predetermined quit dates.</p> <p>Abstinence rates for 1, 3, and 6 months were 43.8%, 31.3%, and 25.0%, respectively.</p> <p>Women were nearly five times more successful in attaining long-term abstinence than were men (33.3% versus 6.7%; P = .047).</p> <p>No significant differences were observed in cessation rates related to age, number of cigarettes smoked per day, level of nicotine dependence, number of previous quit attempts, or method of cessation.</p>	Abstract
Kooij et al 2016 Holland	Multiple	Cluster randomised study	4681	Medication Management	Two groups; one control (n=3,637), one intervention (n=3094).	Tertiary	Pharmacist	<p>Intention to treat analysis (n=4681) showed no difference in adherence rates between the intervention and the usual care arm (74.7% ± 37.5 vs 74.5% ± 37.9) or proportion of</p>	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
[145]					<p>Intervention= telephone counselling intervention 7–21 days after the start of therapy for patients prescribed one of four classes of medication (Renin Angiotensin System (RAS)-inhibitors, statins, bisphosphonates and anti-depressants) to allow for assessment of practical and perceptual barriers and to provide information and motivation.</p> <p>Control=usual care.</p>			<p>adherent patients (69.0% vs 69.9%).</p> <p>In a PP analysis conducted on control versus intervention patients who received counselling (n=1,054) differences were only significant when the model was adjusted for age, gender, medication class and socioeconomic status (intervention group higher- 5.96%,;95% CI 2.57, 8.68).</p> <p>In the PP analysis adherence was statistically significantly higher for patients starting with RAS-inhibitors (84.1% ±31.6 vs 78.5%±36.6),statins (80.5% ±32.4 vs 75.1%±36.8) and bisphosphonates (84.3% ±31.7 vs 73.3%±38.1) and the proportion of adherent patients was also higher post intervention in these three groups (RAS inhibitors 84.1% vs 74.9%; statins 81.3% vs 68.9%; bisphosphonates 81.8% vs 67.1%) .</p> <p>In the ITT analysis the rate of discontinuation was lower in the intervention group for patients taking bisphosphonates (22.6% vs 27.9%; hazard ratio 0.77, 95% CI 0.69, 0.91) and higher in the intervention group for patients taking antidepressants (47.5% vs 42.7%; hazard ratio1.17, 95% CI 1.01, 1.37).</p>	
Kooy 2013 Holland [146]	CVD	Randomised controlled trial	381	Medication Management	<p>Three groups -control (n=128), intervention A (n=130), intervention B (n=123).</p> <p>Intervention A = electronic reminder device + counselling to support adherence. Intervention B = electronic reminder device + written instruction to support adherence.</p>	Tertiary	Pharmacist	<p>No statistically significant improvement of refill adherence was found if an Electronic Reminder Device was used with or without counselling. However, in a subgroup of women using statins for secondary prevention the ERD did improve adherence significantly (p=0.002)</p>	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
Krass et al 2007 Australia [147]	Diabetes (type 2)	Randomised controlled trial	289	Medication Management + Chronic Disease Management	Control = usual care. Two groups; one control (n=140), one intervention (n=149). Intervention = structured pharmaceutical care (monitoring and education to support disease management and adherence to therapy provided at regular intervals over 6 months). Control = usual care.	Tertiary	Pharmacist	For the intervention subjects, the mean blood glucose level decreased over the 6-month study from 9.4 to 8.5 mmol/l (P < 0.01). Significantly greater improvements in glycaemic control were seen in the intervention group compared with the control: the mean reduction in HbA1c in the intervention group was -0.97% (95% CI: -0.8, -1.14) compared with -0.27% (95% CI:-0.15, -0.39) in the control group (p < 0.01). No significant differences between the groups with respect to BP, TC or TG.	Full text article
Krass et al (b) 2005 Australia [148]	Diabetes (type 2)	Randomised controlled trial	188	Medication Management	Two groups - one control (n=82), one intervention (n=106). Intervention = adherence support service delivered monthly over 9 months (medication review to identify and manage drug related problems; strategies to support patient adherence included feedback on self-monitoring of blood glucose levels, education about the disease and medications, adherence devices, reminders, and regular follow-up).	Tertiary	Pharmacist	Statistically significant decrease in self-reported non adherence (as measured by the Brief Medication Questionnaire) in intervention patients (3.89 ± 1.78 vs 2.74 ± 1.39; p< 0.001), no significant difference was seen in control group, between group differences not reported; In patients with complete medication histories the mean number of medications prescribed in the intervention group decreased significantly (8.2 ± 3.0 vs 7.7 ± 2.7; p=0.02), the decrease in the control group (7.6 ± 2.4 vs 7.3 ± 2.4; p=0.27) was not significant. The prevalence of changes in medication regimens was higher in the intervention group (51%) compared with the control group (40%) (P < .001). Reported problems in accessing medications decreased in the intervention group (41% vs 15%; p<0.001) but not the control group.	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					Control = usual care.				
Lecher et al 2015 USA [149]	HIV	Observational study	939	Screening	One group (n=939). Intervention = pharmacist administered rapid oral fluid HIV test	Secondary	Pharmacist	A total of 939 HIV rapid tests were conducted over a median time of 12 months, of which 17 were reactive.	Abstract
Luder et al 2015 USA [150]	CVD + Respiratory	Prospective, quasi-experimental study	90	Medication management	Two groups; one control (n=60) one intervention (n=30). Intervention = medication therapy management for patients discharged from hospital (structured consultation to review medication, identify DRPs, recommend changes to therapy and provide self-management education with follow up call 2 weeks later). Control = usual care	Tertiary	Pharmacist	Within 30 days of intervention more usual care than intervention patients were admitted to hospital (20% vs 6.9%; p=0.019).	Abstract
Lugo De Ortellado et al 2007 Paraguay [151]	CVD	Controlled prospective study	not stated	Medication Management	Two groups; one control (n=not stated), one intervention (n=not stated). Intervention = pharmaceutical care (no detail provided).	Tertiary	Pharmacist	In the intervention group mean decreases in SBP (147 to 128 mm Hg; p<0.05) DBP (89 to 83 mm Hg; p<0.05) were observed. In the control group mean SBP increased (148 to 154 mm Hg; p<0.05) and there was no change in the mean DBP. Of the 45% of the patients classified at stage II hypertension at the beginning of the study, only 9% remained in that stage at the end of it, while the control group either kept or went up to the next classification stage.	Abstract
Luque et al	CVD	Cluster randomised	319	Medication Management	Two groups -one control (n=162), one	Tertiary	Pharmacist	The proportion of BP control at the end of the study was higher in the intervention group compared to the control	Abstract

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
2016 Spain [152]		study			intervention (n=157). Intervention= medication review with at least monthly follow up over 6 months designed to identify and solve drug related problems. Control = usual care.			group (54.6 vs 45.5 %, p<0.001). In the intervention group, there was a decrease of 11.2 mmHg in mean SBP, and of 5.1 mmHg in mean DBP, both statistically and clinically significant (no p values reported). A significant reduction was also achieved in primary and urgent care visits (no p values reported). No significant changes were achieved in specialist visits or hospitalizations. No significant differences were found in the final comparison between groups in QoL (as measured by SF- 36).	
Mac Laughlin et al 2005 USA [153]	Osteo- porosis	Observational study	97	Screening	One group (n=97). Intervention = pharmacist-provided osteoporosis screening with education and referral to GP where appropriate.	Secondary	Pharmacist	Of the 97 study patients who were screened using QUS, 45 (46%) patients were at moderate risk (T-score < -1. to > - 2.5) and nine (9%) were at high risk (T-score:-2.5). Of 54 patients recommended for DXA referral, 20 (37%) completed the scan. All 20 were diagnosed with either osteopenia (9 patients [45%]) or osteoporosis (11 patients [55%]). Correlation was moderate between T-scores obtained by QUS and DXA of lumbar vertebrae 1-4 (r = 0.45, p = 0.026).	Abstract
Malet- Larrea et al 2016 Spain [154]	Multiple	Cluster randomised study	1403	Medication Management	Two groups -one control (n=715), one intervention (n=688). Intervention = medication review with follow up (consultation to identify drug related problems and negative outcomes related to medication and develop and implement and	Tertiary	Pharmacist	The number of medication-related hospitalizations was significantly lower in intervention patients (11 vs 31, p=0.042) as was the percentage of medication-related hospital admissions w (26.2% vs. 73.8%, P < 0.05). The probability of being hospitalized was 3.7 times higher in the control group (odds ratio 3.7, 95% CI 1.2, 11.3, p=0.021).	Full text article *sub- analysis of [141]

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					action plan to address same). Control = usual care				
Malone et al 2003 USA [155]	Risk factor - weight management	Non-randomised controlled study	30	Medication Management	Two groups - one control (n=15) and one intervention (n=15). Intervention = pharmaceutical care (initial consultation, followed by telephone consultation after two weeks and monthly thereafter when collecting medication, designed to identify any problems with orlistat therapy and support medication management). Control = usual care.	Tertiary	Pharmacist	Patients in the intervention group had significantly greater persistence with orlistat therapy as assessed by duration of therapy (p = 0.006) and number of patients completing the 26-week study (7 versus 2; p = 0.046). There was no significant difference in percent of weight loss between groups (p > 0.05).	Full text article
Mangi-apane et al 2005 Germany [156]	Asthma	Non-randomised controlled study	183	Medication Management	One group (n=183). Intervention = structured pharmaceutical care to identify and manage drug related problems, educate patients on asthma pathology, use of asthma medications, inhaler technique and self- management skills.	Tertiary	Pharmacist	Significant improvements were found for asthma-specific quality of life (p<0.001), self-efficacy (p<0.001), knowledge (p<0.001), medication adherence (p<0.001), inhalation technique (p<0.001), self-reported symptoms (p<0.001), asthma severity (p<0.002), dyspnea severity (p<0.05) and peak expiratory flow (p<0.001). Increases in forced expiratory volume in 1 second and vital capacity were not significant over time.	Full text article
Marfo et al 2016	CVD	Observational study	170	Screening	One group (n=170). Intervention =	Secondary	Pharmacy team + pharmacist	Forty-three (25%) patients were pre-hypertensive, 42 (25%) had stage 1 hypertension and 13 (8%) had stage 2 hypertension.	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
Ghana [157]					pharmacy-based screening for hypertension			<p>The most frequent modifiable risk factors identified were lack of exercise 107 (63%), poor diet (42%) and obesity (21%).</p> <p>Lifestyle changes reported at 6 months by participants with pre-hypertension were weight reduction and reduced alcohol intake.</p> <p>Of the 34 participants who were referred to the physician, 10 (29%) were diagnosed with hypertension and an antihypertensive was prescribed.</p>	
Martin Morales et al 2013 Spain + Greece [158]	Erectile dysfunction	Observational study	451	Screening	<p>One group (n=451).</p> <p>Intervention = pharmacy-based screening for erectile dysfunction</p>	Secondary	Pharmacist	<p>Among the 451 men (mean \pm SD age, 54.9 \pm 12.9 years) questioned about ED, 90% had a risk factor (usually hypertension, hypercholesterolemia, or diabetes), 28% had a previous diagnosis, 36% sought internet information, 38% self-medicated, 10% took medication obtained outside the pharmacy setting, and the first health care professional approached was a pharmacist (50%), physician (18%), or nurse (1%) at a median of 6 (range, 0–360) months after symptom onset.</p> <p>The Sexual Health Inventory for Men (SHIM) score was \leq21 (indicative of erectile dysfunction) in 348 (77%) men. Overall, the score indicated mild ED in 160 (46%), mild-to-moderate ED in 111 (32%), moderate ED in 53 (15%), and severe ED in 24 (7%).</p> <p>115/348 men with SHIM score \leq21 responded to a follow-up phone call; 24% (28/115) had visited their physician.</p>	Full text article
Mehuys et al 2008 Belgium [159]	Asthma	Randomised controlled trial	201	Medication Management	<p>Two groups - one control (n=94), one intervention (n=107).</p> <p>Intervention = structured consultation focussed on inhaler technique and medication adherence</p>	Tertiary	Pharmacist	<p>Mean asthma control test (ACT) scores did not change from baseline for either study group. However, a pre-defined subgroup analysis of patients having insufficiently controlled asthma at baseline showed that the intervention had significantly increased the ACT score after 6 months compared with usual care (p=0.038).</p> <p>The need for rescue medication was reduced in both groups from baseline, with a significantly higher reduction in the</p>	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					(3 consultations over 3 months). Control = usual care			<p>intervention group (-0.56 and -0.57 inhalations per day after 3- and 6-month follow-up, respectively) versus the control group (-0.03 and -0.43 inhalations per day after 3- and 6-month follow-up, respectively; p=0.012).</p> <p>Patients in the intervention group experienced less night-time awakenings due to asthma than patients in the control group (p=0.044).</p> <p>Adherence to controller medication during the course of the study, as judged by the prescription refill rates, was higher in the intervention group compared with the control group (mean adherence rate 90.3 versus 74.6%; p=0.016).</p> <p>There was no significant between-group difference in occurrence of severe exacerbations (p=0.158), asthma related quality of life (as assessed by the AQLQ) (p=0.128) and medication adherence as assessed by self-reporting (p=0.108).</p>	
Mehuys et al (b) 2011 Belgium [160]	Diabetes (type 2)	Randomised controlled trial	288	Medication Management + Disease Management	<p>Two groups -one control (n=135), one intervention (n=153).</p> <p>Intervention = structured consultation focused on correct medication use, medication adherence and healthy lifestyle promotion in patients with type 2 diabetes.</p> <p>Control = usual care</p>	Tertiary	Pharmacist	<p>Both study groups showed significant reductions in fasting blood glucose between baseline and the end of the study period [control group: -8.11mg/dL (p= 0.004); intervention group: -14.1mg/dL (p < 0.001) but the between group difference was not significant.</p> <p>For patients whose medication was changed, the fasting blood glucose decreased significantly more in the intervention group, compared to patients to the control group (p = 0.022).</p> <p>The intervention significantly reduced HbA1c (between-group difference: 0.5%, P = 0.009). Eighteen months after the end of the formal study period, the mean HbA1c of the intervention group did not differ significantly from the control group (7.4% vs. 7.2%)</p> <p>Intervention patients had better knowledge of diabetes (knowledge score: +12.7%, p < 0.001; non-significant</p>	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
								increase for control patients) and improved self-management versus control group (physical exercise, p=0.045 and footcare, p<0.001) .	
Messerli et al 2016 Switzerland [161]	Multiple	Randomised controlled trial	450	Medication Management	<p>Two groups - one control (n=232), one intervention (n=218).</p> <p>Intervention = Polymedication Check (PMC); medication review for patients on ≥ 4 medicines designed to identify and address issues with medication knowledge, handling and adherence delivered at the beginning (day 1) and end of a 28 day (day 28) period.</p> <p>Control = usual care followed by PMC at day 28.</p>	Tertiary	Pharmacist	<p>No significant increase of objective adherence (as measured by MPR) was observed.</p> <p>The mean absolute change of subjective (patient self-reported) adherence between T-0 and T-2 was +1.03 % in the intervention and -0.41 % in the control group (p =0.058). Sub-analysis revealed, that the number of patients reporting a change of their adherence of more than ±5 points on a scale 0–100 % between T-0 and T-2 was significantly higher in the intervention group (p = 0.028)</p>	Full text article
Mosca et al 2014 Portugal [162]	Multiple	Non-randomised controlled study	54	Medication Management	<p>Two groups - one control (n=10), one intervention (n=44).</p> <p>Intervention = consultation in pharmacy monthly over four months to assess medication usage and measure blood pressure and cholesterol + medication dispensed in weekly compliance aids.</p>	Tertiary	Pharmacist	<p>No difference was found in the adherence rate between intervention and control patients at month four (p = 1.000).</p> <p>After a bivariate pre-post analysis the only bio-marker to significantly improve from baseline to month 4 in the control group was SBP (p=0.028); in the intervention group fasting glycaemia (p<0.001), HDL-c (p=0.018), systolic (p<0.01) and diastolic (p=0.012) blood pressure significantly improved.</p> <p>When generalised estimating equations were used to include the ‘time in follow-up’ in the analysis, the significance of the use of medicine compliance aids disappeared for all the biomarkers, with ‘time in follow-up’ remaining the only variable associated with the variance in</p>	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					Control = monthly consultations but no weekly compliance aids.			three of the biomarkers analysed: fasting glycaemia, systolic and diastolic blood pressure.	
Murphy et al 2012 UK [163]	Asthma	Uncontrolled before after study	125	Medication Management + Disease Management	One group (n=125). Intervention = consultation to discuss disease management, full medicine review (e.g. instruction on correct inhaler technique, adherence assessment, prescription intervention to ensure appropriate prescribing as per national asthma guideline) and provision of a personalised-asthma action plan.	Tertiary	Pharmacist	Mean ACT scores significantly improved from baseline (17.4 to 20.2, p = 0.002) – increasing for 72% of patients, 40% reaching clinical significance (minimum importance difference of 3). Intention-to-treat analysis confirmed significance (17.1 to 18.9, p ≤ 0.001). The intervention improved QOL scores from 5.1 to 5.6 at 6 months (p = 0.03). Significant improvement in the number of patients who scored 100% in their inhaler technique, from only 23% at baseline to 58% at 6 months (p < 0.001). Significant reduction in the collection of prescriptions for short-acting-beta2-agonists and a highly significant increase in the prescription refill of inhaled corticosteroids (ICS) (p < 0.001). 92% of patients at the end of six months collected at least 80% of their ICS inhalers. The proportion of patients with asthma action plans increased from 15% at baseline to 78% at 6 months.	Abstract
Nau et al 2002 USA [164]	Diabetes (type 2)	Observational study	47	Medication Management + Disease Management	One group (n=32). Intervention = pharmacist provided basic, standardized diabetes education program during three 1-hour sessions accompanied by a clinical assessment and a report to the patient's primary care physician.	Tertiary	Pharmacist	Significant improvement in total cholesterol (p=0.015) and LDL (p=0.017). HbA1c, BMI, BP, HDL and TG did not change significantly across all patients but in 10 patients with baseline HbA1c >8%, the average HbA1c declined significantly, from 9.8% to 8.6% (p=0.015).	Full text article
Nietert et	Multiple	Randomised	3048	Medication	Three groups - control	Tertiary	Pharmacist	No significant difference in adherence (as measured by	Full text

Author(s)	Disease	Study design	Sample	Intervention				Main	Record	
al 2009 USA [165]		controlled trial		Management	(n=1,014), intervention A (n=1,018), intervention B (n=1,016). Intervention A = pharmacist contact with the patient via telephone to remind them their medications were overdue for collection; to identify any adherence problems and to help patients to overcome adherence problems where possible. Intervention B = pharmacist contact with the patient's prescribing physician via facsimile to notify them that medications were overdue and to provide written prompts to support patient adherence. Control = usual care.				time to refill prescription) between groups.	article
Nola et al 2000 USA [166]	CVD	Controlled before after study	51	Medication Management	Two groups; one control (n=26), one intervention (n=25). Control = usual care. Intervention = pharmacist led disease management program which provided diet and	Tertiary	Pharmacist	No statistically significant between or within group differences were observed for TC, LDL-C and TG. HDL-C levels increased significantly from pre to post test in both groups (<0.01) but there was no significant between group difference observed. In the intervention group 32% of patients achieved their cholesterol goals, compared with 15% of control group patients; this between group difference was not significant	Full text article	

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					exercise evaluation and instruction, monitoring of cholesterol levels and drug therapy, education to increase patient knowledge and compliance to diet, exercise and drug therapy and collaboration with physician where suspected or potential drug therapy problems were identified.			(p=0.08). The treatment group's hyperlipidemia knowledge scores improved significantly from pretest to posttest (p<0.01) but no significant between group differences were observed at study end.	
Obarcanin et al 2015 Germany [167]	Diabetes (type 1)	Randomised controlled trial	68	Medication Management	Two groups -one control (n=28), one intervention (n=40). Control = usual care. Intervention = structured pharmaceutical care (a minimum of 6 consultations over six months to identify and address drug related problems, provide self-management education and encourage attainment of a least one treatment goal).	Tertiary	Pharmacist	The improvement from baseline in HbA1c was significantly greater in the intervention group than in the control group after 6 months (change from baseline -0.54 vs. +0.32 %, p=0.0075), even after adjustment for country-specific variables (p = 0.0078). However, the effect was more pronounced after only 3months (-1.09 vs. +0.23 %, p = 0.00002). There was no significant between-group difference in the number of severe hypoglycemia events. (p=0.1276). Wellbeing scores (as measured by WHO-5) improved significantly to 59.2 % at 3 months (p = 0.0002) and to 63.3% at 6 months (p = 0.00002).	Full text article
Odegard et al 2012 USA [168]	Diabetes (type 2)	Randomised controlled trial	265	Medication Management	Two group - one control (n=145), one intervention (n=120). Control = usual care. Intervention =	Tertiary	Pharmacist	At 12 months, MPR was significantly improved for the intervention group (p = 0.004) compared with the control group (difference between groups, p= 0.01). The intervention showed greater effect for patients with baseline MPR less than 80% (difference between groups p=0.02).	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					telephone-initiated adherence support by pharmacists following computer-generated missed refill alerts (two consultations over 1 month)			The likelihood of MPR above 80% at the 12-month follow-up for any patient significantly favoured the intervention group (odds ratio 4.77 [95% CI 2.00-11.40]).	
Olenak et al 2010 USA [169]	CVD	Observational study	239	Screening	One group (n=239). Intervention = pharmacy-based screening for metabolic syndrome (including assessment of Framingham risk score and medication usage).	Secondary	Pharmacist	The prevalence of metabolic syndrome in the sample was 36%. The Framingham risk assessment of patients with metabolic syndrome and no known history of diabetes revealed that 65.3% were at low risk, 26.4% were at moderate risk, and 8.3% were at high risk for CHD. Of the study population with no known history of prediabetes or diabetes, 26% had an abnormal glucose reading. Of those with metabolic syndrome, 87% self-reported a lifestyle modification in the area of diet, exercise, or weight loss in the following 3- to 6-month follow-up period.	Abstract
Oparah et al 2006 Nigeria [170]	CVD	Uncontrolled before after study	42	Medication Management + Disease Management	One group (n=42). Intervention = structured pharmaceutical care (verbal counselling, provision of an information leaflet, and subsequent monitoring with reinforcement).	Tertiary	Pharmacist	There was a significant difference between mean SBP at baseline (187.67 ± 29.46 mmHg) and at the end of the study (137.22 ± 21.65 mmHg), $p < 0.0001$ and for changes in mean DBP at (117.56 ± 21.65 vs 89 ± 17.23), $p < 0.0001$. Some 27 (75%) reached systolic blood pressure goals while 25 (69%) attained diastolic blood pressure goals. Self-reported compliance scores were greater (higher score = greater compliance) at study completion (30.23 ± 6.40 vs 25.57 ± 7.46) ($p = 0.006$).	Full text article
O'Reilly et al 2015 Australia [171]	Depression	Observational study	41	Screening	One group (n=41). Intervention = pharmacy-based screening for depression using one of three	Secondary	Pharmacist	40/41 assessments involved the use of a screening tool. 70% of screening assessments involved female patients. 29 referrals (71% of patients) were made - 25 to GP, 3 to psychologist, 1 unknown.	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					screening tools (Beyondblue Depression Checklist, the Patient Health Questionnaire-9 (PHQ-9) and the WHO Well-being index 5 (WHO-5)).				
Ottensbros et al 2014 Holland [172]	Asthma/ COPD	Prospective cohort study	109264	Medication Management	Two groups - one control (n=105,507), one intervention (n=3,757). Intervention = structured pharmacy care to identify drug related problems and liaise with GP to resolve such problems. Control = usual care (patients were not actively recruited to the control group, but their medication records were reviewed).	Tertiary	Pharmacist	The mean number of prescriptions for high dose antibiotics or corticosteroids (as a proxy for exacerbations) decreased in selected intervention group patients by 0.54 (95 % CI 0.21-0.86) treatments. Statistically significant between group differences were reported favouring the intervention when comparing the reduction in a range of drug related problems (e.g. use of obsolete medicine, use of contra-indicated co-medication, use of powder inhalers in the elderly) except for cessation of long acting beta mimetic drugs; however, no p values reported.	Full text article
Park et al 1996 USA [173]	CVD	Randomised controlled trial	53	Medication Management + Disease Management	Two groups - one control (n=27), one intervention (n=26). Intervention = monthly consultations with blood pressure and heart rate assessments and counselling on lifestyle modifications and drug therapy.	Tertiary	Pharmacist	Results stated that blood pressure control was significantly improved in the study group (no p value given)	Abstract

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					Control = initial and final blood pressure measurements and minimal counselling.				
Paulos et al 2005 USA [174]	CVD	Randomised controlled trial	42	Medication Management + Disease Management	<p>Two groups- one control (n=19), one intervention (n=23).</p> <p>Intervention = pharmaceutical care (consultation to identify, resolve or prevent drug related problems and to provide disease and medication management education).</p> <p>Control= usual care.</p>	Tertiary	Pharmacist	<p>Significant decrease in TC in the intervention group (mean decrease 27.0 ± 41.1 mg/dL, $p = 0.0266$); in the control group, the average blood cholesterol level decreased by a mean of 1.4 ± 37.2 mg/dL ($p = 0.6624$).</p> <p>In the intervention group, the TC level decreased an average of 50.5 ± 80.3 mg/dL ($p = 0.0169$), while the control group experienced a mean triglyceride level increase of 29.6 ± 118.5 mg/dL ($p = 0.1435$).</p> <p>The BMI of the intervention group participants decreased by 0.4 ± 0.5 kg/m² ($p = 0.0176$).</p> <p>At the end of the study, there was a significant difference in the quality-of-life index between the 2 groups ($p = 0.002$) where none was observed at start of study.</p>	Full text article
Petkova et al 2012 Bulgaria [175]	Asthma/ COPD	Randomised controlled trial	86	Medication Management + Disease Management	<p>Two groups - one control (n=43), one intervention (n=43).</p> <p>Intervention = asthma and COPD self-management and medication education.</p> <p>Control = usual care.</p>	Tertiary	Pharmacist	<p>The health-related quality of life of the intervention patients improved at 3 months ($P = 0.044$).</p> <p>PEF and FEV1% significantly improved for the intervention patients compared to the control groups ($p < 0.05$) at three months.</p> <p>Inhaler technique improved in the intervention groups ($p = 0.021$).</p> <p>Self-reported hospitalisation rates were lower in the intervention group ($p = 0.001$).</p> <p>After the education, significantly more patients in the intervention group than in the control group (37 % vs. 9 %) reported no occurrence of asthma symptoms (cough, chest tightness and shortness of breath) at all ($p = 0.013$).</p>	Full text article
Petkova, V. B	Asthma	Randomised controlled	50	Medication Management	Two groups - one control (n=28), one	Tertiary	Pharmacist	The difference in PEF and inhaler technique between the 4-month stage and baseline was significantly higher (and	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
2008 Bulgaria [176]		trial		+ Disease Management	intervention (n=22). Intervention = asthma self- management and medication education Control = usual care.			improved scores) in the intervention group than in the control group (no p values reported). After the education session significantly more patients in the intervention group than in the control group (32% versus 4%) reported no occurrence of certain asthma symptoms (cough, chest tightness and shortness of breath) (p = 0.013). The self-reported hospitalization rates were significantly different between the two groups and lower in the intervention group (p = 0.001).	
Petkova, V. B (b) 2009 Bulgaria [177]	Arthritis	Randomised controlled trial	86	Medication Management + Disease Management	Two groups - one control (n=43), one intervention (n=43). Intervention= disease and medication management program delivered in pharmacy over 4 months	Tertiary	Pharmacist	Patients in the intervention group experienced a greater reduction in pain (p=0.001) than control patients. Intervention patients were more adherent to prescribed medication at 4 months versus baseline (88.4% vs 53.5%; p <0.0001); same effect not seen in control patients (72.1% vs 65.1%, p=0.083). There was a reduction in the frequency of urgent medical aid calls in the intervention group (65.1% vs 41.9%, p=0.001); this increased in the control group (58.1% vs. 62.8%, p=0.16). Adverse drug reactions (ADRs) decreased in the intervention group (79.1% vs 30.2%, p<0.001); they dropped slightly in control group but not significantly (86.0% vs. 79.1%, p=0.083). No significant differences in overall QoL scores in either group but some improvements seen in the intervention group for certain domains (general activity, mood, relations with other people and enjoyment of life; p<0.05).	Full text article
Petroni et al 2013 Malta [178]	Risk factor - weight management	Unclear - controlled study but no randomisation described	200	Risk factor management	Two groups - one control (n=60), one intervention (n=69). Control = not defined.	Primary	Pharmacist	Waist circumference decreased significantly in both the experimental (p = 0.000) and the control groups (p = 0.000). There was a trend towards an increase in BMI, BP, HR	Abstract

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					Intervention = weight monitoring program (weight management education and monitoring).			(heart rate), blood glucose and cholesterol for the control group and a decrease in BMI and BP for the experimental group (none statistically significant).	
Planas et al 2012 USA [179]	Diabetes (type 2)	Randomised controlled trial	55	Medication Management + Disease Management	<p>Two groups - one control (n=27), one intervention (n=38).</p> <p>Intervention=all control visits/measurements + diabetes education and self- management services on a monthly basis (one on one 1hr consultation with pharmacist to receive education, coaching in self-management skills (e.g. blood glucose monitoring, medication adherence) and medication management to identify and manage drug therapy problems).</p> <p>Control = visits at baseline and 3, 6, and 9 months, during which A1C, blood pressure, and LDL cholesterol levels of participants were recorded and participants were informed of goal levels</p>	Tertiary	Pharmacist	<p>The percentage of individuals in the intervention group meeting the goal for A1C was significantly higher than in the control group at 9 months (P < 0.002; 46.7% vs 9.1%).</p> <p>The percentage of individuals in the intervention group meeting the goal for BP was significantly higher than in the control group at 9 months (P < 0.02; 53.3% vs 22.7%).</p> <p>Intervention patients had significant better improvements than control patients in HbA1c (p<0.02) and SBP (p<0.01) measurements between baseline and 9 months, levels decreased (improved) for intervention patients and increased for control groups.</p> <p>No significant changes in LDL cholesterol or DBP were found between the two groups from baseline to 9 months.</p> <p>The odds of the intervention group attaining the composite goal (where two of the three treatment goals of A1C, BP LDL were reached) were 5.87 times greater than the control group.</p>	Full text article
Planas, L. G	Diabetes (type 2)	Randomised controlled	65	Medication Management	Two groups - one control (n=27), one	Tertiary	Pharmacist	An intention to treat analysis showed a greater reduction in mean A1 c after nine months in the intervention group (-	Abstract

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
2007 USA [180]		trial		+ Disease Management	intervention (n=38). Intervention = diabetes medication therapy management, monthly visits over 9 months. Control =HbA1v monitoring once every 3 months.			0.41) than in the control group (+0.07); no p values reported At nine months, a greater percentage of intervention group patients (42.11%) were at goal BP than were control group patients (11.1%); no p values reported.	
R. Martínez Pérez et al 2009 Spain [181]	CVD	Observational study	2574	Screening	One group (n=2574). Intervention = pharmacy-based screening of risk factors for cardiovascular disease combined with measurement of arterial pressure.	Secondary	Pharmacist	Prevalence of high blood pressure in the sample was 33.6%, and prevalence of arterial hypertension was 22.8%. The risk of having arterial hypertension was 4.23 times higher in patients aged 65 years and over (p<0.001), 2.88 times greater in those who had been previously diagnosed with arterial hypertension (p<0.001), 2.79 times higher in overweight or obese patients (p<0.001) , 2.69 times more in those with diabetes mellitus (p<0.001) and 2.22 times higher in men compared with in women (p<0.001).	Full text article
Richmond et al 2010 UK [182]	Multiple	Randomised controlled trial	760	Medication Management	One group (n=760); Multiple interrupted time-series design where participants acted as their own controls. Intervention= pharmaceutical care (medication review to identify drug related problems and plan interventions to address same in conjunction with patients GP) monthly over 12 months	Tertiary	Pharmacist	The intervention did not lead to any statistically significant change in the appropriateness of prescribing or health outcomes.	Full text article
Robinson et al	CVD	Non-randomised	376	Medication Management	Two groups - one control (n=196), one	Tertiary	Pharmacist	A larger proportion (50%) of intervention patients who had poorly controlled hypertension at baseline (>140/90	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
2010 USA [183]		controlled study			intervention (n=180). Intervention= structured pharmaceutical care (disease management education, drug therapy review and monitoring). Control = usual care.			mmHg) were controlled compared with control patients (22%) at study completion; no p values reported. Intervention patients demonstrated larger improvements in QOL in physical and social function ($p < 0.05$) compared with control patients, although intervention patients at baseline reported lower levels of QOL for these dimensions compared with control patients. The average reduction in SBP was 9.9 mm Hg in intervention patients compared with 2.8 mmHg in control patients ($p < 0.05$). Changes in DBP were similar in the intervention and control groups. Based on patient self-report, intervention patients were more likely to say that they take their medicines as prescribed compared with control patients ($p < 0.05$). The 1- to 6-month antihypertensive adherence rate was higher in intervention patients (0.91 ± 0.15) compared to control patients (0.78 ± 0.30) ($p = 0.02$); there was no significant difference in adherence rate during the 7- to 12-month period.	
Rodriguez - Chamorro et al 2013 [184]	CVD	Uncontrolled before after study	117	Medication Management	One group (n=117). Intervention = structured pharmaceutical care to identify and resolve any potential or actual drug related problems.	Tertiary	Pharmacist	Statistically significant increase in the percentage of patients achieving their hypertension (67.5% vs 43.6%; $p < 0.001$) and total cholesterol (52.9% vs 37.6%; $p < 0.001$) targets from baseline to six months. Statistically significant decreases in SBP(137.6 vs 130mmHg) , DBP (80.8 vs 77.4mmHg) and TC levels (80.8 vs 77.4mg/dL) (all: $p < 0.001$) as well as BMI (29.2 vs 28.9, $p = 0.004$) . Statistically significant decreases in the average Wilson-Grundy CVR (-1.5%, $p < 0.001$), and the quantitative CVR SCORE (-0.5%, $p = 0.003$).	Full text article
Rosser et al 2013	Depression	Observational study	3,726	Screening	One group (n=3,726). Intervention: Screening	Secondary	Pharmacist	A total of 67 (1.8%) patients screened positive on the PHQ-2.	Abstract

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
USA [185]					for depression using the Patient Health Questionnaire (PHQ-2 ± PHQ-9) with referral to physician where indicated.			Of the patients who completed the PHQ-9, approximately 25% met the criteria for consideration of diagnosis and were referred to their physician. Five patients presented with suicidal thoughts and were referred for urgent treatment. Approximately 60% of patients with a positive PHQ-9 had initiated or modified treatment at the time of follow-up.	
Rubio-Valera et al 2013 Spain [186]	Depression	Randomised controlled trial	179	Medication Management	Two groups -one control (n=92), one intervention (n=87). Intervention= medication therapy management (education to support medication knowledge and adherence delivered over a six-month period). Control = usual care.	Tertiary	Pharmacist	Patients in the intervention group were more likely to remain adherent at 3 and 6 months follow-up but the difference was not statistically significant (ITT p=0.209; PP p=0.055). Patients in the intervention group showed greater statistically significant improvement in HRQoL compared with control patients both in the ITT (p=0.034) and PP (p=0.042) analyses. No statistically significant differences were observed in clinical symptoms.	Full text article
Saini et al 2008 Australia [187]	Asthma	Non-randomised controlled study	90	Medication Management + Disease Management	Two groups - one control (n=39), one intervention (n=51). Intervention= Rural Asthma Management Service (RAMS) - needs analysis for asthma management (disease and medication management), identifying and documenting goals, delivering interventions e.g. inhaler technique	Tertiary	Pharmacist	Significantly lower asthma severity scores (composite score based on recency, frequency and severity of asthma symptoms, and asthma history) in the intervention group compared to control group at final visit (month 6) (7.9 ± 2.6 versus 10.4 ± 2.6 , $P < 0.001$); severity score decreased significantly from baseline to final visit in intervention group only (no p value reported). Within the intervention group there was significant improvement between the post-bronchodilator PEF readings at baseline and the final visit (a 4% increase from 369.8 ± 103.2 L min ⁻¹ to 385.0 ± 111.0 L min ⁻¹ , $P = 0.002$), improvement in the peak flow index (minimum morning peak flow/recent best peak flow x 100) values between visits 1 and 4 ($75.4 \pm 13.6\%$ to $85.6 \pm 16.4\%$, $P <$	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					education and monitoring progress over a 6-month period (minimum 3 consultations with pharmacist). Control = Usual care.			0.001), inhaler technique for aerosol inhalers (from 81.0± 21.1% to 96.1 ± 18.3%, P = 0.01) , for accuhalers (from 80.5 ± 27.5% to 97.2 ± 7.2%, P = 0.02). Comparing groups at final visit the intervention group had significantly better scores for risk of non-adherence (BMQ score, scale 1-11:1 lowest risk) (1.6 ± 0.7 versus 2.3 ± 1.1; p=0.002) , level of confidence in managing an asthma attack (scale 1-5: 1=most confident)(1.7 ± 1.0 versus 2.3 ± 1.2; p=0.04), perceived control over asthma (scale 11-55: 11=lowest confidence)(43.4 ± 5.6 versus 40.5 ± 5.1; p=0.02).	
Saini et al (b) 2004 Australia [188]	Asthma	Randomised controlled trial	102	Medication Management + Disease Management	Two groups - one control (n=50), one intervention (n=52). Intervention= structured pharmaceutical care - needs analysis for asthma management (based on the Australian Six-Step Asthma Management Plan), identification, documentation and delivery of personalised interventions based on needs analysis, collaborative (patient and pharmacist) goal setting, monitoring progress over a 6 month period (minimum 3 consultations with pharmacist) and collaborating with other health care professionals involved	Tertiary	Pharmacist	In the intervention group, between baseline and final visit, mean asthma severity score (2.6 ± 0.5 to 1.6 ± 0.7; p = 0.001) and peak flow index (from 82.7% ± 8.2% to 87.4% ± 8.9%; p < 0.001) improved, mean daily dose of salbutamol decreased (374.8 ± 314.8 µg to 198.5 ± 196.9 µg; p = 0.01), mean daily dose of Seretide (a device containing salmeterol and fluticasone) increased (600.0 ± 0.0 µg to 933.3 ± 250.0; p = 0.008) and the number of patients on an ideal profile of reliever, preventer, and symptom controller medication increased from 7.7% to 28.8% (p < 0.001). A greater level of asthma management plan ownership was seen in intervention group at final versus the control group (p < 0.001). Better scores for the following measures were seen post intervention for the intervention group versus control group: quality of life (p<0.001), perceived control over asthma (p<0.001) and asthma knowledge (p=0.04).	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					in the asthma care of the patient as required. Control = Usual care.				
Schulz et al 2001 Germany [189]	Asthma	Cluster randomised study	242	Medication Management + Disease Management	Two groups - one control (n=81), one intervention (n=161). Intervention= pharmaceutical care to detect and solve individual drug and health related problems, inhaler technique assessment, education on disease and adherence as well as medication usage including inhaler technique instruction where required. Control = Usual care.	Tertiary	Pharmacist	Intervention patients had significantly better scores versus control group at study completion for: inhalation technique (6.7 ± 0.1 versus 5.8 ± 0.3 ; $p=0.001$), asthma-specific quality of life (66.6 ± 4.4 versus 55.8 ± 6.2 ; $p=0.018$), the mental health summary score of the SF-36 (45.6 ± 2.0 versus 42.8 ± 2.7 ; $p=0.003$), self-efficacy score (66.7 ± 2.7 versus 59.4 ± 3.6 ; $p=0.05$).	Full text article
Shen et al 2014 USA [190]	Risk factor - smoking cessation	Observational study	1437	Smoking Cessation	One group (n=1437). Intervention= pharmacist-assisted tobacco cessation program (at initial visit pharmacists prescribed tobacco cessation medication and/or patients received free counselling sessions with pharmacist and patients were followed up at month 1,3 and 6 to provide additional	Primary	Pharmacist	The average point prevalence quit rate at 1 month, 3 months, and 6 months was 29.3%, 23.3%, and 18.0%, respectively. Based on the authors definition for quitting patterns, the study sample consisted of 145 (10.1%) immediate quitters (achieved initial abstinence by 1 month and remained abstinent at month 3 and 6), 113 (7.9%) delayed quitters (did not successfully quit at 1 month or at both 1 month and 3 months but eventually succeeded at 6 months), 298 (20.7%) once quitters (quit smoking at either 1 month or 3 months but relapsed by 6 months), and 881 (61.3%) never quitters (failed to quit).	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					counselling and support as required).				
Shibley et al 1997 USA [191]	CVD	Uncontrolled before after study	25	Medication Management	One group (n=25). Intervention = pharmaceutical care (patient assessment, assistance in setting therapeutic goals, one visit with registered dietician, drug therapy recommendations to doctor if required).	Tertiary	Pharmacist	TC and LDL cholesterol values were significantly decreased at 12 months compared with either the baseline or 6-month values (p < 0.02). Significant improvement was found in several domains of the surveys; quality of life, patient satisfaction with pharmacy services, and patient opinions on the role of the pharmacist improved after the intervention (p value not reported).	Abstract
Smith et al 2013 UK [192]	Hayfever	Cluster randomised study	125	Disease Management	Two groups - one control (n=65), one intervention (n=60). Intervention = disease management (developing strategies for setting goals to avoid/minimise triggers for, and eliminate/minimise symptoms of, allergic rhinitis). Control = usual care.	Tertiary	Pharmacy team	One week after intervention, the median change in quality of life as measured by the validated mini-Rhinoconjunctivitis Quality of Life Questionnaire (miniRQLQ) was 1.07 points for the control group and 0.57 for the intervention group (where a change of 0.5 points is clinically significant), and by six weeks, the median change from baseline was 1.25 (usual care) and 1.54 (intervention).	Abstract
Søndergaard et al 2006 Denmark [193]	Migraine	Randomised controlled trial	2463	Medication Management	Two groups -one control (n=1,340), one intervention (n=1,123). Intervention = pharmaceutical care in the form of an information leaflet and structured consultation to identify and reduce	Tertiary	Pharmacist	The pharmaceutical care consultation had no statistically significant impact on the patients' consumption of triptans	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					any potential overuse of triptans. Control=usual care.				
Stergachis et al 2002 USA [194]	Asthma	Randomised controlled trial	330	Medication Management + Disease Management	Two groups- one control (n note reported); one intervention (n not reported). Intervention = pharmaceutical care; individualized asthma management services during patient-pharmacist encounters for up to 1 year following the patient's enrollment into the study. Control = usual care.	Tertiary	Pharmacist	The intervention had no significant effect on the health or health services use outcomes of study subjects. When compared with the control group, there was no evidence that patients from the intervention group experienced improvements in pulmonary function, functional status, quality of life, asthma management, or satisfaction with care. In addition, there were no differences between groups in use of anti-inflammatory medications, total or asthma-related medical care utilization, or total or asthma-related school days lost.	Abstract
Sturgess et al 2003 Northern Ireland [195]	Multiple	Randomised controlled trial	191	Medication Management + Disease Management	Two groups; one control (n=81), one intervention (n=110). Intervention = structured pharmaceutical care (individual consultation to identify actual and potential drug related problems and to develop an intervention and monitoring plan). Control=usual care.	Tertiary	Pharmacist	A significantly higher proportion of intervention patients were compliant (self-reported) at the end of the 18-month study and experienced fewer problems with medication compared to control patients (P < 0.05). No significant impact on quality of life and health care utilisation.	Full text article Country specific report of the intervention in [97]
Stuurman-	CVD	Controlled	1002	Medication	Two groups- one	Tertiary	Pharmacist	In the first year after treatment initiation of lipid-lowering	Full text

Author(s)	Disease	Study design	Sample	Intervention			Main	Record	
Bieze et al 2013 Holland [196]		before after study		Management	control (n=502), one intervention (n=500). Intervention = pharmaceutical care for patients on lipid lowering medication (structured consultation to identify any drug related problems, continuous monitoring of patients' adherence to lipid-lowering drugs and personalised counselling with nonadherent patients). Control= usual care.			drugs, 130 (25.9%) usual care patients discontinued therapy, compared with 68 (13.6%) patients in the intervention group (P < .001); 38 (7.6%) usual care patients and 16 (3.2%) intervention patients continued use but were nonadherent (P = 0.003). 33.5% of patients in the control group initiating lipid- lowering drugs discontinued or were nonadherent, compared with 16.8% of patients in the intervention group (P < .001). The rate of drug discontinuation was significantly lower in the intervention group compared with the usual care group: hazard ratio = 0.49; 95% confidence interval [CI] = 0.37- 0.66. The intervention decreased the risk for discontinuation by 51% (95% CI = 0.34-0.63) compared with usual care. Multivariate correction for age, gender, and increased risk for cardiovascular events did not influence this effect.	article
Stuurman- Bieze et al (b) 2014 Holland [197]	Osteo- porosis	Controlled before after study	937	Medication Management	Two groups - one historical reference group (n=442), one intervention (n=495). Intervention = MeMO (MedicationMonitoring and Optimization) - two initial structured consultations (2 weeks apart) to discuss medication administration, effectiveness and possible side effects followed by continuous monitoring of patients' adherence to their	Tertiary	Pharmacist	The rate of drug discontinuation or nonadherence was significantly lower in the intervention group compared to the usual care group [hazard ratio 0.54 (95 % confidence interval (CI) 0.42–0.70)]. In the usual care group, 32.8 % of patients initiating osteoporosis medication discontinued or were nonadherent, compared to 19.0 % of patients in the intervention group (P<0.001). In the first year after treatment initiation of osteoporosis medication, 123 (27.8 %) usual care patients discontinued therapy, compared to 78 (15.8 %) patients in the intervention group (P<0.001).	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					osteoporosis medication over a one-year period and tailored counselling sessions with nonadherent patients. Control=usual care.				
Sushil-kumar et al 2015 India [198]	CVD	Observational study	98	Screening	One group (n=98). Intervention = screening for high blood pressure, blood glucose, height, weight and BMI in patients ≥18yrs previously diagnosed with diabetes (Type 1 and 2) and/or hypertension.	Secondary	Pharmacist	58 out of 98 (59.18%) patients had both diabetes and hypertension, 26 (26.53%) were hypertensive and 14 (14.28%) were diabetic. 44 patients (44.89%) were in normal range for BMI, 40 (40.81%) were overweight and 14 (14.28%) were classed as obese. 42/98 (42.9%) patients were classed as Stage 1 hypertensive (SBP 140-159mmHg) and 12/98 (12.2%) as Stage 2 hypertensive (SBP>160mmHg). 33/98 (33.7%) had blood glucose measurement in the normal range (60-160mg/dl), 44/98 (44.9%) in the moderate range (160-200mg/dl) 21/98 (21.4%) in the severe range (>200mg/dl).	Full text article
Svarstad et al 2013 USA [199]	CVD	Cluster randomised study	576	Medication Management	Two groups - one control (n=300), one intervention (n=276). Intervention = medication adherence support in the form of structured consultations to identify and address barriers to adherence as well as take home education leaflets, encouragement to monitor blood pressure and implement lifestyle	Tertiary	Pharmacy team + pharmacist	Compared with control participants at 6 months, intervention participants achieved better refill adherence (60% vs. 34% p<0.001), reduction in SBP (-12.62 vs. -5.31 mm Hg, p < 0.001), DBP (-8.63 vs. -5.68 mm Hg, p =0.01) and improved blood pressure control (50% vs. 36%, p=0.01). At 12 months, intervention participants continued to show better refill adherence (62% vs. 44% p<0.001 and reduction in SBP (-13.64 vs. -8.30 mm Hg, p = 0.004).	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					change where appropriate. Control=patient education in the form of a booklet about hypertension, guide on lowering BP and information on their BP level.				
Teichert et al 2012 Holland [200]	Multiple	Observational study	980 +	Medication Management	Two groups; one control (n not reported); one intervention (n=980). Intervention = medication use review. Control = usual care.	Tertiary	Pharmacist	At follow-up mean number of HARM (drug related risks) items decreased in intervention participants by 0.05 (0.09 in patients with complete medication review) and 0.07 in controls. Between-group differences were not significant.	Abstract
Tommelein et al 2014 Belgium [201]	COPD	Randomised controlled trial	734	Medication Management + Disease Management	Two groups - one control (n=363), one intervention (n=371). Intervention = structured pharmaceutical care in the form of two consultations, one month apart, addressing disease awareness, medication management including inhaler technique and adherence, self-management education and smoking cessation	Tertiary	Pharmacist	Inhalation score [mean estimated difference (Δ), 13.5%; 95% confidence interval (CI), 10.8–16.1; $P < 0.0001$] and medication adherence (Δ , 8.51%; 95% CI, 4.63–12.4; $P < 0.0001$) were significantly higher in the intervention group compared with the control group post intervention. After 3 months, the odds of obtaining an inhalation score of 100% after receiving the intervention vs. no intervention was 3.03 (95% CI, 2.12–4.34; $P < 0.0001$). In the intervention group, a significantly lower hospitalization rate was observed (9 vs. 35; rate ratio, 0.28; 95% CI, 0.12–0.64; $P = 0.003$).	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					support where relevant. Control=usual care.				
Tsuyuki et al 2002 Canada [202]	CVD	Randomised controlled trial	675	Disease Management	Two groups- one control (n=331), one intervention (n=344). Intervention= pharmacy program focussed on providing verbal and written education on risk factors, point-of-care cholesterol measurement, physician notification of any risk factors identified and any suggestions recommended, referral to their physician if required, and regular follow-up for 16 weeks. Control = brochure on risk factors, general advice, minimal follow up.	Tertiary	Pharmacist	The primary end point (composite measure representing improvement in the process of cholesterol risk management) was reached in 57% of intervention patients vs 31% in usual care (odds ratio, 3.0; 95% confidence interval, 2.2-4.1; p<0.001). Measurement of a fasting cholesterol panel performed by the primary care physician was attained in 53% of patients in the intervention group vs 29% in usual care group (OR, 2.8; 95% CI, 2.0-3.7; p<0.001). New prescription for a cholesterol-lowering medication was attained in 10% of patients in the intervention group vs 4% in the usual care group (OR,2.5; 95% CI, 1.3-4.6; p<0.003). The external monitoring committee recommended early study termination owing to benefit.	Full text article
Tsuyuki et al (b) 2016 Canada [203]	CVD	Randomised controlled trial	99	Pharmacist prescribing	Two groups - one control (n=50), one intervention (n=49). Intervention = pharmacist-directed dyslipidemia care, including assessment of cardiovascular risk, review of LDL-c, prescribing of	Tertiary	Pharmacist	A higher proportion of intervention patients achieved LDL-c target at 6 months (43% vs 18% control, p = 0.007). Adjusted odds of achieving target LDL-c were 3.3 times higher for the intervention group (p = 0.031), who also achieved greater reduction in LDL-c (1.12 mmol/L vs 0.42 mmol/L; adjusted mean difference =0.546 mmol/L, p < 0.001).	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					<p>medications, health behaviour interventions and follow-up every 6 weeks for 6 months.</p> <p>Control = usual care + lipid results and disease awareness leaflet.</p>				
Van Boven et al 2016 Holland [204]	COPD	Controlled before after study	88	Medication Management + Disease Management	<p>One group (n=88). Intervention = MeMO (Medication Monitoring and Optimization) which involved a structured consultation to provide education on medication (inhalation technique, adherence) and disease/lifestyle (smoking cessation, diet, exercise) management.</p>	Tertiary	Pharmacist	<p>Mean quality of life scores (measured by the CCQ, Clinical COPD Questionnaire) showed improvement 1 year after intervention but the only statistically significant improvement was in the mental sub-score (p<0.05).</p> <p>There was a significant decrease in exacerbations (-0.82) per patient per year (p<0.05).</p> <p>There were no other statistically significant changes in clinical or medication adherence outcomes.</p>	Full text article
Van De Steeg-Van Gompel et al 2010 Holland [205]	CVD	Cluster randomised study	74	Medication Management	<p>Two groups - one control (n=24), one intervention (n=50).</p> <p>Intervention =structured adherence support (2 consultations over 2 months + electronic monitoring) delivered in pharmacies where pharmacy teams received intensive training on the intervention.</p> <p>Control = structured adherence support (2</p>	Tertiary	Pharmacist	<p>Pooled patient outcomes from both group (as no between group differences were observed). After 5 months mean change in blood pressure was -12 mmHg SBP and -6 mmHg DBP, (no p value for difference was reported).</p> <p>20.9% (vs 13.7% at baseline) of all patients had SBP <140 mmHg (no p value reported).</p> <p>In 13.6% of patients control of SBP was achieved without treatment intensification.</p>	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					consultations over 2 months + electronic monitoring) delivered in pharmacies where training consisted of written material only.				
Vinks et al 2009 Holland [206]	Multiple	Non-randomised controlled study	174	Medication Management	Two groups - one control (n=87), one intervention (n=87). Intervention =structured medication review (SMOG - Screening Medications in the Older Drug User) to identify actual and potential DRPs and suggest interventions to address them. Control = usual care.	Tertiary	Pharmacist	The intervention led to a significant reduction in the mean number of potential DRPs between the intervention and control patients (-20.3% vs -4.0%; mean difference -16.3% 95% CI -24.3, -8.3; no p value reported). No significant reduction in the number of drugs was seen in any patient group.	Full text article
Weidle et al 2014 USA [207]	HIV	Observational study	1,540	Screening	One group (n =1,540). Intervention = screening for HIV using a point of care test in community pharmacy (rapid HIV antibody test on oral fluid).	Secondary	Pharmacist	There were 1,508 nonreactive test results, 24 (1.6%) reactive test results (preliminary positives), and 8 invalid tests. In each instance of a reactive test the patient was counselled and referred for confirmatory testing. In 16 of these cases, the outcome of confirmatory testing was unknown to site staff. Of the remaining eight reactive test results, five were determined to be false-positive on confirmatory testing, two involved persons previously diagnosed with HIV, and one was confirmed as a new HIV case.	Full text article
Wermeille et al 2004 Scotland [208]	Diabetes (type 2)	Uncontrolled before after study	62	Medication Management	One group (n=62). Intervention = structured pharmaceutical care	Tertiary	Pharmacist	A reduction in HbA1c (8.3% vs 7.5%; p<0.001), blood pressure (SBP: 152.0mmHg vs 141.6mmHg; p<0.001, DBP 81.2mmHg vs 79.2mmHg; p<0.001) and TC (5.3 mmol/L vs 4.9 mmol/L; p<0.001) was observed over the study period.	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
					(consultation to identify actual and potential drug related problems, propose solutions and develop a pharmaceutical care plan with follow up after 1 month).			An improvement in patients' knowledge (as measured by % correct questions) of their oral hypoglycaemic therapy (51% vs 72%; p=0.002) and anti-hypertensive therapy (75% vs 85%; p=0.077) observed.	
Winfrey et al 2011 USA [209]	Peripheral arterial disease	Observational study	39	Screening	One group (n=39). Intervention = pharmacy-based screening for peripheral arterial disease	Secondary	Pharmacist	17 of the 39 patients screened (44%) were referred to their physician for follow-up because they had ABI scores indicating PAD, symptoms indicating PAD, or non-compressible vessels. Using ABI scores, PAD was detected in nine patients (23.1%).	Abstract
Wright et al 2015 UK [210]	COPD	Observational study	137	Medication Management + Disease Management	One group (n=137). Intervention= COPD service (structured consultation with pharmacist which included medication counselling, adherence support, lifestyle advice, smoking cessation support and education to recognise exacerbations along with a recommendation to obtain a rescue pack containing steroid and antibiotic to prevent hospitalisation as a result of chest infection).	Tertiary	Pharmacist	A significant improvement in patient reported adherence was observed (+0.564 (0.304, 0.824) P< 0.001). No other significant differences were observed (authors noted that utilisation of rescue packs improved significantly but no p value reported).	Full text article
Zaragoza-Fernandez et al	CVD	Randomised controlled trial	150	Risk factor management	Two groups - one control (n=74), one intervention (n=76).	Primary	Pharmacist	The intervention group's systolic and diastolic blood pressure (BP) levels fell by 16.08 and 9.95 mm Hg, respectively, and the control group by 1.79 and 0.95 mm	Full text article

Author(s)	Disease	Study design	Sample	Intervention				Main	Record
2012 Spain [211]					Intervention= education and support to promote diet and lifestyle modification to support disease management (2 x face to face meeting 1 month apart with weekly phone calls in between over 2 months).			Hg, (p < 0.001).	

2.4.3 Characteristics of studies

Almost all studies were carried out in developed countries with the majority of the reported studies conducted in Europe (n=64, 49.2%). Other regions included the USA (n=45, 34.6%), Australia (n=10, 7.7%), South America (n= 5, 3.8%), Canada (n=5, 3.8%) Africa (n=3, 2.3%), New Zealand (n=2, 1.5%) and Asia (n=1, 0.8%).

Randomised controlled trials accounted for 35.4% (46/130) of all studies. There were 12 cluster randomised studies (12/130; 9.2%), 13 non-randomised controlled trials (13/130; 10.0%), 5 controlled before after studies (5/130; 3.8%), 16 uncontrolled before after studies (16/130; 12.3%) and 33 observational studies (33/130; 25.4%). For one study, insufficient information was available to determine the specific type of study conducted (1/130; 0.8%). The vast majority of interventions were carried out by pharmacists with just 3 studies reporting interventions delivered by trained members of the pharmacy team in collaboration with a pharmacist [192, 199, 212].

There was a large variation in the number of participants recruited to the various initiatives (10 – 109,264) with just over half (n=72, 55.4%) reporting sample sizes of less than 200 participants. Fifteen studies had less than 50 participants, twenty-six had between 50 and 100 participants and there were twenty-nine studies that recruited between 100 and 200 participants. Twenty-one studies (16.2%) reported on outcomes for over 1,000 patients with two notably large samples 15,933 [112] and 109,265 [172] patients respectively. Both of these studies reported on medication adherence rates as calculated from a prescription refill database, one from a large US chain of community pharmacies [112] and the other from a national database in the Netherlands [172]. Two studies [86, 151], which were only available as abstracts did not report on the number of participants recruited.

Medication therapy management (MTM) was the intervention type reported on most frequently (n=97, 74.6%). In some cases (n=24, 18.5%) the MTM intervention included advice and support designed to help patients manage a chronic condition (e.g. advice on self-care and diet for patients with type 2 diabetes [119], provision of an asthma management plan [163, 187] and monitoring of blood pressure [170, 173]). Seventeen of the MTM studies were medication focussed interventions focussed on supporting patients with adherence to their medication [122, 130, 145, 162, 165] or on conducting a structured medication usage review designed to detect drug related problems and potential inappropriate prescribing [86, 95, 97, 105, 111, 141, 143, 154, 161, 182, 200, 206]. Of the seventeen medication focussed interventions, seven (7/17;

41.2%) [86, 97, 111, 141, 154, 182, 206] were directed at elderly (>65 years of age) patients with the remainder (n=10) open to patients over the age of 18. A large proportion were linked to broad disease categories such as cardiovascular disease (n=27), type 2 diabetes (n=10) and respiratory disease (n=10). Other disease states included depression (n=2), HIV (n=1), chronic kidney disease (n=1), migraine (n=1) and osteoporosis (n=1).

2.4.4 Classification by type of disease prevention activity

The studies were grouped into a number of distinct groups in line with the focus of the research thesis, namely the role of community pharmacy in providing clinical services targeted at primary, secondary and tertiary prevention of disease. Where it was not possible to link a study into such a classification they were noted as “other”. The classification is reported in Table 2.1.

Table 2-2: Reported clinical pharmacy services characterised by type of disease prevention activity

Dimension (n, %)	Type of Intervention, (n, %)	Disease State Targeted, (n, %)
Primary prevention (5, 3.8%)	Smoking cessation (2/5, 40%)	N/A – risk factor management
	Weight management (3/5, 60%)	N/A – risk factor management
Secondary prevention (19, 14.4%)	Screening (19/19,100%)	Osteoporosis (5/19, 26.3%) Cardiovascular disease (5/19, 26.3%) Depression (3/19, 15.8 %) Erectile dysfunction (1/19, 5.3%) HIV (3/19, 15.8%) Multiple (general health) (1/19, 5.3%) Peripheral arterial disease (1/19, 5.3%)
Tertiary prevention (104, 79.5%)	Disease management (6/104, 5.8%) Medication therapy management (97/104, 93.3%) Pharmacist prescribing (1/104, 1.0%)	Arthritis (1/104, 1.0%) Respiratory disease (asthma/COPD) (19/104, 18.3%) Chronic kidney disease (1/104, 1,0%) Cardiovascular disease (34/104, 32.7%) Depression (2/104, 1.9%) Diabetes, type 1 (1/104, 1.0%) Diabetes, type 2 (19/104, 18.3%) Eczema (1/104, 1.0%) Hayfever (1/104, 1.0%) Hepatitis C (1/104, 1.0%) HIV (1/104, 1.0%) Infectious disease (1/104, 1.0%) Migraine (1/104, 1.0%) Multiple (18/104, 17.3%) Obesity (1/104, 1.0%) Osteoporosis (1/104, 1.0%)
Other (2, 1.5%)	Supply of emergency hormonal contraception (1/50, 50%) Supply of oral contraceptive pill (1/2, 50%)	N/A – Prevention of pregnancy N/A – Prevention of pregnancy

2.4.5 Impact of the interventions

There was a large degree of heterogeneity in study designs, intervention types and disease states amongst the retrieved study making an assessment of the overall impact of the interventions difficult. What follows is a descriptive review of some of the pertinent findings reported for interventions classified by type of disease prevention activity.

2.4.5.1 Impact of primary prevention interventions

Two of the five primary prevention interventions (three weight management interventions and two smoking cessation interventions) were conducted as randomised controlled trials [85, 213]. Ahrens *et al.* [85] looked at the effect of two pharmacist delivered weight reduction strategies (a meal replacement plan and a calorie controlled diet) on markers of obesity and cardiovascular disease whereas Zaragoza-Fernandez *et al.* [213] looked at the impact of structured education and support to promote diet and lifestyle modification on blood pressure measurements in a sample of patients. In Ahrens *et al.* [85] statistically significant between group differences in blood pressure reduction were not observed but it was noted that participants in both groups had significant reductions in waist circumference, systolic and diastolic blood pressure, and triglyceride levels (within group differences, no p values reported). Intervention participants in the Zaragoza-Fernandez *et al.* [213] study had a reduction in blood pressure that was significantly greater than that observed in the control group ($p < 0.001$). The third weight management study involved a structured weight management programme (weight management education and monitoring) and, apart from a significant reduction in waist circumference in both groups (reported as $p=0.000$), did not show any statistically significant effects associated with the intervention [178]. The two smoking cessation interventions (one on one smoking cessation counselling and a structured smoking cessation programme) were reported as observational studies with one study reporting a 12-month abstinence rate of 25% in a sample of 48 patients [144] and the second an 18% point-prevalence quit rate at six months [190].

2.4.5.2 Impact of secondary prevention interventions

All nineteen studies classed as reporting on secondary prevention activities related to screening activities in the community pharmacy setting and given the nature of the intervention all were reported as observational studies. Bone mineral density [109, 121, 132, 142, 153] and cardiovascular disease screening [107, 157, 169, 181, 198] were the most commonly reported screening interventions, each accounting for over a quarter of all reported interventions in this category. Four out of the five bone mineral density screening interventions noted that 50% or

more of patients screened were at moderate to high risk of fracture [121, 132, 142, 153]. Within the studies reporting on patients' awareness of their risk prior to screening over 75% of patients were unaware of their low bone mass [121, 132]. Two studies reported patients' uptake of a recommendation to visit their general practitioner (GP) and in both cases it was 37% of the respective samples [132, 153].

The cardiovascular screening interventions reported on the prevalence of various risk factors for cardiovascular disease. In two of the studies a single risk score for the development of future disease was reported [107, 169], the other studies reported the prevalence of various risk factors such as inactivity, smoking and obesity. Only one study followed up with patients who were referred to their GP on suspicion of having hypertension and it found that of the 20% of patients referred, 29% of those (10/34) were subsequently diagnosed with hypertension and started on an antihypertensive medication.

All other screening interventions were successful in detecting previously undiagnosed conditions with the prevalence varying by disease state. Three studies involved HIV screening and the numbers screened ranged from 806 individuals to 1,540 individuals [133, 149, 207]. The proportion of screened patients with reactive HIV tests (possibility of HIV infection) ranged from 0.85% [133] to 1.8% [149]. These patients were then referred for confirmatory testing but follow up data was limited. Screening for depression was described in three studies [136, 171, 185] and the proportion of patients referred for follow on assessment ranged from 16.6% [136] to 70% [171]. Studies involving screening for erectile dysfunction [158] and multiple risk factors for disease in men [103] were also retrieved.

2.4.5.3 Impact of tertiary prevention interventions

The vast majority of the tertiary prevention initiatives involved a medication management intervention (99/106, 94.3%). One study described a pharmacist prescribing initiative [203] (1/106, 0.95%) and the other six studies [90, 118, 125, 140, 192, 202] described disease management interventions which focussed solely on supporting patients to reduce additional risk factors for disease (*e.g.* supporting patients with established cardiovascular disease to reduce their cholesterol levels [118, 202]) (6/106, 4.8%). Patients receiving the pharmacist prescribing intervention obtained significantly better lipid control than those in the usual care group (adjusted odds of achieving target LDL-c were 3.3 times higher for the intervention group ($p = 0.031$)) [203]. The impact of the disease management interventions was mixed. Two

studies (one involving pharmacist delivered wellness coaching for patients with cardiovascular disease and the other a structured program focussed on identification of risk factors for cardiovascular disease progression followed by patient education, monitoring, follow up and physician referral where required) reported improvements in intervention participants' cholesterol levels [118, 202]. Two studies reporting on disease management for patients with type 2 diabetes reported improvements in Haemoglobin A1c (HbA_{1c}) levels in participants receiving the interventions [90, 125]. The other two studies focussed on disease management (one involving pharmacist counselling on healthy behaviours and one involving goal setting to support reduction in allergic rhinitis symptoms) showed no positive effect on outcomes measured (blood pressure [140], HbA_{1c} [140] and hay fever control [192]).

Cardiovascular disease (34/106, 32.07%), type 2 diabetes (20/106, 18.87%) and respiratory disease (asthma and/or COPD) (19/106, 17.92%) were the disease states most commonly reported. Eighteen studies (18/106, 16.98%) did not focus specifically on a single disease state. All 18 involved medication management interventions that focussed on reviewing all medication therapy to identify potential drug related problems and adherence problems.

Twenty (20/99, 20.2%) of the medication management interventions focussed on addressing suboptimal adherence. Two studies [146, 205] assessed the effects of electronic monitoring on adherence and no significant differences between intervention and control groups were found in either case. A study reporting on the use of a compliance aid to support adherence [162] did not show any significant effects nor did one that aimed to improve adherence by reminding patients when their medication was due for refill [165]. Where there was a greater level of pharmacist involvement in terms of coaching and support [91, 99, 102, 120, 122, 124, 126, 137, 145, 168, 196, 197, 199, 205] the effects of the adherence interventions, in the main, reported significant effects. Across 13 studies intervention participants (interventions described in Table 2.1) showed improved adherence [99, 102, 112, 120, 122, 126, 137, 214] and/or lower discontinuation of therapy [124, 137, 168, 197, 199, 215] compared to controls. Improvements in blood pressure control in the more adherent intervention groups were reported in three studies describing medication adherence support in the form of structured consultations to identify and address barriers to anti-hypertensive medication adherence [99, 120, 199]; no other disease related clinical outcomes were reported. In three of the studies no significant differences between intervention and comparator patients were found [91, 130, 145].

Of the remaining medication management interventions thirty-three were reported as randomised controlled trials which involved interventions focussed on the identification and

management of actual and potential problems with prescribed medication therapy. Most studies were restricted to a single disease state such as arthritis, asthma, cardiovascular disease, chronic obstructive pulmonary disease, depression, migraine, type 1 diabetes and type 2 diabetes. One study looked at medication therapy in infectious disease [93], one included patients with both asthma and chronic obstructive pulmonary disease [175] and five studies involved a general medication review of all medication prescribed to the participants regardless of indication for therapy [105, 161, 182, 195, 216]. In studies looking at interventions designed to detect and manage problems with cardiovascular therapy reported on blood pressure management as an outcome measure results were mixed. Some studies reported improvements (Park *et al* [173] reported better blood pressure control in intervention participants but did not quote a p value, Amariles *et al* [88] reported better blood control in intervention versus control participants ($p < 0.001$) and Garco *et al* [128] noted that uncontrolled blood pressure decreased significantly in intervention participants ($p < 0.0001$) but not in control participants ($p = 0.48$)). Other similar studies did not show any significant blood pressure improvements in intervention participants [82, 101, 131]. The situation was similar when looking at studies in patients with asthma. In one study reporting on a structured pharmaceutical needs analysis for asthma management based on the Australian Six-Step Asthma Management Plan a reduction in disease severity was observed [188] whereas in another looking at a structured consultation designed to identify and improve inhaler technique and usage no significant clinical impact was observed [159]. Improvements in patient reported quality of life [113, 175, 176], inhaler technique [113] and adherence [159] were other outcomes reported across the studies in patients with asthma. In the main, studies looking at medication management in patients with type 2 diabetes that used HbA_{1c} levels as an outcome measure showed that pharmacist interventions were successful in terms of reducing HbA_{1c} levels [87, 127, 147, 160, 179, 180] although this finding was not consistent across all studies [119].

Where identification of drug related problems (such as overtreatment with too many medications, sub optimal treatment, incorrect medication dosage and hospital visits due to medication related side effects) was the main outcome of interest pharmacists were successful at identifying and resolving problems [111, 123, 141, 143, 206, 217]. Adherence as an outcome of interest (where the intervention described was not focussed solely on improving adherence) was also noted and a number of studies reported improvements in this measure [183, 195, 201, 210]; however, the way adherence was measured varied across studies and the relationship between improved adherence and disease control was frequently unclear.

2.5 DISCUSSION

This review provides a narrative description of the types of clinical services conducted in the community pharmacy setting that have been reported in the literature. The search strategy was purposely designed to be broad in scope in order to identify the various different types of expanded services conducted in community pharmacy setting. Whilst an objective of the review was to classify community pharmacy services into those relating to primary, secondary or tertiary disease prevention activities, a preliminary review of the literature identified that these terms were not commonly used to describe such services. As such a decision was made to conduct a broad search excluding these terms and to classify retrieved articles thereafter.

A large number of studies were retrieved highlighting the range of services provided. Whilst the review was restricted to one setting, community pharmacy, the retrieved studies were conducted in over 25 different countries worldwide which have differing health systems, populations and arrangements for the provision and re-imburement of pharmacy services. The fact that the review was not limited by the type of intervention being conducted nor the disease state being targeted meant that a broad spread of activity undertaken in the community pharmacy setting was identified. A range of different study types were included, and in many cases the available data were limited as a result of the study only being presented as a conference abstract (n=33). This meant that the quality of reporting was very variable and the quality of the service(s) being provided was difficult to determine in a large number of cases. As a result of this heterogeneity it was not possible to conduct any form of meta-analysis of the collated data nor make any commentary as to the relative effectiveness of the different interventions.

The prevalence of chronic disease such as diabetes, asthma, cancer and cardiovascular disease is increasing rapidly [218]. Non-communicable chronic diseases are the leading cause of death worldwide and almost 40% of death from such causes occur in those under the age of 70 [219]. A number of modifiable risk factors (smoking, excessive alcohol consumption, inactivity and obesity, raised blood pressure) contribute to the development of a range of non-communicable diseases and as such intervening to reduce the prevalence of such risk factors at a population is a global priority [219]. Interventions designed to promote healthy behaviours have been shown to be successful in reducing risk factors for disease [220]. The studies identified in this literature review showed that primary prevention initiatives aimed at reducing risk factors for disease can be delivered in the community pharmacy setting. The variable results observed showed that

whilst some interventions such as structured smoking cessation programs [144, 190] and education/support to promote diet and lifestyle modification [211] have proven successful in reducing risk factor prevalence more work needs to be done on identifying the elements of the interventions that are effective in practice.

As delayed diagnosis of disease can lead to poorer outcomes, effective strategies for identifying previously undetected disease in apparently healthy people can reduce deaths and disability as well as improving overall quality of life [221]. Screening is an important intervention in this regard and many of the studies identified in this review highlighted community pharmacy screening programmes [103, 107, 109, 121, 132, 133, 136, 142, 153, 157, 158, 169, 171, 181, 185, 198, 207, 209]. All of the screening interventions identified some patients at risk which suggests that community pharmacy may be a feasible location for such services. However, all were opportunistic in nature and there are some drawbacks to this approach. Population based programmes such as cervical cancer screening programmes for women tend to be more easily monitored and systematically evaluated whilst also being more cost effective [222, 223]. They also tend to be more equitable in nature providing equal access to all as a result of being commonly funded by the state and free at the point of access [224]. Nonetheless they are not always effective at reaching all persons within their target population, with access to the screening sites sometimes acting as a barrier [225]. Providing screening services in readily accessible community based locations such as community pharmacy may support uptake amongst lower socio-economic groups [226] who very often bear the heavier burden of disease.

Chronic disease causes significant morbidity and mortality and as a result the development of effective disease management strategies is essential [227]. It is felt that primary care is the natural location for chronic disease management [228] and many examples of such programmes exist [210, 229, 230]. The chronic disease management interventions described in the studies retrieved in this literature review were variable in terms of their effect on chronic disease outcomes. It is interesting to note that an intervention that coupled disease assessment (measurement of LDL cholesterol) with therapy initiation and modification based on results of such assessment showed significant results. This intervention was delivered entirely by community pharmacists in a country that has a legislative provision for pharmacist prescribing [203] and thus reproducibility will be hampered where such provisions are not in place. The underlying intervention would be possible but it would necessitate a co-ordinated multidisciplinary team based approach. As successful chronic disease interventions generally

involve such approaches [231] the fostering of team based chronic disease management within the primary care setting is likely to be beneficial in terms of patient care.

Three quarters (99/132; 75%) of all studies retrieved reported on a medication therapy management intervention such as identification of drug related problems or addressing sub-optimal adherence to prescribed medication. This is perhaps not surprising given that the core role of a community pharmacist is the safe supply of medication. It does however highlight some limitations with the classification of the expanded range of services provided in the community pharmacy setting. Despite using common pharmacy services terminology in the intervention search terms (pharmaceutical care/ clinical pharmacy services/ professional pharmacy services/ cognitive services) only two studies looking at the delivery of smoking cessation services were retrieved despite the well-established nature of such services as evidenced in the literature [232-238]. Additionally; no reports of community pharmacy involvement in immunisation services were retrieved despite pharmacist involvement with this primary prevention initiative in a number of jurisdictions worldwide [239-243].

This review has a number of limitations. The review was conducted as part of a PhD research project and thus the nature of the work and the resources available meant that all abstract/article screening was conducted by a single researcher meaning that there is a risk of selection bias. Only articles written in English were included which may have introduced some language bias and publication bias cannot be excluded as only published studies were included.

To someone having a background knowledge of delivery of advanced clinical services in the community pharmacy setting it is clear that the search strategy did not retrieve a comprehensive overview of the range of advanced clinical services provided. Whilst it is possible that not all service types may be described in the published literature, it is likely that a number of services/studies may have been missed. This could have been due to the selection of key words used in the search strategy. Intervention key words were deliberately selected in order to reflect the most common terms used to describe advanced clinical pharmacy services. It is possible that studies reporting on services such as e.g. smoking cessation may not describe the services as advanced clinical pharmacy services. Even though provision of such services in community pharmacy requires different professional knowledge and skills than those required for the dispensing of and counselling on medication, the classification of the service as a clinical *pharmacy* service suggests, perhaps, that they can only be delivered in the pharmacy setting. This is clearly not true of services such as smoking cessation services which are delivered in a range of different settings such as hospitals [244], general practice [245], university [246] and

community settings [247] and by different personnel such as nurses [248], psychologists [249] and trained counsellors [250]. To capture the full range of studies relating to delivery of smoking cessation services in the community pharmacy setting would therefore require inclusion of key words related to smoking cessation services within the set of intervention related key words. This process would need to be repeated for each different service type (e.g. weight management services, screening services) and would likely retrieve more studies than those included in this review. As this review was solely intended to give an overview of the types services being provided these keywords were not included. Literature reviews undertaken for other chapters in this thesis utilised the key words specific to the type of service being reviewed.

Expanding the range of databases searched may have increased the number of relevant articles retrieved. EMBASE was selected over PubMed for its focus on biomedical and pharmaceutical content [251, 252] but in hindsight PubMed should also have been included. Indexing of articles is treated differently [253] across both databases and PubMed has the advantage of mapping keywords to relevant Medical Subject Heading (MeSH) terms [254, 255] which would likely have allowed for different articles relevant to the search to be retrieved. Whilst searching across multiple databases can be time consuming it is recommended to maximise yield and support a comprehensive review [256].

Chapter 3: Community pharmacy smoking cessation service

3.1 INTRODUCTION TO THE CHAPTER

Cigarette smoking is one of the greatest causes of illness and premature death in Ireland with Ireland having the second highest ranking of smoking related deaths in Europe (EU15) [7]. The annual death toll from smoking-related diseases in Ireland is at least 5,200 [15], with many thousands more smokers, and their families, affected through chronic illness and disability. The Irish government has an ambition to reduce smoking prevalence in the country to 5% by 2025 [15]. As provision of smoking cessation services in the community pharmacy setting has been shown to improve abstinence rates amongst smokers [232-234], there is a role for community pharmacy in the national tobacco cessation agenda.

This chapter describes a cross-sectional observational study of a sample of patients enrolled on a community pharmacy-based smoking cessation programme. The study is reported using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement [257] checklist for cross-sectional studies [258].

3.2 BACKGROUND

3.2.1 Smoking related harm

Tobacco addiction has grave consequences for the health of the smoker with one in every two lifetime smokers dying prematurely as a result of their addiction [259, 260]. Nicotine, a highly addictive substance, is the primary chemical that contributes to tobacco addiction and it does this by acting on nicotinic cholinergic receptors in the brain to release dopamine and other neurotransmitters that sustain addiction [259]. Whilst nicotine is responsible for the addiction, it is the other components found in tobacco products such as cigarettes that are responsible for smoking related toxicity and ill health [261].

With over 1 billion smokers worldwide, the tobacco epidemic is the major public health threat of our time [262] and it is expected that tobacco smoking will kill in excess of 10 million people globally each year by 2030 [15]. It is estimated that there are over 1 million current smokers in Ireland [263] and tobacco use is the leading cause of preventable death amongst the Irish

population [15]. Aside from the health consequences of smoking, the costs associated with tobacco addiction are also significant both for the individual smoker and the State. Expenditure on smoking related diseases in Ireland was approximately €506m in 2013 with productivity losses and long-term incapacity due to smoking related illness costing over €2.4bn in that same year [264].

Given the level of smoking related harm and knowing that the risks associated with smoking are significantly reduced by quitting at any age [259], it is not surprising that reducing smoking prevalence is a major public health agenda. Ireland has made significant progress in the area of tobacco control over the last two decades. Policies such as increasing marketing bans, raising taxes on tobacco products, increasing the availability of smoking cessation services and introducing the first national smoke-free workplace law which prohibited smoking in places of work including pubs and restaurants are thought to have resulted in a relative reduction in smoking prevalence of 22% between 1998 and 2010 [265]. Such national focus means that Ireland is seen as a European leader in the field of tobacco control, second only to the UK [266].

3.2.2 Interventions to support smoking cessation

A number of support interventions exist to help people to stop smoking. The initial aim of smoking cessation interventions is to prompt a quit attempt and then to support with any such attempt [267]. Brief interventions are opportunistic in nature, typically take 5 to 10 minutes, and involve enquiring about a person's smoking status as well as advising, discussing and encouraging a quit attempt [268]. It has been suggested that up to 40% of smokers make some attempt to quit after such advice and that for every 100 people receiving the advice up to three extra people will be successful in quitting for at least 6 months compared with the situation if no advice is given [267]. Initiatives such as the UK's "Making Every Contact Count" model seek to exploit these insights by requiring every health care professional in the system who may have contact with a smoker to have the confidence and competence to help them quit [269].

Behavioural support services provide people with advice, support and tools to help them in their quit attempt [250]. They can be provided in the form of multi-person group therapy or individual counselling sessions [250, 270]. Behavioural support interventions are effective on their own [271, 272] but many clinical practice guidelines recommend that they be offered in combination with pharmacotherapy as together they may have an additive effect [250].

Pharmacotherapy improves long term quit rates compared to no therapy or placebo [273] and, where appropriate, should be offered to anyone who smokes more than 10 cigarettes per day [270] or has their first cigarette within an hour of waking [267] . There are three main forms of pharmacotherapy currently licensed in Ireland. Nicotine Replacement Therapy (NRT) is available as an over the counter product and works by providing the user with a controlled dose of nicotine designed to reduce nicotine withdrawal symptoms and hence motivation to smoke [274]. The exact mechanism of action of bupropion is not fully clear but as a selective inhibitor of the neuronal re-uptake of catecholamines (noradrenaline and dopamine), it is presumed that its ability to enhance one's ability to abstain from smoking is mediated by noradrenergic and/or dopaminergic mechanisms [275]. Varenicline is a selective nicotinic receptor partial agonist having both agonist and antagonist actions, thereby alleviating symptoms of craving and withdrawal as well as causing a reduction in the rewarding and reinforcing effects of smoking [276]. Both bupropion and varenicline are restricted to supply on foot of a prescription in Ireland.

Combined pharmacotherapy plus behavioural support interventions have been shown to increase quitting success in a wide range of settings [250] and appear to be better in combination [277]. However, given that the majority of smokers do not use this option [277, 278] more could be done to encourage smokers to use this dual approach.

3.2.3 The role of the community pharmacist

Nearly half (48%) of all smokers in Ireland in 2016 made at least one attempt to quit during that year [263]. With three in five smokers thinking about trying to quit and 11% actively trying to quit [263] it is important that smokers have ready access to services that can support them in their quit attempt. The ready accessibility of community pharmacy coupled with its role in the safe sale and supply of smoking cessation pharmacotherapies mean that it is a prime location for delivery of health promotion initiatives aimed at reducing the prevalence of smoking.

Smoking cessation as a health promotion initiative is one in which pharmacists showed early interest [279] and a number of studies have been conducted on the effectiveness of such interventions. A number of systematic reviews [232-238] addressing smoking cessation programmes in community pharmacy have been published. The evidence as to the value of such programmes as reported by the different reviewers was somewhat mixed. Nevertheless, it is felt that overall these reviews demonstrate that community pharmacists trained in smoking cessation support and providing counselling and monitoring can achieve improved smoking cessation

rates [232]. The results of two recent meta-analyses [232, 236] have concluded that smoking cessation interventions delivered in community pharmacy resulted in better abstinence rates compared with controls thus confirming the view that such interventions are effective. Evidence also suggests that they are cost effective [280-282] with emerging evidence that pharmacy based services are more cost effective than those offered in other settings such as general practice [283].

3.2.4 Boots Stop for Good smoking cessation programme

The Boots Stop for Good (SFG) programme is a smoking cessation service which has been delivered in Boots pharmacies in Ireland since 2010. Based on the psychology of behavioural change, this 12-week personalised, smoking cessation service is available to eligible patients free of charge.

The service consists of a personalised, one on one behavioural support programme and includes carbon monoxide (CO) monitoring along with provision of advice and information on nicotine replacement therapy (NRT), where appropriate. It is available to all persons aged 18 and over who want to quit smoking.

Patients are encouraged to reflect on their smoking habits and desire/readiness to quit in advance of their first consultation with a trained Stop for Good Advisor. The Stop for Good Advisor is a healthcare advisor, pharmacy technician, pharmacy intern, pharmaceutical assistant or pharmacist who has successfully completed the Stop for Good training programme. This programme consists of a distance learning programme and associated eTest as well as an Observed Structured Clinical Examination (OSCE) assessment.

Once the patient has made a decision to quit they are supported in creating a personalised quitting plan, setting a quitting date and preparing strategies that will help them deal with cravings and the withdrawal process. This is followed by a 12-week monitoring and support period after their quit date, aimed to help encourage and motivate a person to stop smoking for good. An initial breath CO reading is taken at this first consultation and repeated at each face to face visit conducted over the 12-week period. Programme participants are encouraged to return for a face to face consultation at weeks 2, 4, 8 and 12 post their initial consultation. The initial visit typically takes approximately 20 minutes with subsequent visits lasting from 10-15 minutes.

3.3 OBJECTIVES

3.3.1 Primary objective

The primary aim of this research was to report on the CO verified smoking cessation rates observed in a sample of patients accessing a community pharmacy based smoking cessation service between January and June 2014.

3.3.2 Secondary objectives

The secondary objectives were as follows:

- To describe the characteristics of the patients accessing the service;
- To determine the level of Nicotine Replacement Therapy (NRT) usage amongst the study sample;
- To identify trends influencing successful completion of the programme.

3.4 METHODS

3.4.1 Study Design

This study is a cross-sectional observational study of patients enrolled on a smoking cessation programme in a community pharmacy setting in Ireland. It was non-interventional in nature and drew on data routinely collected as part of the smoking cessation service.

3.4.2 Setting

Patients enrolled on the Boots Ireland Stop for Good smoking cessation programme between January and June 2014 were eligible for inclusion in the study. A total of 72 pharmacies within this chain of community pharmacies with national coverage in Ireland were offering the Stop for Good service between these dates.

3.4.3 Data collection

A paper based consultation record form (CRF) was developed for recording patient information upon enrolment to the service (Appendix 2). Baseline data is collected at the point of entry to the programme (first consultation) and follow up information on smoking status is collected during structured consultations at weeks 2, 4, 8 and 12 (final consultation). Breath carbon monoxide levels are measured at each consultation and information on any pharmacological support aids employed is also recorded.

Demographic data for each participant were collected upon enrolment as were details of their smoking and relevant medical history.

When enrolling on the smoking cessation programme patients were notified that Boots may use anonymous data collected during the service for medical analysis and research. They were also informed that anonymous data may be shared with carefully selected third parties for conducting such research. Patients were able to decline to have their anonymous data used/shared for research purposes. For this study only patient record forms for those patients who agreed to allow their anonymous data to be used/shared for research purposes were used for the purposes of data collection and analysis.

Data collection on the paper based service CRF took place in each of the study pharmacies from January-September 2014 for patients who enrolled on the Stop for Good Programme between January-June 2014. Pseudonymised data were then entered into a specially designed electronic data collection spreadsheet (Excel 2007) as per instructions provided by the lead researcher, an Irish registered pharmacist employed by Boots Retail Ireland Limited. The lead researcher then collated all pseudonymised data into a master data collection spreadsheet (Excel 2007) using a coding template for data entry. This spreadsheet was then anonymised, encrypted and password protected and the pseudonymised database was deleted.

All study related information and patient record forms were treated confidentially to protect the privacy of individuals. Original paper copies of all informed consents continue to be kept in the study pharmacies and all original patient records are kept under the personal supervision of the pharmacist(s) in each study pharmacy. Pseudonymised records are kept in the pharmacy of collection and the master anonymised electronic database is held centrally by the lead researcher.

3.4.4 Ethics

Ethical approval to conduct the study was provided by the School of Pharmacy and Pharmaceutical Science Research Ethics Committee in Trinity College Dublin (December 2015).

3.4.5 Pharmacy team training

All pharmacists and authorised pharmacy team members who conducted any service related procedures must have completed a programme of training and must have successfully passed an associated test of knowledge before undertaking any service related procedures. The training

programme covers information on the health benefits of smoking cessation, motivational interviewing techniques and information relating to service delivery; training on the consent process (informed consent, capacity to consent) is also included. Information on identifying a patient's readiness to change based on the Stages of Change model [284] is included in the training programme as is instruction on how to conduct a brief intervention based on the 5As (Ask about smoking, Advise on benefits of quitting, Assess willingness to make a quit attempt, Assist in quit attempt and Arrange follow-up) [285].

3.4.6 Participants

3.4.6.1 Inclusion criteria

All male and female patients over the age of 18 who enrolled on the smoking cessation programme in a Boots pharmacy between January and June 2014 were eligible for inclusion in the study provided they had not declined to their anonymous data being used for medical research/analysis. Patients could have been referred to the service via a national marketing campaign, requested the service themselves or availed of the service on foot of a recommendation from the pharmacy team.

3.4.6.2 Exclusion criteria

The following exclusion criteria applied:

- Patients who enrolled on the smoking cessation programme but declined to allow their anonymous data to be used for medical analysis/research;
- Patients under the age of 18.

3.4.6.3 Consent Procedures

Patients consented to join the service in the pharmacy of their choosing. A patient information leaflet outlining the service and what it entails was provided to all patients. Details relating to the patient, and the service provided to them were recorded on the service CRF; consent to take part in the service was also recorded. On this form, the patient was asked to indicate if they did not wish for their data to be anonymised and shared with the research team; if they indicated a desire to be excluded from any third-party research activity then this was classed as non-consent on the part of the patient and they were excluded from this study.

3.4.7 Measures

3.4.7.1 Carbon monoxide measurement

Carbon monoxide (CO) monitoring was employed in this study as a method of biochemically validating abstinence in patients enrolled on the smoking cessation programme. The handheld PiCO⁺ Smokerlyzer (Bedfont[®] Scientific Limited, Kent, England) was used to monitor breath CO levels on enrolment and at subsequent visits. This monitor, which has previously been shown to be effective [286-288], measures breath CO in parts per million (ppm), has an accuracy of 2 ppm/5% and a repeatability of $<\pm 5\%$ [289].

The CO test was conducted according to a standard operating procedure (SOP). The patient was instructed to take a deep breath, hold their breath for 15 seconds and then exhale slowly into the mouthpiece with the aim of emptying their lungs as much as possible. The CO level as recorded was noted on the patient's CRF in ppm. The Russell standard for a CO-verified quitter was employed whereby self-report of quitting coupled with an expired air CO of less than 10 ppm allowed for patient classification as a CO-verified quitter [290].

Carbon monoxide testing was offered to every patient at each visit. Patients could decline to have their CO measured if they wished.

3.4.7.2 Other measurements

Medical history and medication taking were recorded at the initial visit. Patients were asked to indicate if they were pregnant or breastfeeding and this was noted on the CRF. Eligibility for a medical card was recorded as a measure of social status.

3.4.8 Outcome criteria

Smoking status at the outset of the programme was self-reported by patients. Patients were asked to indicate:

- How many cigarettes they normally smoked in a day;
- Number of years smoking ;
- Number of previous quit attempts;
- Level of nicotine dependence using the Fagerstrom Test for Nicotine Dependence (FTND) [291];
- Level of importance they attached to stopping smoking on a scale of 1-10;
- Level of confidence that they could succeed in their quit attempt on a scale of 1-10.

Patients were classed as a treated smoker if they attended for at least one Stop for Good consultation on or prior to their quit date and they set a firm quit date [290] which was recorded on their CRF. They were classed as a self-reported quitter if they attended for a follow up consultation(s) through the 12-week programme and as a CO verified quitter if this self-report was accompanied by an expired air CO level of <10 ppm on testing [290, 292]. Patients not attending for follow up were assumed to have relapsed.

3.4.9 Sample size

This was an observational study designed to report on the smoking cessation rates observed in a sample of patients accessing a community pharmacy based smoking cessation service within a defined time period (six months). The sample size for analysis was therefore determined by engagement with the programme and not based on a pre-determined sample size calculation.

3.4.10 Data analysis

Statistical analysis was carried out using IBM SPSS Statistics for Windows, Version 21.0. (Armonk, NY: IBM Corp). Qualitative variables are expressed as numbers and percentages with quantitative variables expressed as mean \pm standard deviation. A *P*-value of <0.05 was considered to be statistically significant.

An intention to treat approach was taken, where any patient lost to follow up was classed as a smoker and all patients enrolled on the programme at baseline were included in the cessation rates analysis. Descriptive statistics were used for patient characteristics. Quit rates were calculated at 4 and 12 weeks respectively. Differences in quit rates by gender and use of pharmacotherapy were assessed for significance using chi squared analyses. Logistic regression was conducted to examine baseline characteristics such as nicotine dependence, confidence in quitting and smoking history as predictors of cessation at week 4 and week 12.

3.5 RESULTS

3.5.1 Participants

Service records for 1,335 patients who were assessed for enrollment on the Stop for Good smoking cessation programme across 58 pharmacies between January and June 2014 were available for analysis. The mean number of patients enrolled on the programme per pharmacy was 23 (SD \pm 12; range 1-70).

Of the 1,335 patients screened 1,287 enrolled on the programme and were asked to indicate a firm quit date. 112 patients indicated that they had already stopped smoking at the time of attendance for this first visit and were classed as “Ex-smokers”. 165 set a vague quit date and were classed as “Other smokers”. 1,010 set a firm quit date and were classed as “Treated smokers” as per the Russell Standard definition [290].

A total of 120 patients completed the 12-week programme (9.3%). This figure was broken down as 93 (9.2% of 1,010) patients in the treated smoker group, 16 (14.3% of 112) in the group who had ceased smoking prior to enrolling on the programme and 11 (6.7% of 165) in those patients who did not set a firm quit date at the first consultation.

The flow of patients through the programme is shown in figure 3.1

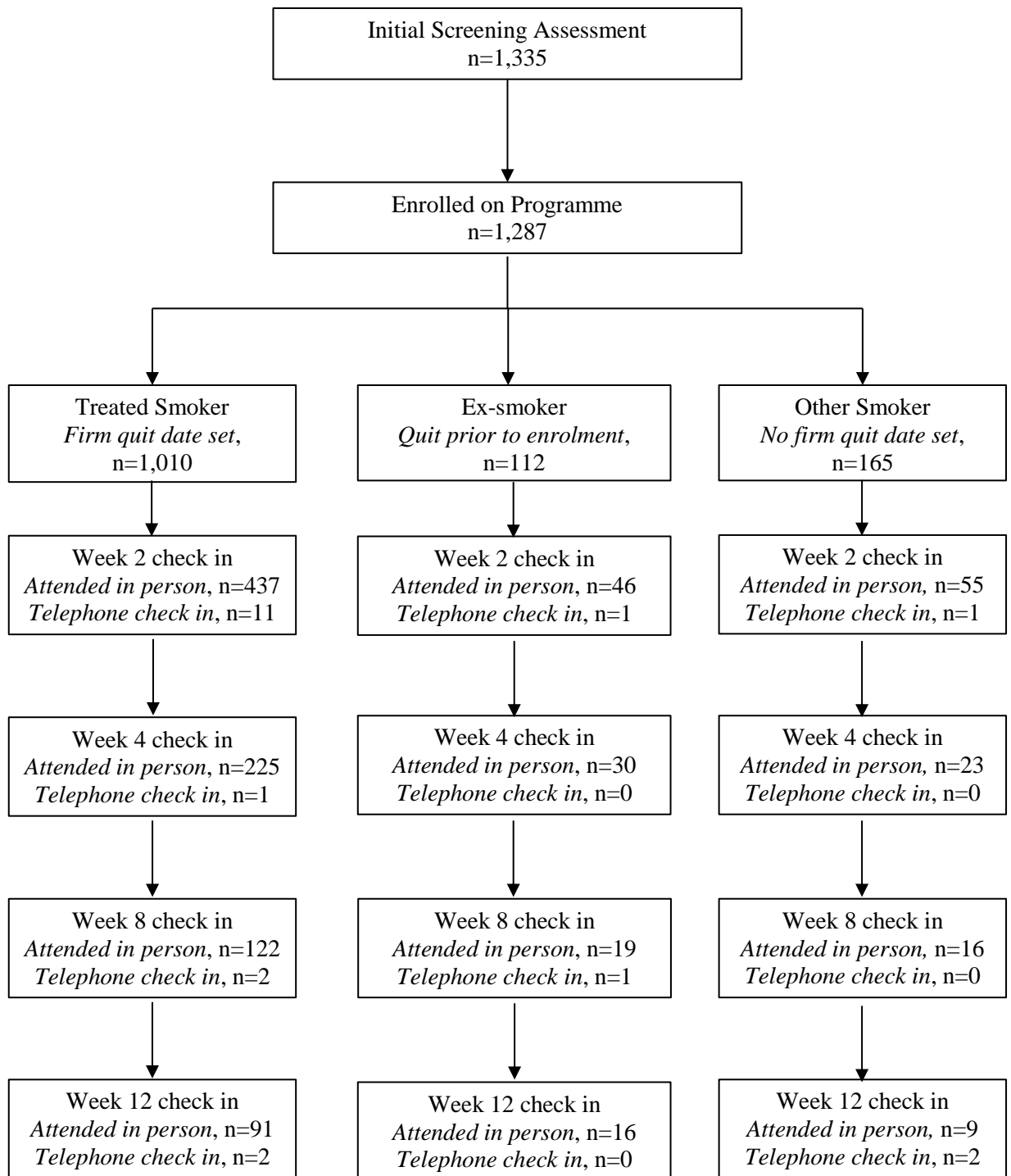


Figure 3-1: Flow of patients through the Stop for Good programme

3.5.2 Demographic profile of the participants

69.5% of the patients who enrolled on the programme were female and the median age was 42. Three hundred and sixty-four patients (28.3%) reported having one or more medical conditions with the most common conditions being cardiovascular (e.g. high blood pressure, high cholesterol) and respiratory (e.g. asthma, COPD) in nature. The characteristics of the patients at the time of enrolling on the smoking cessation programme are shown in Table 3.1

Table 3-1: Characteristics of patients enrolled on the Stop for Good programme

<i>Characteristic</i>	
Median age at enrolment (SD; range)	42.0 (10.9; 18-80)
Gender	
Male (n, %)	389 (30.2)
Female (n, %)	894 (69.5)
Missing (n, %)	4 (0.31)
Pregnant	7 (0.5)
Breastfeeding	5 (0.4)
Medical card eligibility	341 (26.5)
Medical condition	
Cardiovascular (n, %)	119 (9.2)
Respiratory (n, %)	71 (5.4)
Nervous System (n, %)	45 (3.5)
Thyroid (n, %)	31 (2.4)
Pain (n, %)	26 (2.0)

The age of the patients enrolled on the programme ranged from 18-80. The majority of patients were aged between 25 and 54. The proportions of males and females were similar across all age ranges except for age 55-64 where the proportion of females was higher ($\chi^2 = 9.71, p=0.002$).

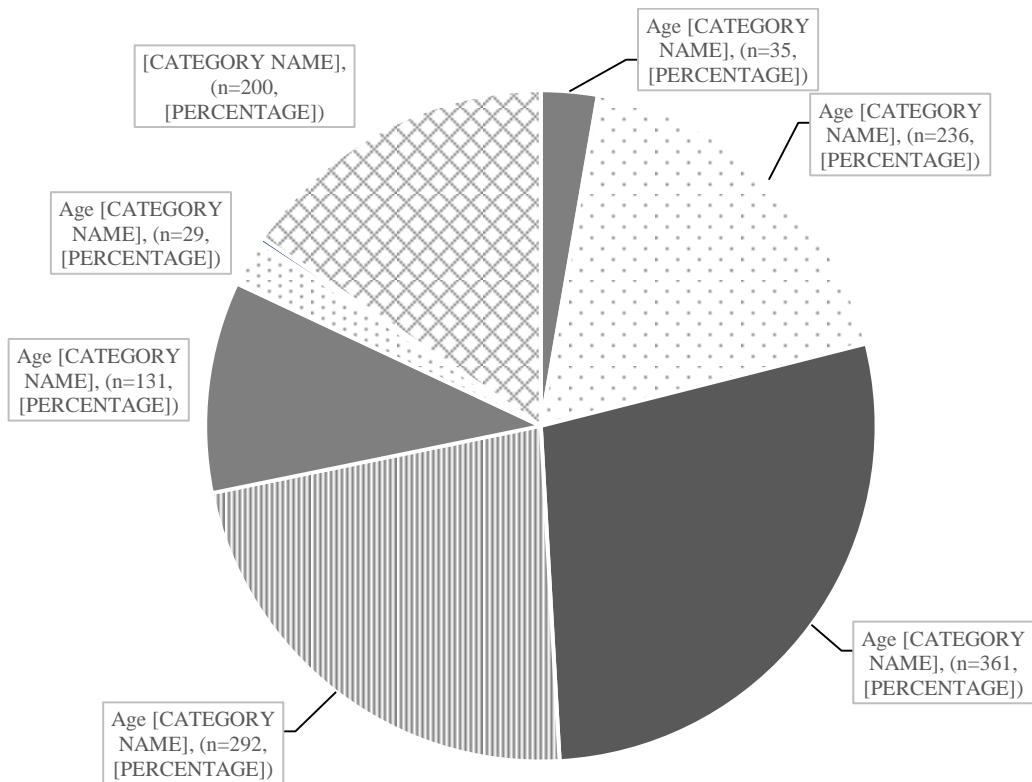


Figure 3-2: Age profile of patients enrolled on the Stop for Good Programme

3.5.3 Smoking history

Patients enrolled on the programme had been smoking for a mean of 22.6 ± 10.7 years and the mean number of quit attempts was 3.6 ± 6.4 . There was a medium to high level of nicotine dependence amongst the sample (mean \pm SD Fagerstrom score = 5.4 ± 2.4). A high level of importance was attached to the quit attempt (9.3 ± 1.2) but a lower level of confidence in one's ability to quit was observed (6.8 ± 2.0).

Table 3-2: Smoking history of patients on the Stop for Good programme at time of enrolment

<i>Characteristic</i>	
Mean number of years smoking (SD; range)	22.6 (10.7; 0.5-60)
Cigarettes smoked per day	
10 or fewer (n, %)	257 (20.0)
11 to 20 (n, %)	727 (56.5)
21 to 31 (n, %)	219 (17.0)
31 or more (n, %)	58 (4.5)
Missing, (n, %)	26 (2.02)
Previous quit attempts	
None (n, %)	117 (9.1)
1 to 5 (n, %)	856 (66.5)
6 to 10 (n, %)	138 (10.7)
11 to 15 (n, %)	20 (1.6)
16 to 20 (n, %)	10 (0.8)
>20 (n, %)	8 (0.6)
Missing, (n, %)	138 (10.72)
Readiness to Quit	
Confidence Score (mean, SD)	6.8 (2.0)
Dependence Score (mean, SD)	5.4 (2.4)
Importance Score (mean, SD)	9.3 (1.2)

3.5.4 Nicotine replacement therapy usage

550 patients (42.7% of total 1,287 enrolled on programme) reported using NRT to support their quit attempt. The proportion of patients using NRT was similar by gender. Patients classed as having a medium or high dependency on cigarettes were more likely to use NRT to support their quit attempt (χ^2 medium dependence=4.96, p=0.026; χ^2 high dependence=10.80, p=0.001). There was no significant difference in quit rates observed between patients who did and did not use NRT.

3.5.5 Carbon monoxide readings

The mean CO level as measured for all patients enrolled on the programme at their initial consultation was 18.5 ± 12.8 ppm. Details on the numbers of patients availing of a CO test and the proportion of patients with CO readings below 10 ppm at each visit are shown in Table 3.3.

Table 3-3: Carbon monoxide levels across the 12-week programme classified according to initial smoker classification

	Initial Consultation, (n, %)	Week 2 check in, (n, %)	Week 4 check in, (n, %)	Week 8 check in, (n, %)	Week 12 check in, (n, %)
Attended[†]	1,287 (100)	551 (42.8)	279 (21.7)	160 (12.43)	120 (9.32)
Treated Smokers (n=1,010)					
Attended ^{††}	1,010 (100)	448 (44.4)	226 (22.4)	124 (12.3)	93 (9.2)
CO ≥ 10 ppm ^{†††}	770 (76.2)	49 (10.9)	19 (8.4)	7 (5.6)	3 (3.2)
CO < 10 ppm ^{†††}	200 (19.8)	250 (55.8)	145 (64.2)	71 (57.3)	57 (61.3)
No CO level available ^{†††}	40 (4.0)	149 (14.8)	62 (27.4)	46 (37.1)	33 (35.5)
Ex-smokers (n=112)					
Attended ^{††}	112 (100)	47 (42.0)	30 (26.8)	20 (17.9)	16 (14.3)
CO ≥ 10 ppm ^{†††}	24 (21.4)	5 (10.6)	0 (0)	0 (0)	0 (0)
CO < 10 ppm ^{†††}	77 (68.8)	26 (55.3)	20 (66.7)	14 (70.0)	10 (62.5)
No CO level available ^{†††}	11 (9.8)	16 (34)	10 (33.3)	6 (30.0)	6 (37.5)
Other smokers (n=165)					
Attended ^{††}	165 (100)	56 (34.0)	23 (14.0)	16 (9.7)	11 (6.7)
CO ≥ 10 ppm ^{†††}	108 (65.5)	10 (17.9)	1 (4.3)	0 (0)	0 (0)
CO < 10 ppm ^{†††}	41 (24.8)	20 (35.7)	15 (65.2)	6 (37.5)	4 (36.4)
No CO level available ^{†††}	16 (9.7)	26 (46.4)	7 (30.4)	10 (62.5)	7(63.6)

Treated smokers = smokers attending at least one treatment session on or prior to quit date and who set a firm quit date; **Ex-smokers** = smokers attending at least one treatment session post quit date; **Other smokers** = smokers attending at least one treatment session prior to quit date but who did not set a firm quit date

[†] For % calculation the denominator= total number of participants

^{††} For % calculation the denominator= number participants within smoker type

^{†††} For % calculation the denominator= number attendees within participants of the smoker type

3.5.6 Rates of smoking cessation

Out of an initial 1,287 patients enrolled on the programme a total of 279 (21.68%; 95% CI: 19.51 – 24.02) completed 4 weeks of the programme. 180 (13.98%; 95% CI: 12.19-15.99) of these patients had CO levels of less than 10 ppm on measurement and thus could be classified as CO-verified quitters. Looking at the treated smoker population the proportion of CO-verified week-4 quitters was found to be 0.14 (95% CI: 0.12-0.17).

The number of patients completing the full 12-week programme was 120 (9.32%; 95% CI: 7.85 – 11.0), the number classed as CO-verified quitters was 71 (5.52%; 95% CI: 4.39 - 6.91) and the proportion of treated smokers classed as CO-verified week-12 quitters was 0.06 (95% CI: 0.04 – 0.07).

No differences in the proportion of CO-verified quitters by gender or NRT usage were observed. Patients with medium dependence were more likely to be classed as a CO verified quitter than not at week 4 ($\chi^2 = 6.87$, $p=0.009$) and at week 12 ($\chi^2 = 5.40$, $p=0.02$). Patients with high dependence were less likely to be classed as a CO verified quitter than not at week 4 ($\chi^2 = 12.53$, $p<0.001$) and at week 12 ($\chi^2 = 8.99$, $p=0.003$).

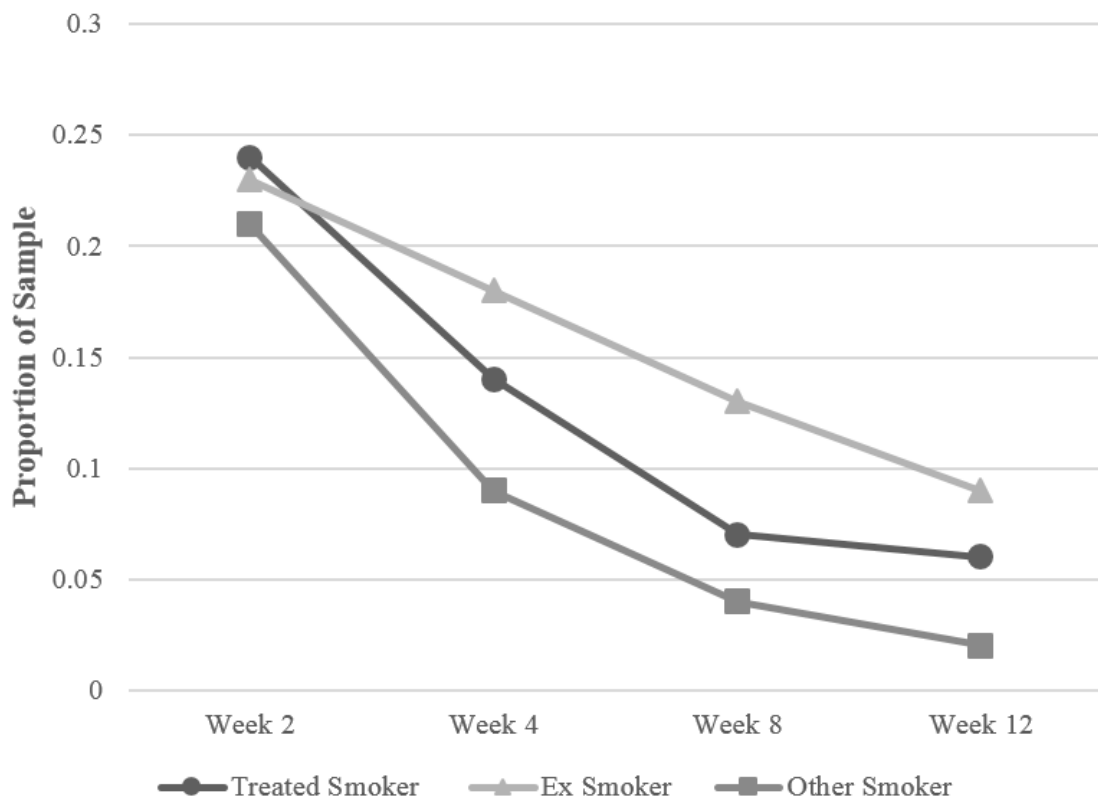


Figure 3-3: CO-verified quit rates over time classified by smoker type

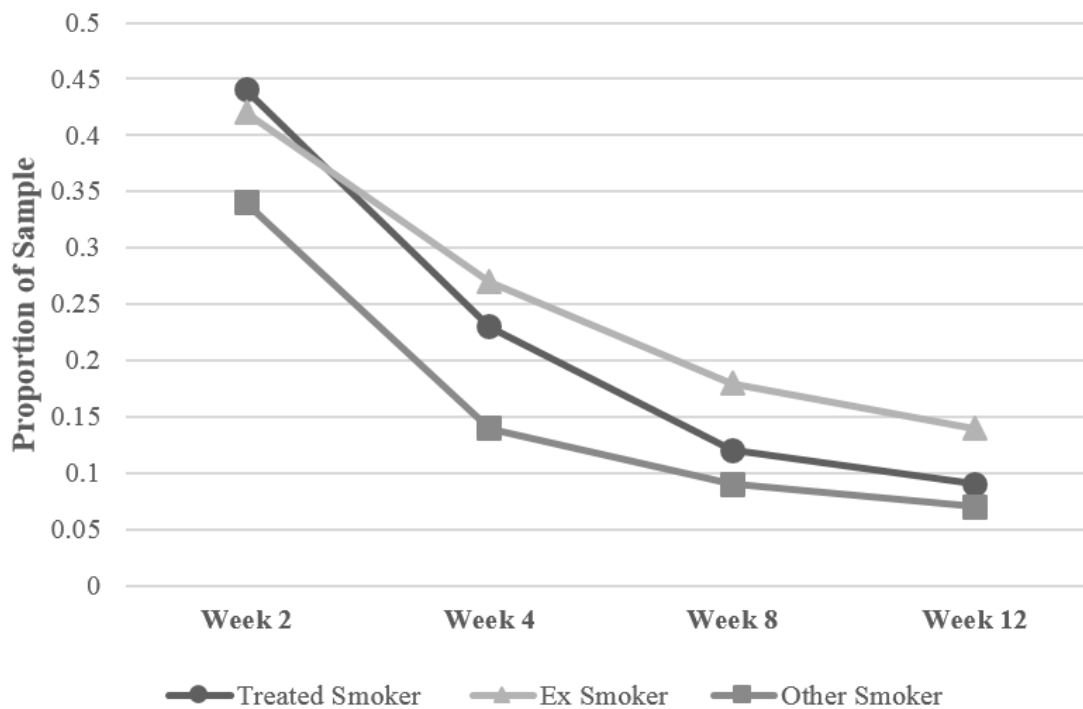


Figure 3-4: Completion rates over time classified by smoker type

3.5.7 Predictors of a successful quit attempt

In a logistic regression model built to predict the relationship between CO verified quit status and patient and smoking cessation characteristics and which included the following predictor variables: levels of importance, confidence and dependence, age, gender, number of years smoking, number of previous quit attempts, medical card eligibility and concomitant use of NRT, only the level of nicotine dependence at the outset significantly predicted quitting success at week 4 ($p=0.005$) with those more heavily dependent less likely to be successful in their quit attempt. The success rate amongst patients with high dependence (10.6% (95% CI 8.4-13.4)) was lower than for those with medium (17.8 % (95% CI 14.4-21.8)) or low (18.2 % (95% CI 12.8-25.1)) dependence; OR 0.54 (95% CI 0.39-0.77). No significant relationships were observed between week 12 quitting success and patient/smoking cessation characteristics.

3.6 DISCUSSION

3.6.1 Effect of the intervention

The results of this study show that delivery of a smoking cessation programme in the community pharmacy setting is feasible and can support individuals in their quit attempt. Whilst the rate of participant engagement with the programme and associated quit rates fell over time, the service successfully supported 71 patients (5.52% of 1,287 patients; 95% CI: 4.39 - 6.91) to achieve a CO verified quit at 12 weeks. The service attracted more women than men. Just over half (50.55%) of patients utilised NRT in combination with the behavioural support intervention. Higher nicotine dependence at the outset was associated with a lower chance of successfully quitting.

3.6.2 Comparison with relevant findings from other published studies

A variety of different smoking cessation interventions (online, telephone, group [272] or individual [271] behavioural support and pharmacotherapy) are delivered in different settings (hospital [293], general medical practice [294], dental practice [283], pharmacy [232]). These interventions are delivered by a range of different providers (dentists, general practitioners, nurses [248], pharmacists, addiction counsellors, health care assistants [295]) all of which have shown success in supporting increased abstinence in smokers accessing the service(s).

Smoking cessation services delivered in the community pharmacy setting have been found to be both effective [232, 279, 296] and cost effective [280-283]. Evaluations of community pharmacy based smoking cessation programmes have been conducted in the UK [282, 297-299], United States [144], Canada [300] , Sweden [301] and Qatar [302]. Results from these studies have been reported in one or more systematic reviews [232-238] with the exception of the Qatar based service which has only recently (2017) been published [302]. Direct comparisons between the current study and those reported in the literature are difficult to make due to heterogeneity in interventions delivered, follow up periods and outcome reporting. Nonetheless the common setting of the studies means that descriptive comparisons may be of value.

Looking at programmes that involved more than one intervention/counselling session with the pharmacy staff 12 month point prevalence abstinence rates of between 2.8% [303] and 32.9% [301] have been reported. Costello *et al.* reported an abstinence rate of 40.5% in patients

enrolled on a pharmacy programme that consisted of NRT plus behavioural support delivered over 3 sessions but this was based on a self-reported 7-day point prevalence abstinence rate [300]. Whilst one might expect that a CO verified abstinence rate would be lower this is still much higher than the 4-week abstinence rate reported in the current study. One of the reasons for this may be that all patients in the Costello *et al.* study received a combination of NRT and behavioural support which has been shown to be more effective than either intervention alone [277] and also the NRT was provided free of charge meaning there was no financial barrier to accessing the combined programme.

Of the other studies using patient reported abstinence as their primary outcome measure, rates of 11.6% at 9 months [297] and 32.9% [301] and 25% [144] at 12 months are reported. Results that reported biochemically validated quit attempts (saliva cotinine [298] and breath CO [302, 303] showed lower 12-month abstinence rates (14.3% [298], 3.4% [302] and 2.8% [282]). Given the shorter follow up of patients in the current study comparisons of 12-month abstinence rates are not possible. Maguire *et al.* note a self-reported quit rate of 27.5% at 4 weeks [298], Bauld *et al.* an 18.6% CO verified 4 week quit rate [303] and El Hajj *et al.* a self-reported continuous abstinence rate of 15% in the intention to treat population at three months [302], all of which are somewhat higher than the 13.98% CO verified quit rate observed in the current study. In all cases, and in common with Costello *et al.* [300], the rates of NRT usage were much higher ($\geq 87\%$) than those observed in this study although given the fact that no significant differences between success rates for NRT and non NRT users in the current study the significance of this is unclear.

The current study was conducted as an observational service evaluation and not as a randomised controlled intervention and as a result no control group comparisons were made. This differs from the majority of the other studies which were conducted as randomised controlled trials [297, 298, 300, 302] or controlled before-after studies [299, 301]. The patient follow-up inherent in such trials may have contributed to the higher abstinence rates reported. Patients who did not attend for Stop for Good visits were not followed up to check on whether they had relapsed or remained abstinent and all drop outs were classed as smokers for the purposes of data analysis. This approach has the potential to under-estimate abstinence rates when one considers that some studies on treatment outcomes for substance abusers enrolled on abstinence programmes similar to smoking cessation programmes have found that substance abusers who were initially lost to follow up but eventually located were not necessarily functioning worse than those followed up easily [304]. Of the two observational studies reported Kennedy *et al.*

[144] reported a 25% abstinence rate at 12 months but this was based on patient self-report. Bauld *et al.*[303] reported an 18.6% CO verified 4 week quit rate but the service is not directly comparable to the Stop for Good model as it was an NHS funded service that reimbursed pharmacists for service delivery as well as providing free NRT to patients enrolled on the programme. Given that these factors may have influenced both pharmacist and patient behaviour and encouraged greater engagement with the programme, the fact that the Stop for Good CO verified quit rate at 4 weeks (13.98%) was not too dissimilar to that reported by Bauld *et al.* [303] is encouraging.

There was a strong recruitment of smokers to the Stop for Good programme (n=1,287 over a six month period) with only Bauld *et al.* [303] (3 month recruitment n=1,374) and Costello *et al.* [300] (12 month recruitment n=3,588) reporting higher recruitment levels. This was achieved by a combination of in-pharmacy conversation with patients presenting to the healthcare counter, online promotion via the pharmacy website and national television promotion which involved the cessation programme being featured on a national health and wellbeing show which aired at prime time to an estimated audience of over 550,000 people. This promotion had a significant effect on patient awareness of and initial enquiry about the program, an important consideration when considering how to reach out to potential enrollees of pharmacy-based programmes.

3.6.3 Strengths and limitations

To the best of the author's knowledge this is the first study reporting outcomes for a large scale medium intensity smoking cessation intervention in the community pharmacy setting in the Republic of Ireland. Strengths of the study include the real world setting in which it was conducted and the information that the observational nature of the study provides on uptake and outcomes of a community pharmacy smoking cessation service in routine practice. The service being evaluated was offered in all Boots pharmacies nationwide and there was no fee for participation meaning the barriers to entry were minimal with the only exclusion criteria being if the patient was under 18 years of age or incapable of providing valid informed consent. The inclusion of a CO validated measure of quitting and an ITT analysis means the observed quit rates are conservative.

The study also has some important limitations. The non-randomised nature of the study and the absence of a comparator group mean it is not possible to comment on the efficacy of the

intervention relative to other supports routinely offered in community pharmacy practice, the most common of which in the Irish setting is supply of NRT and provision of information on its use. The short-term follow-up means conclusions on the sustainability of abstinence after the 12 weeks observed cannot be made. Additionally, whilst point prevalence abstinence is reported (abstinence as verified by a CO breath test on the day of presentation), assessment of prolonged abstinence (defined as not smoking for a continuous period, often several months, post a quit date [305]) is also recommended [306]. Reporting bias cannot be discounted as, whilst training on the importance of robust record keeping was provided, data were recorded on paper based forms at the discretion of the Stop for Good advisor. Combined with the possibility of recall bias for questions relating to smoking history for example, some element of information bias may exist.

3.6.4 Implications for practice and research

Tobacco dependence is recognised as a chronic relapsing condition that typically requires on-going assessment and repeated intervention [285]. As most smokers require repeated quit attempts before achieving permanent abstinence [259] patients suffering from tobacco addiction should be offered behavioural and pharmacological support as well as regular review within a system that offers repeated support to quit [267].

The World Health Organisation (WHO) has called for smoking cessation to be specifically integrated into primary health care which is seen as the most suitable location for providing advice and support on smoking cessation [267]. This study adds to the body of evidence that smoking cessation services can be delivered successfully in the community pharmacy setting. However, despite the evidence in the literature of effectiveness and cost effectiveness, conclusions on how to encourage such services to be delivered as a matter of national policy are lacking [307]. In the Irish context cost effectiveness is yet to be determined and future research should seek to address this issue.

The benefits of provision of advice and support to smoking patients are clear but the challenge for practice is the systematic identification of smokers and offering such advice as a matter of routine [294]. The results of this study show a wide variation in the numbers of patients recruited across different pharmacies (range 0 -70) and thus further work on how to encourage greater engagement of pharmacy teams would be of benefit.

A significant number of patients (57.2%) only attended one visit. Whilst this is often a feature of multi-session behavioural interventions [300], programmes that provide several sessions of contact are recommended over those with minimal/no contact for achieving significant cessation outcomes [308]. Provision of incentives to encourage repeat visits may be necessary. People tend to be more motivated by tangible gains such as a financial benefit, than by long-term intangible gains like the reduction in a chance of a negative health outcome [309]. Some programmes, typically those funded by national health services [300, 303], offer rewards in the form of free NRT but it has been suggested that this may not be enough of an encouragement [300]. Future development of the Stop for Good programme could seek to test different rewards and incentives in an effort to increase cessation rates.

Chapter 4: Community Pharmacy Ambulatory Blood Pressure Monitoring Service

4.1 INTRODUCTION TO THE CHAPTER

Detection and management of raised blood pressure and atrial fibrillation are important factors which contribute to the prevention of stroke [310]. It is estimated that 950,000 (62.2%) of adults aged 45+ in Ireland have high blood pressure [311]. Of these almost 595,000 are undiagnosed [310]. Approximately 6% of over 65s in Ireland are affected by atrial fibrillation [312] and many cases remain undetected or untreated [310]. Health policy in Ireland has identified the need for more effective detection and management of both high blood pressure and atrial fibrillation within the primary care setting [310].

This chapter describes a cross-sectional observational study of a sample of patients attending community pharmacy for ambulatory blood pressure monitoring (ABPM). The study is reported using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement [257] checklist for cross-sectional studies [258].

4.2 BACKGROUND

4.2.1 Hypertension

Hypertension can be defined as “*elevation of the arterial blood pressure above the normal range expected in a particular age group*” [5]. This somewhat simplistic definition of hypertension belies the complex nature of the condition, its role in the development of cardiovascular disease and its inter-relationship with other cardiovascular risk factors.

There is a continuous independent relationship between usual blood pressure and incidence of cardiovascular events such as stroke [313], heart failure [314] and death from vascular disease [315]. This relationship is observed for blood pressure measured in the doctor’s surgery (office BP) as well as out of office measurement such as that provided by ABPM or home blood pressure monitoring (HBPM) [316]. It has been documented across all age groups [313, 315], genders [313, 315, 317] and ethnicities [317, 318].

Prevalence estimates for hypertension vary according to the methods, outcomes and age ranges used in their calculation [319]. The global prevalence of hypertension in adults over the age of 18 is currently estimated at around 22% [219]. European prevalence in the general population appears to be somewhat higher (30-45%) [316] with prevalence in persons aged 16 years and older in the Republic of Ireland estimated at 25.1% [320]. Prevalence increases steeply with advancing age [316] and in the Irish context it is estimated that 950,000 (62.2%) of adults aged 45+ in Ireland have high blood pressure [311]. This estimate includes those adults with raised blood pressure who are unaware of their diagnosis, estimated to be some 595,000 adults.

Given the number of undiagnosed cases of hypertension and the known benefits of therapy, diagnosis is important. Hypertension has traditionally been diagnosed on the basis of high clinic blood pressure readings. Studies conducted in primary care have shown clinic blood pressure measurements to be higher than those obtained in the same patients undergoing ABPM [321], a phenomenon known as the white coat effect [322]. The white coat effect is common, being present to some extent in most hypertensive patients [323]. It occurs in patients not on antihypertensive treatment, in whom blood pressure is elevated in the clinic/office setting on repeated visits but normal out of the clinic on ABPM or HBPM [316]. Diagnosis of white coat hypertension is important as it prevents the inappropriate initiation of antihypertensive treatment in patients who do not require it. ABPM as a diagnostic tool allows the presence of white coat hypertension to be assessed and thus it is being increasingly recommended and used in clinical practice [322, 324].

4.2.2 Atrial Fibrillation

Atrial fibrillation (AF) arises when chaotic electrical activity in the heart leads to loss of synchronicity of contractions resulting in a rapid and irregular pulse rate [5]. It is a very common cardiac arrhythmia [18, 325] and frequently leads to cardiovascular complications such as congestive heart failure [326] and in particular stroke [326, 327], with one in five of all strokes attributed to AF [328]. Ischaemic strokes associated with AF are often fatal and where the patient survives they are often left more debilitated than patients who experience strokes due to other causes [328]. Additionally they remain at greater risk of recurrence [328]. The costs of care are significant and as a result prevention of stroke is a focus both nationally [310] and internationally [328].

Reported estimates put the prevalence of AF in the general population at around 1-2% [18, 329, 330]. Prevalence increases with increasing age [330] and men are more often affected than women [328]. As with hypertension, AF is under-diagnosed [328, 331] with recent estimates suggesting that 50% of Irish individuals with the condition remain undetected [18]. Given the evidence base supporting the efficacy of oral anticoagulant medication in reducing AF related stroke risk [332], prevention of strokes could be facilitated by early detection of AF and initiation of anticoagulant therapy where indicated [316].

Screening for atrial fibrillation can take various forms but usually involves some combination of both pulse palpation and ECG recordings [333], with a 12-lead ECG interpreted by a cardiologist considered the current gold standard for detection [331]. Opportunistic screening for atrial fibrillation in primary care, where 12-lead ECG was carried out on patients with an opportunistically identified irregular pulse, has been shown to increase atrial fibrillation detection rates [334]. Cost effectiveness of this approach when applied to patients aged 65 years and older has been demonstrated [331] and it is recommended by the European Society of Cardiology (ESC) [335] as a means of early detection of AF.

Several new electronic devices have been developed which appear to have higher specificity than pulse palpation and thus have the potential to be useful triage tests for AF [336-338]. One such device, the Microlife® WatchBP® O3 Afib device (Microlife Watch BP AG Switzerland, Widnau, Switzerland) is endorsed by the National Institute of Health and Care Excellence in the UK for the opportunistic detection of atrial fibrillation in patients undergoing blood pressure measurements in primary care [339].

4.2.3 Ambulatory Blood Pressure Monitoring

ABPM is a method that is used to monitor blood pressure over a prolonged period, usually 24 hours. Repeated measurements taken at set intervals (usually every 30 minutes) provide a profile of blood pressure fluctuations over an entire day giving information on both daytime and, importantly, night-time blood pressure patterns [340]. The advantages of ABPM over other methods of blood pressure measurement (such as office blood pressure measurement and home blood pressure measurement) have been widely reported [322, 340-342]. They include the ability to provide detail on an individual's usual level of blood pressure control outside the clinic setting and over a twenty four hour period thus facilitating the diagnosis of patterns of blood pressure behaviour that are not readily identifiable by other means such as white coat

hypertension, masked hypertension (where an individual has normal blood pressure when measured in a clinic setting but elevated 24 hour readings outside of this setting [322]) and abnormal nocturnal patterns of blood pressure control (an important predictor of cardiovascular outcome [322]). Such advantages have influenced international recommendations for the technique to be employed in the diagnosis of hypertension in clinical practice [324, 343-345].

Studies conducted in primary care have shown clinic blood pressure measurements to be higher than those obtained in the same patients undergoing ambulatory blood pressure monitoring [321]. Furthermore they identified the role of ABPM in the detection of white coat hypertension [346] and confirmed the cost effectiveness of the service [347]. This has prompted the suggestion that wider availability of ABPM would improve diagnosis and treatment of hypertension [348] and led to calls for wider implementation of the service in the primary care setting [349].

4.2.4 The role of the community pharmacist

National policy recommends a shared care approach to cardiovascular disease risk assessment and ongoing management in the primary care setting [18] with the role of both general practice and pharmacy noted in this regard. The role of community pharmacy in delivery of an ABPM service has been recognised [348, 350] but to date there has been limited availability of the service in this setting. Community pharmacist involvement in screening for atrial fibrillation is also limited but has been explored [351].

Community pharmacies represent a primary healthcare resource that is both accessible and convenient. A recent Irish study has indicated the opening hours of pharmacies as being popular with patients in terms of ability to easily access an ABPM service [348]. With the average community pharmacy in Ireland open 50% longer than General Practice clinics [33] and no appointments necessary to avail of a consultation, there are more visits to community pharmacies on a monthly basis than any other element of the primary health care service [33]. Provision of ambulatory blood pressure monitoring services in community pharmacy can make such services more accessible [348]. Ambulatory blood pressure monitoring devices with the ability to detect atrial fibrillation exist [352, 353] and the use of such devices in a community pharmacy based ambulatory blood pressure monitoring service may support the opportunistic detection of atrial fibrillation in the population accessing such a service.

4.2.5 Boots 24-hour blood pressure monitoring service

The Boots 24-hour blood pressure monitoring service allows patients to be fitted with a 24-hour blood pressure monitor which assesses their blood pressure control over a 24-hour period. A report based on the 24-hour measurements is then prepared. Boots pharmacists provide an overview of the report to the patient followed by onward referral to their general practitioner. The monitor used in the service is Microlife® WatchBP® O3 Afib device (Microlife Watch BP AG Switzerland, Widnau, Switzerland) which allows for detection of abnormal pulse patterns which may be indicative of atrial fibrillation. Therefore, opportunistic screening for atrial fibrillation is conducted at the time of blood pressure assessment and this information is in turn shared with the patient and their GP (where consent is provided).

4.3 OBJECTIVES

4.3.1 Primary objective

The primary aim of the research was to determine the prevalence of (1) hypertension and (2) pulse patterns indicative of atrial fibrillation in a sample of patients attending community pharmacy for ABPM as part of the Boots 24-hour Blood Pressure Monitoring Service.

4.3.2 Secondary objectives

The secondary objectives were as follows:

- To determine the prevalence of other blood pressure profiles (white-coat hypertension, masked hypertension) in a sample of patients attending community pharmacy for ambulatory blood pressure monitoring;
- To describe the demographic and clinical profiles of patients with hypertension as indicated by 24-hour measurements;
- To describe the demographic and clinical profiles of patients with pulse patterns indicative of atrial fibrillation as indicated by 24-hour measurements;
- To describe the demographic and clinical profiles of patients with white coat hypertension as indicated by 24-hour measurements;

- To describe the cardiovascular disease risk factor profiles of patients attending community pharmacy for ambulatory blood pressure monitoring;
- To conduct a follow up survey with a subsample of patients post ABPM assessment in order to determine their satisfaction with the service and to understand what, if any, diagnosis and/or therapy adjustments they received as a result of the ABPM assessment.

4.4 METHODS

4.4.1 Study Design

This study is a cross-sectional observational study of patients availing of an ambulatory blood pressure monitoring service in a community pharmacy setting in Ireland. It is non-interventional in nature and draws on data routinely collected as part of the ABPM service.

4.4.2 Pharmacist training

All pharmacists and authorised pharmacy team members who conducted any service related procedures must have completed a programme of training and must have successfully passed an associated test of knowledge before undertaking any service related procedures. The training programme covered information on cardiovascular disease and service delivery and also included training on the consent process (informed consent, capacity to consent).

4.4.3 Setting

Patients availing of the ABPM service in twenty-one pharmacies within the Boots Ireland chain of community pharmacies, between November 2014 and February 2016, were eligible for inclusion in the study. Inclusion and exclusion criteria applied and are described in section 4.4.6.

4.4.4 Data collection

Patients consented to join the service in the pharmacy of their choosing. A patient information leaflet outlining the service and what it entails was provided to all patients. This leaflet contains the Consultation Record Form (CRF) that is completed during the service consultation. This record form is subsequently removed from the leaflet and kept on file in the pharmacy as a record of service delivery. A copy of the CRF is provided in Appendix 3.

Demographic and cardiovascular risk profile data for each patient were collected on the date of presentation to have the ambulatory blood pressure monitor fitted. Ambulatory blood pressure measurements were downloaded from the monitor 24 hours later and a blood pressure measurement report was generated at this time. A sample ABPM report is presented in Section 4.4.7.

When attending for a 24-hour blood pressure monitoring assessment, patients were notified that Boots may use anonymous data collected during the service for medical analysis and research. They were also informed that anonymous data may be shared with carefully selected third parties for the purpose of conducting such research. Patients were able to decline to have their anonymous data used/shared for research purposes.

For this study only CRFs for those patients who did not decline to allow their anonymous data to be used/shared for research purposes were used for the purposes of data collection and analysis.

Patients were also asked if they would be happy to be contacted for feedback post ABPM assessment. In the event that a patient did not decline to allow their anonymous data to be used/shared for research purposes and indicated a willingness to be contacted for feedback, efforts were made to contact those patients for the follow up survey.

Data collection took place in each of the study pharmacies from March – May 2016. The data collection was undertaken by the lead researcher, an Irish registered pharmacist employed by Boots Retail Ireland Limited. The lead researcher was solely responsible for the entry of anonymous data into a specially designed data collection spreadsheet (Excel 2007). This spreadsheet was encrypted and password protected. A coding template for data entry was created and the data collection exercise was undertaken as follows:

- The CRF and corresponding ABPM read out for each patient who availed of the service between November 2014 and January 2016 were located.
- The CRF was reviewed to identify if the patient was happy to share anonymous data for research.
- In the event that the patient was not happy to share anonymous data for research then no data pertaining to that patient was entered into the database and the form was returned to the secure record holder.

- In the event that the patient agreed to the sharing of anonymous data, the ABPM report was reviewed for validity as per pre-defined criteria (a “valid” report is defined as one which includes a minimum of twenty daytime readings, a minimum of seven night-time readings and 70% or more of all readings taken over the 24-hour period being classed as valid readings).
- Where a valid report was available, non-identifiable data were entered into the database as per the patient responses on the CRF and the ABPM read out. Where appropriate, responses were coded for entry. A template for codes was prepared in advance.
- On the CRF the following data were considered identifiable and thus were not entered into the results database: First name/surname/address/email/phone number/date of birth.
- On the ABPM read out the following data were considered identifiable and thus were not entered into the results database: Patient ID/name/date of birth. Age in years was recorded as noted on the ABPM read out.

The follow up survey was conducted in conjunction with pharmacy staff working in the 21 study pharmacies. A survey was designed by the lead researcher and circulated to all study pharmacies along with instructions on its administration. Only pharmacists, pharmacy interns or authorised ABPM advisors were eligible to conduct the survey with patients who had attended their pharmacy and patients were contacted in the following manner:

- Patients who were happy to share anonymous data for research and to be contacted for feedback were contacted by telephone in the first instance and asked if they wished to complete the follow up survey.
- Where the patients provided consent to take part in the survey via telephone the telephone survey template (ABPM Follow-up Survey – Telephone) was used for recording patient responses, a copy of which is presented in Appendix 4.
- In the event that a patient did not answer their phone a message outlining the reason for the call along with a name and contact number for the pharmacy was left on the patient’s answering machine where possible. A maximum of two attempts to contact the patient by telephone were made.

- Patients who could not be contacted by telephone, or who requested to be contacted via alternate means, were sent a postal survey. A postal survey template (ABPM Follow-up Survey – Post) was used in this instance and a stamped addressed return envelope was provided. The postal survey template is presented in Appendix 5.
- Completed surveys were returned to the lead researcher and a researcher assistant supported with the entry of anonymous data into a specially designed data collection spreadsheet (Excel 2007). A coding template for data entry was created and the spreadsheet was encrypted and password protected.

In order to correlate the responses of the follow-up surveys with the demographic and clinical data obtained at the time of ABPM assessment the data were matched using two common variables between the datasets (location and date of ABPM assessment). Once correlated the survey database was updated to form a pooled database for analysis.

All study related information and CRFs were treated confidentially to protect the privacy of individuals. Original paper copies of all informed consents were kept in the study pharmacies and all original patient records were kept under the personal supervision of the pharmacist(s) in each study pharmacy.

4.4.5 Ethics

Ethical approval to conduct the study was provided by the School of Pharmacy and Pharmaceutical Science Research Ethics Committee in Trinity College Dublin (December 2015).

4.4.6 Participants

4.4.6.1 Inclusion criteria

Male and female patients over the age of 18 who attended for an ABPM measurement in the study pharmacies between November 2014 and February 2016 were eligible for inclusion in the study provided they had not declined to their anonymous data being used for medical research/analysis. Patients could have been referred to the service by their general practitioner,

requested the service themselves or availed of the service on foot of a recommendation from the pharmacy team.

Where a patient availed of repeated 24-hour blood pressure measurements over the data collection period only the first valid 24-hour assessment was included.

4.4.6.2 Exclusion criteria

The following exclusion criteria applied:

- Patients who attended for the ABPM service but declined to allow their anonymous data to be used for medical analysis/research;
- Patients with an initial pharmacy recorded systolic blood pressure (SBP) reading of 180 mmHg or greater and/or a diastolic blood pressure reading of 110 mmHg (this being indicative of severe hypertension and thus requiring immediate medical care). The exception to this exclusion was if a doctor was aware of the high blood pressure reading and requested ABPM for the patient.

4.4.7 Measurements

4.4.7.1 Blood pressure measurement

Blood pressure was measured in the clinic and ambulatory setting using the Microlife® WatchBP® O3 Afib device (Microlife Watch BP AG Switzerland, Widnau, Switzerland); a 24-hour blood pressure monitor with atrial fibrillation (Afib) detector. The Watch BP® O3 device has been validated according to an internationally accepted protocol [354] and the algorithm employed for detection of atrial fibrillation has been shown to reliably detect this condition [336, 352]. The device is endorsed by the National Institute of Health and Care Excellence in the UK for the opportunistic detection of atrial fibrillation in patients undergoing blood pressure measurements in primary care [339].

To avoid over-cuffing (use of a cuff with too wide or long a bladder which can underestimate BP) and/or under-cuffing (use of a cuff with too narrow or short a bladder which can overestimate BP) [322] the upper arm circumference was measured for each patient before cuff selection and fitting.

Clinic blood pressure was measured twice, once in each arm using the Microlife® WatchBP® O3 Afib device in “Casual” mode with a wait of approximately two minutes between each measurement. Measurements were taken in the pharmacy consultation room; a quiet room where the patient was seated and his/her arm was supported by an arm rest. The patient was advised to remain still and quiet, with both feet on the floor and arm at heart height while the measurement was taken. A standardised measurement protocol/SOP was used.

Comparison of readings in each arm was made and where there was a difference of ≥ 20 mm Hg SBP or ≥ 10 mm Hg diastolic blood pressure (DBP) [341, 355] the arm with the higher reading was selected as the arm for ambulatory blood pressure measurement. In all other cases the non-dominant arm was used [322].

Ambulatory blood pressure and pulse patterns over a 24-hour period were measured using the Microlife® WatchBP® O3 Afib device as previously noted.

Patients were fitted with the Microlife device in the community pharmacy setting and measurements were programmed to be taken every 30 minutes over a 24-hour period. Patients were provided with verbal and written advice on what to expect over the 24-hour measurement period. The patient was advised to carry out daily activities as normal and the importance of remaining as still as possible with the arm relaxed at heart level during BP measurement was emphasised [341]. The patient was also provided with a diary to record activity and mood at time of measurement as well as awake/asleep hours and quality of sleep [322] (Note: these records were for patient use and they were not used for data analysis). Daytime and night-time hours were different for each patient depending on their individual reported asleep and awake hours.

Measurements from the device were downloaded to the WatchBP® O3 Afib Analyzer software programme (version V2.0.1.1) and a report of blood pressure and pulse profile over the 24-hour period was generated, a sample of which is provided in Figure 4.1. Reports were considered valid if there were a minimum of 20 daytime and 7 night-time readings and at least 70% of expected measurements were obtained [322].

WatchBP[®] O3

Ambulatory Blood Pressure Measurement Report

Physician : test

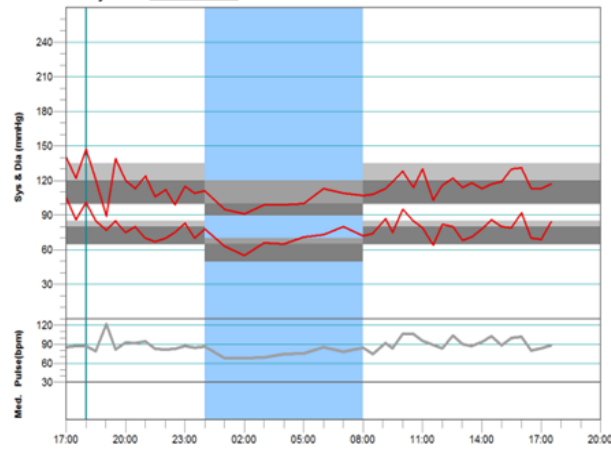
Patient ID : 223
 Name : test test
 Sex : Male
 Age : 63
 DOB : 1950/1/1

Day and Night Period
 Time Interval
 Day : 08 ~ 00 30 min
 Night : 00 ~ 08 60 min

Actual Awake / Asleep
 Awake : 08 ~ 00 h
 Asleep : 00 ~ 08 h

BP Threshold
 Day : 135/85 mmHg
 Night : 120/70 mmHg

Study Date 2013/11/8



Readings	Average Blood Pressure (SD)						White Coat Window				
	Sys	Dia	HR	MAP	PP	Afib	Sys	Dia	HR		
Total Readings : 42 Successful : 42 (100.0%)	24-hr	113 (10)	76 (9)	85 (10)	86	37	8(42)	Readings	2	2	2
BP Load	Awake	118 (7)	79 (8)	90 (7)	88	39	7(34)	1st hr Max	140	105	87
Day readings ≥ 135/85 29.4% Night readings ≥ 120/70 50.0%	Asleep	102 (8)	69 (8)	75 (7)	78	33	1(8)	Night-time Dip%			
								Sys	Dia		
								Dip%	13.2	13.2	

Date / Time	Sys	Dia	HR	MAP	Afib	Date / Time	Sys	Dia	HR	MAP	Afib
2013/11/8						08:30	108	74	74	87	
17:00	140	105	85	112	D	09:08	113	87	91	94	
17:30	122	86	87	98		09:30	119	75	83	81	
18:00	147	101	87	117	D	10:00	128	95	106	106	
18:30	121	85	79	94		10:33	114	85	106	93	D
19:03	89	77	121	84	D	11:00	130	79	95	89	
19:30	139	85	81	96		11:33	103	64	89	76	
20:00	120	75	92	83		12:00	116	82	83	89	
20:30	113	80	91	94		12:33	122	80	103	92	D
21:00	124	70	94	78		13:03	114	68	90	80	
21:30	106	67	82	76		13:30	118	71	87	84	
22:03	112	70	81	76	D	14:00	113	78	93	87	
22:30	99	75	82	81		14:30	117	86	102	94	
23:00	115	83	87	87		15:00	119	80	88	89	
23:30	109	70	84	78		15:30	130	79	100	88	
2013/11/9						16:00	131	92	101	96	D
00:00	111	78	86	86		16:30	113	70	80	78	
01:00	95	63	68	74		17:00	113	69	83	79	
02:00	91	55	68	62		17:30	117	84	88	90	
03:00	99	66	69	72	D						
04:00	99	65	74	74							
05:00	100	71	75	79							
06:00	113	73	85	91							
07:00	109	80	78	88							
08:00	107	72	84	80							

Comments:

24-h Normotension, Daytime Normotension, Nighttime Normotension, White Coat Hypertension, Dipper

Signature: _____



Figure 4-1: Microlife Watch BPO3 AFib[®] ABPM Report

4.4.7.2 Body mass index measurement

Each patient's height, weight and body mass index (BMI) were measured using an automated weighing scales (DaviVendy® multifunctional scales) or manually by measuring the height in metres (m), weight in kilograms (kg) and calculating the BMI using the calculation:

$$\text{BMI (kg/m}^2\text{)} = (\text{weight in kg}) / (\text{height in m})^2$$

4.4.8 Diagnostic criteria

4.4.8.1 Hypertension

Threshold values for hypertension diagnosis were based on consensus values determined by the European Society of Hypertension in 2013 [322] and are outlined in Table 4.1 below.

Table 4-1: Threshold values for diagnosis of hypertension based on ambulatory blood pressure monitoring

Category	Systolic BP (mm Hg)		Diastolic BP (mm Hg)
24-hour average	≥ 130	and/or	≥80
Awake average	≥135	and/or	≥85
Asleep average	≥120	and/or	≥70

4.4.8.2 Nocturnal hypertension

Ordinarily it is expected that BP declines when a patient goes to sleep [322]; however this does not always occur [356]. As a result, it is common to describe the ‘dipping status’ of a patient; that is to describe whether the BP falls, rises or remains constant once the patient moves from wakefulness to sleep [322]. In this study four patterns of dipping were considered as per Table 4.2.

Table 4-2: *Dipping patterns of nocturnal blood pressure*

Dipping Category	Nocturnal Blood Pressure Fall (%)
Non-Dipper	> 0% and \leq 10%
Dipper	> 10% and \leq 20%
Extreme Dipper	> 20%
Reverse Dipper	Increase in nocturnal blood pressure

4.4.8.3 White coat hypertension

The situation where blood pressure is elevated in the clinic/office setting on repeated visits but normal out of the clinic on ABPM (or HBPM) is referred to as white coat hypertension (WCH) [316].

Comparison of the clinic/office BP obtained in routine clinical practice and the ambulatory BP provides a measure of the degree of white coat hypertension present [357].

The definition of white coat hypertension for this study is based on that proposed by the European Society of Hypertension in 2013 [322]; namely an office/clinic BP of \geq 140 mm Hg

systolic and/or ≥ 90 mm Hg diastolic and a mean awake ambulatory BP of $< 135/85$ mm Hg systolic/diastolic and a mean 24-hour ambulatory BP of $< 130/80$ mm Hg systolic/diastolic.

4.4.8.4 Masked hypertension

Masked hypertension refers to the situation where a patient exhibits normal BP in the office setting and elevated BP on ABPM [358]. This term should be reserved for untreated patients, with the term ‘masked uncontrolled hypertension’ used when describing this phenomenon in patients taking antihypertensive medication [322].

The definition of masked hypertension for this study is based on that proposed by the European Society of Hypertension in 2013 [322]; namely an office/clinic BP of $< 140/90$ mm Hg and a mean 24-hour ambulatory BP of $\geq 130/80$ mm Hg and/or a mean awake ambulatory BP of $\geq 135/85$ mm Hg and/or a mean asleep ambulatory measurement of $\geq 120/70$ mm Hg in untreated patients. Masked uncontrolled hypertension is defined by the same values but only applies to patients taking antihypertensive medication.

4.4.8.5 Atrial Fibrillation

The Microlife® WatchBP® O3 Afib device automatically detects pulse irregularity when recording blood pressure [339, 359]. Detection of pulse patterns indicative of atrial fibrillation is based on the calculation of an irregularity index by the embedded Microlife AFIB algorithm [339]. The irregularity index is calculated by dividing the standard deviation of the time interval between successive heartbeats by the mean number of intervals for the total number of beats analysed [360]. Where a pulse irregularity is identified during the measurement this is noted as a “D” symbol on the ABPM report. In patients over the age of 50 in whom $>15\%$ of blood pressure readings are associated with a “D” reading it is considered that atrial fibrillation could be present and the patient is referred to their GP for further investigation.

4.4.8.6 Smoking status

Smoking status was self-reported by patients. Patients were asked to indicate whether they were a current smoker or had ever smoked in the past by answering the question:

“Do you smoke, or have you ever smoked?”

Patients who answered no to this question were classed as “non-smokers”. Patients who answered yes were asked to indicate how many cigarettes they smoked each day and for how many years as well as noting whether they currently smoked at the time of ABPM assessment. Current smokers were classed as “smokers” and patients who previously smoked but were non-smokers at the time of ABPM assessment were classed as “ex-smokers”.

Smoking pack years (number of packs (where 1 pack =20 cigarettes) smoked per day multiplied by number of years smoking) was calculated for all current and ex-smokers where possible. Where a range of cigarettes smoked per day was given the upper value was used in the pack years calculation and one cigar was treated as equal to 4 cigarettes [361].

4.4.8.7 Drinking habits

Patients were asked to indicate the number of standard drinks they consumed each week. In Ireland a standard drink is defined as one which contains 10 grams of alcohol [362] and it is approximately equal to a half pint of normal beer/lager/cider or one small glass of wine [363]. Where patients indicated a range of drinks consumed per day the upper value was used for classification. Patients were classed as “never/rarely drinks”, “low risk drinker”, “medium risk drinker” or “high risk drinker” based on similar* thresholds set out by the Health Service Executive [364] for both males and females as outlined in Table 4.3 below.

Table 4-3: Drinking habit classification

Classification	Female	Male
Never/rarely drinks	< 1 standard drink per week	< 1 standard drink per week
Low risk drinker	1-11 standard drinks per week	1-17 standard drinks per week
Medium risk drinker	12-28 standard drinks per week	18-40 standard drinks per week
High risk drinker	≥29 standard drinks per week	≥41 standard drinks per week

*The HSE classifications also take into account the number of alcohol free days per week. This information was not collected as part of the study.

4.4.8.8 Cholesterol level

Patients were asked to indicate yes, no or unsure as an answer to the following question:

“Do you have high cholesterol?”

Patients were not asked to provide details of their total cholesterol level nor were cholesterol levels tested in the pharmacy. Patients were classed as having high cholesterol if they answered yes to the above question, if they indicated that they were on a cholesterol lowering medication or if they noted a cholesterol value of 5 mmol/L or greater [365] on their CRF.

4.4.8.9 Diabetes

Self-reported diagnosis of diabetes was obtained by patients indicating on the CRF if they had Type I, Type II or no diabetes.

4.4.8.10 Medication

Medication was based on patient self-report. Medications were reviewed to determine if patients were taking antihypertensive therapy. Doctor diagnosis of a patient’s medical condition and hence indication for therapy was unavailable.

If a patient was taking any medication with antihypertensive effects at the time of ABPM assessment, they were classed as having diagnosed hypertension. Based on the results of ABPM this hypertension was further classed as controlled or uncontrolled. For patients not on antihypertensive medication at the time of assessment, the results of ABPM allowed for classification of normotension, white coat hypertension, or (newly diagnosed) hypertension.

4.4.8.11 Body Mass Index

Body mass index classifications are outlined in Table 4.4 and are based on the classifications set out by the World Health Organisation [366].

Table 4-4: Body Mass Index Classification

BMI	Classification
<18 kg/m ²	Underweight
18-24.9 kg/m ²	Normal
25-29.9 kg/m ²	Overweight
≥30 kg/m ²	Obese

4.4.9 Sample size

Patients over the age of 18 years are eligible to join the Boots 24-hour blood pressure monitoring service and for this reason prevalence estimates for both atrial fibrillation and hypertension in the general population over the age of 18 were chosen.

Varying prevalence rates for hypertension in Irish population exist. A 2007 study noted the rate of clinically diagnosed hypertension for all adults in the Republic of Ireland aged 18 years and above as 12.7% [311]. The same study noted that 38.9% of adults over the age of 45 had undiagnosed hypertension [311]. Recent estimates published by the Institute of Public Health in Ireland note a higher prevalence of 25.1% for adults over the age of 16 with prevalence increasing sharply with advancing age [320]. Population prevalence in that report referred to both diagnosed and undiagnosed cases. Whilst it seems reasonable to assume that the “true” prevalence in adults over the age of 18 may be higher than 12.7%, this figure was selected as the prevalence estimate for this study so as not to underestimate the sample size required.

Irish specific data for the prevalence of atrial fibrillation in the general population are lacking. The 2012 estimate for prevalence of atrial fibrillation in the developed world is approximately 1-2% of the general population [326]. Whilst more recent studies in the European context

estimate the prevalence at 2% [367], a prevalence of 1.5% was chosen for this study to avoid under-estimation of the sample size.

A sample size of 568 allows for the detection of atrial fibrillation at a prevalence of 1.5% with precision of 1% and 95% confidence level. This also allows for the detection of hypertension at a prevalence of 12% with precision of 3% and 95% confidence. The sample size was calculated using the following formula:

$$n = Z^2 \times P(1-P) / d^2$$

where:

n= sample size

Z= z statistic for confidence level

P= expected prevalence

d = precision

4.4.10 Data analysis

Statistical analysis was carried out using IBM SPSS Statistics for Windows, Version 21.0. (Armonk, NY: IBM Corp). Categorical variables are expressed as numbers and percentages with continuous variables expressed as mean \pm standard deviation. Prevalence estimates are reported with 95% confidence intervals. Chi squared analysis was used to compare groups for categorical variables. A *P*-value of <0.05 is considered to be statistically significant.

4.5 RESULTS

4.5.1 Participants

A total of 856 patients availed of a 24-hour blood pressure assessment in 21 pharmacies between November 2014 and February 2016. The service records were reviewed for suitability for inclusion in the data analysis. A total of 276 records were excluded and the reasons for exclusion are shown in Figure 4.2. 580 records from 21 pharmacies (mean number of patients per pharmacy 28 ± 21 , range 2-84) were available for analysis.

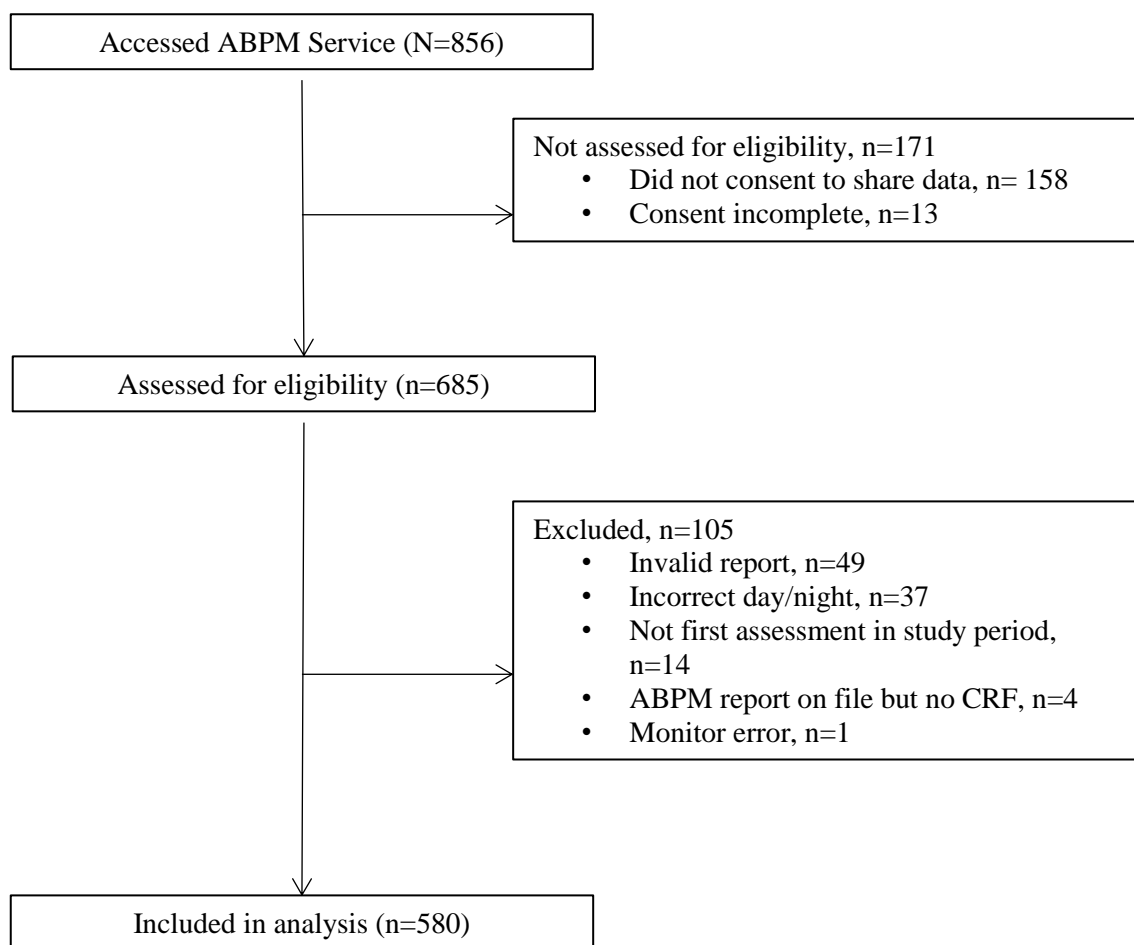


Figure 4-2: Flowchart of patients accessing the ABPM service and their inclusion/exclusion in the observational study

4.5.1.1 Demographic profile of the participants

52.9% of patients were female and the mean age was 57 (range: 21-86). Data on ethnic origin was available for 551 patients; of that sample 96.9% of patients were white. 58.3% (338/580) of the total sample had private medical insurance and 17.4% (101/580) had medical card eligibility. Three women (1% of all women) were pregnant at the time of assessment.

Table 4-5: Demographic characteristics of patients accessing the ABPM service

Demographic characteristic	Number (%) of patients
Sex	
Male (n, %)	273/580 (47.1%)
Female (n, %)	307/580 (52.9%)
Mean age in years at enrolment (SD)	57.28 (13.32)
Ethnic Origin	
White (n, %)	534/551 (96.9%)
Asian (India, Pakistan, Bangladesh, Sri Lanka) (n, %)	6/551 (1.1%)
Other Asian (n, %)	5/551 (0.9%)
Black African (n, %)	3/551 (0.5%)
Black Caribbean (n, %)	1/551 (0.2%)
Middle Eastern (n, %)	2/551 (0.4%)
Missing data	29/580 (5%)
Pregnant (n, % females)	3/307 (1.0%)
Health pay status	
Medical Card (n, %)	101/580 (17.4%)
Doctor Visit Card (n, %)	31/580 (5.3%)
Health Amendment Card (n, %)	2/580 (0.3%)
Long Term Illness Scheme (n, %)	15/580 (2.6%)
Private Health Insurance (n, %)	338/580 (58.3%)
None of the above (n, %)	130/580 (22.3%)

4.5.1.2 Risk factor profile of patients

57.6% of patients were overweight or obese and 35% were current or ex-smokers. The majority of patients were low risk drinkers. The proportion of patients with self-reported hypercholesterolemia was 25.9% and the proportion of patients who experienced previous cardiovascular events was low. The risk factor profile of patients is outlined in Table 4.6.

Table 4-6: Risk factor profile of patients accessing the ABPM service

Variable	Result
BMI (kg/m²)	
<18 kg/m ² , underweight (n, %)	1 (0.2%)
18-24.9 kg/m ² , normal (n, %)	103 (17.8%)
25-29.9 kg/m ² , overweight (n, %)	204 (35.2%)
≥30 kg/m ² , obese (n, %)	130 (22.4%)
Missing data	142 (24.5%)
Smoking status (%)	
Current	53 (9.1%)
Ex - smoker	150 (25.9%)
Never smoker	368 (63.4%)
Weekly alcohol intake	
Rarely/never drink (< 1 sd*)	172 (29.7%)
Low risk female (1-11 sd, % females)	151 (49.2%)
Low risk male (1-17 sd, % males)	159 (58.2%)
Increased risk female (12-28 sd, % females)	21 (6.8%)
Increased risk male (18-40 sd, % males)	39 (14.3%)
High risk female (>28 sd, % females)	2 (0.7%)
High risk male (>40 sd, % males)	1 (0.4%)
Missing data	38 (6.5%)
Previous cardiovascular event	
Ischaemic stroke (n, %)	6 (1.0%)
Trans Ischaemic Attack (n, %)	11 (1.9%)
Haemorrhagic Stroke (n, %)	1 (0.2%)
Heart Attack (n, %)	3 (0.5%)
Atrial Fibrillation (n, %)	26 (4.5%)
Heart Failure (n, %)	6 (1%)
Vascular Disease (n, %)	14 (2.4%)
Other conditions	
Type 1 diabetes (n, %)	7 (1.2%)
Type 2 diabetes (n, %)	17 (2.9%)
Hypercholesterolemia (n, %)	150 (25.9%)

4.5.1.3 Medication usage

567 patients indicated whether or not they were taking medication at the time of ABPM assessment. 14 of these patients indicated that they were taking medication but did not note what medication. Of the 553 patients for whom medication information was available, 68.4% (378/553) were taking medication to treat a medical condition. 19.9% (110/553) were taking medication for hypercholesterolemia and 36.3% (201/553) of patients were taking one or more antihypertensive medications. Patients with a medical card were more likely to be taking antihypertensive medication ($\chi^2 = 9.96$, $p = 0.002$).

Table 4-7: Medication usage of patients accessing the ABPM service

Medication Profile	Number (%) of patients
Antihypertensive treatment	
On antihypertensive therapy (n, %)	201/553 (36.3%)
Monotherapy (n, % of patients on treatment)	87/553 (15.7%)
Two-drug combination (n, % of patients on treatment)	43/553 (7.8%)
Three-drug combination (n, % of patients on treatment)	13/553 (2.4%)
Four or more drugs (n, % of patients on treatment)	3/553 (0.54%)
Mean number of hypertensive drugs (SD)	1.5 (0.74)
Other medication	
On any medication (n, %)	378/553 (68.4%)
On medication for hypercholesterolemia (n, %)	110 /553(19.9%)
On anticoagulant medication (n, %)	6/553 (1.1%)
On antiplatelet medication (n, %)	55/553 (9.9%)

4.5.2 Blood pressure measurement profiles

4.5.2.1 Average 24-hour blood pressure

The mean systolic blood pressure across all patients based on 24-hour readings was 128 mm Hg (95% CI: 127-129). The mean diastolic blood pressure was 75.1 mm Hg (95% CI: 74.5-75.8). Systolic blood pressure increased from 124.9 mm Hg (95% CI: 122.5-127.3) in the youngest age range (18-29) to 132.5 mm Hg (95% CI: 129.5-135.5) in those over 75 years. Diastolic blood pressure decreased from 77.0 mm Hg (95% CI: 75.3-78.8) in youngest patients to 69.6 mm Hg (96% CI: 67.9 -71.2) in the oldest group.

Distribution of mean systolic and diastolic blood pressure in the sample by age and gender is shown in Figure 4.3.

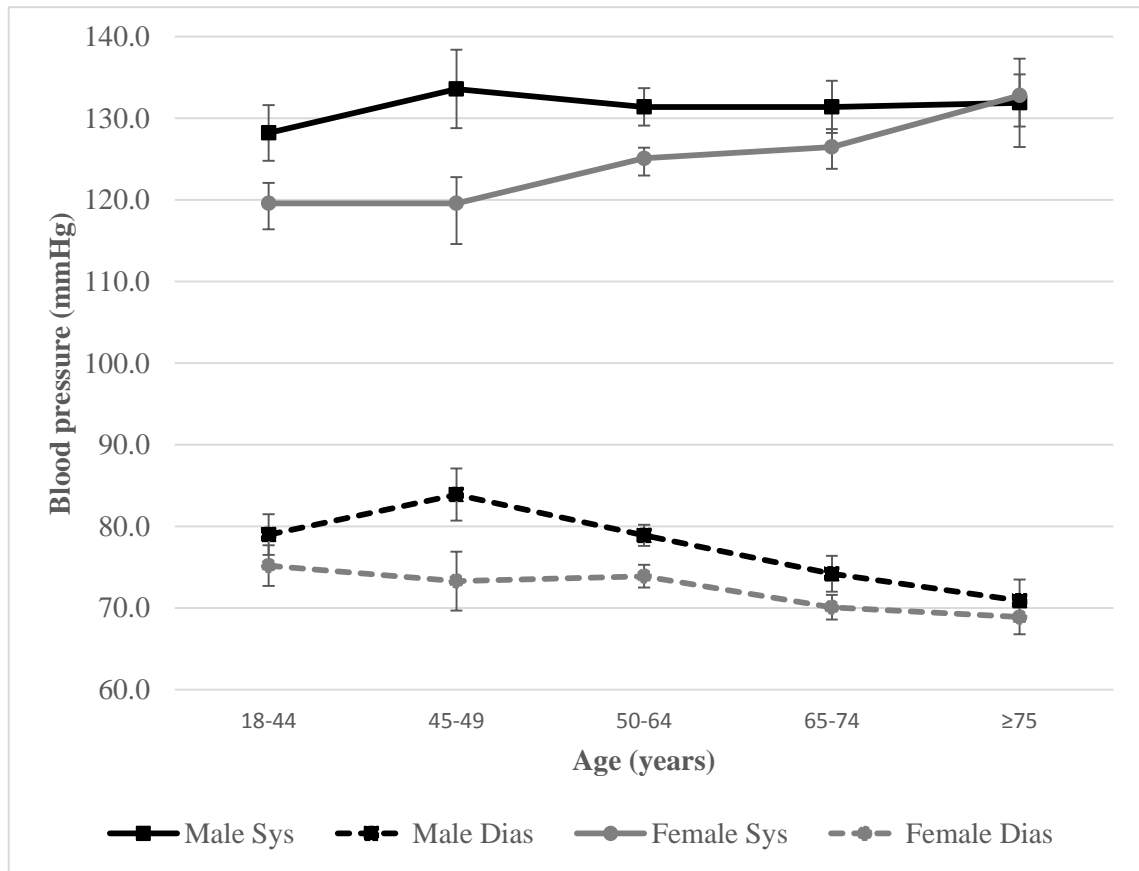


Figure 4-3: 24-hour mean blood pressure, classified by gender and age group

4.5.2.2 Blood pressure classification

The blood pressure classification for all patients based on ambulatory blood pressure monitoring is shown in Table 4.8. Prevalence of any hypertension in the sample of patients attending community pharmacy for ABPM was 64.3% (95% CI: 60.4-68.2). Prevalence was higher in males ($\chi^2 = 19.50$, $p < 0.001$). It was possible to determine prevalence of white coat hypertension and masked phenomena where patients had a clinic bp measurement, ambulatory measurements and information on their medication status available. As a result, white coat hypertension was detected in 50/549, 9.1% (95% CI: 6.8-11.4) patients with no significant difference in prevalence observed between genders ($\chi^2 = 3.63$, $p = 0.057$). Masked hypertension was observed in 38/548 6.9% (95% CI: 4.8-9.0) of patients and masked uncontrolled hypertension in 20/548

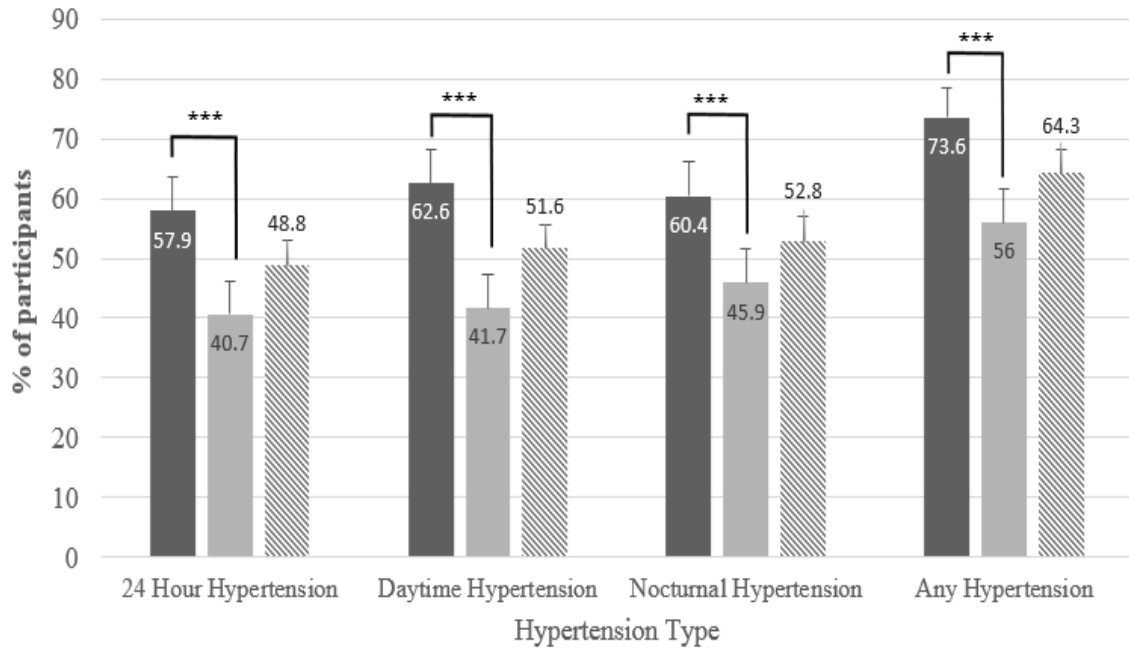
3.6% (95% CI: 2.1-5.1) of patients. Neither was statistically more prevalent in one gender versus the other. No significant differences in prevalence by age range were observed for any measures.

Table 4-8: Blood pressure profile of patients accessing the ABPM service classified by age and sex

	Any Hypertension (n=580)		White Coat Hypertension (n=549)		Masked Hypertension (n=548)		Masked Uncontrolled Hypertension (n=548)	
	<i>%</i>	<i>95% CI</i>	<i>%</i>	<i>95% CI</i>	<i>%</i>	<i>95% CI</i>	<i>%</i>	<i>95% CI</i>
<i>Gender</i>								
Male (n=273)	73.6 (201/273)	68.1-78.5	6.6 (17/257)	3.7-9.5	6.2 (16/257)	3.3-9.1	3.1 (8/257)	1.0-5.2
Female (n=307)	56.0 (172/307)	50.4-61.6	11.3 (33/292)	7.8-14.8	7.6 (22/291)	4.6-10.6	4.1 (12/291)	1.9-6.3
Total (n=580)	64.3 (373/580)	60.4-68.2	9.1 (50/549)	6.8-11.4	6.9 (38/548)	4.8-9.0	3.6 (20/548)	2.1-5.1
<i>Age Range</i>								
18-44 (n=109)	56.9 (62/109)	47.6-66.2	14.8 (16/108)	8.1-21.5	8.9 (9/101)	3.5-14.2	1.0 (1/101)	-0.09-2.9
45-49 (n=44)	68.2 (30/44)	53.4-80.0	11.9 (5/42)	2.3-21.5	9.5 (4/42)	8.4-18.2	0 (0/42)	0.0-0.0
50-64 (n=237)	66.7 (158/237)	60.4-72.4	9.3 (21/226)	5.6-13.0	7.6 (17/225)	4.2-11.0	3.6 (8/225)	1.2-6.0
65-74 (n=146)	62.3 (91/146)	54.4-70.2	3.8 (5/133)	0.7-6.9	2.9 (4/139)	0.2-5.6	7.2 (10/139)	3.0-11.4
≥75 (n=44)	72.7 (32/44)	58.2-83.7	7.5 (3/40)	-0.3-15.3	9.8 (4/41)	1.0-18.6	2.4 (1/41)	-2.1-6.9
Total (n=580)	64.3 (373/580)	60.4-68.2	9.1 (50/549)	6.8-11.4	6.9 (38/548)	4.8-9.0	3.6 (20/548)	2.1-5.1

4.5.2.3 Prevalence of hypertension in the sample

Hypertension was classified by type and the results are shown in Figure 4.4. Hypertension of all types was more prevalent in males than in females (24-hour hypertension $\chi^2 = 17.03$, $p < 0.001$; daytime hypertension $\chi^2 = 25.38$, $p < 0.001$; and night-time hypertension $\chi^2 = 12.21$, $p < 0.001$).



*** $p < 0.001$

Chi Square Analysis

■ Male (n=273) ■ Female (n=307) ▨ Total (n=580)

24 Hour Hypertension = Systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 80 mmHg

Daytime Hypertension = Systolic BP ≥ 135 mmHg and/or diastolic BP ≥ 85 mmHg

Nocturnal Hypertension = Systolic BP ≥ 120 mmHg and/or diastolic BP ≥ 70 mmHg

Any Hypertension = 24hr hypertension and/or daytime hypertension and/or nocturnal hypertension

Figure 4-4: Blood pressure classification on ABPM assessment classified by gender

Hypertension type was also analysed by age range. No significant differences in prevalence by age range were observed.

Table 4-9: Prevalence of hypertension in the sample of patients accessing the ABPM service classified by type, gender and age range

	24 Hour Hypertension		Daytime Hypertension		Nocturnal Hypertension		Any Hypertension	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Gender								
Male (n=273)	57.9	51.9-63.6	62.6	56.8-68.2	60.4	54.5-66.1	73.6	68.1-78.5
Female (n=307)	40.7	35.2-46.2	41.7	36.2-47.2	45.9	40.3-51.5	56.0	50.4-61.6
Total (n=580)	48.8	44.7-52.9	51.6	47.5-55.7	52.8	48.7-56.9	64.3	60.4-68.2
Age Range								
18-44 (n=109)	45.9	36.5-55.3	48.6	39.2-60.0	44.0	34.7-53.3	56.9	47.6-66.2
45-49 (n=44)	56.8	42.2-70.3	61.4	46.6-74.3	63.6	48.9-76.2	68.2	53.4-80.0
50-64 (n=237)	48.5	42.2-54.9	51.9	45.6-58.2	51.9	45.6-58.2	66.7	60.4-72.4
65-74 (n=146)	47.3	39.2-55.4	48.6	40.5-56.7	54.1	46.0-62.1	62.3	54.4-70.2
≥75 (n=44)	54.5	40.1-68.3	56.8	42.2-70.3	63.6	48.9-76.2	72.7	58.2-83.7
Total (n=580)	48.8	44.7-52.9	51.6	47.5-55.7	52.8	48.7-56.9	64.3	60.4-68.2

4.5.2.4 Patterns of isolated systolic and diastolic hypertension

Different patterns of isolated hypertension can be observed with ABPM. The patterns of isolated hypertension observed are shown in Figure 4.5. Isolated daytime systolic hypertension was the pattern with the highest prevalence (23.3%, 95% CI: 19.5-26.5) in the sample population. Isolated daytime diastolic hypertension was the only pattern to show a significant difference by gender with males more likely to exhibit this pattern ($\chi^2 = 5.2$, $p=0.023$).

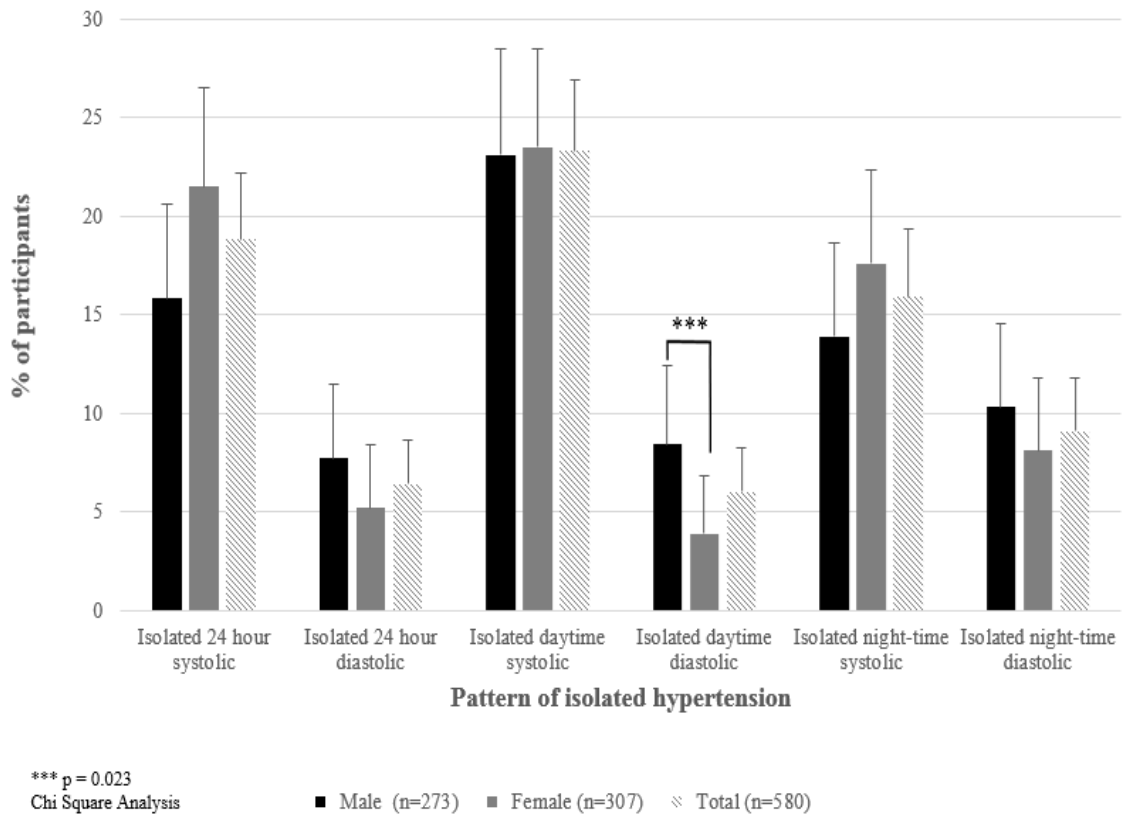


Figure 4-5: Percentage of patients with different types of hypertension classified by gender

4.5.2.5 White coat phenomena

Prevalence of the white coat effect within the sample was also analysed. Overall 18.2% of patients displayed some degree of white coat effect (95% CI: 15.1-21.3) with prevalence higher in women ($\chi^2 = 4.73$, $p=0.03$). White coat hypertension was detected in 9.1% (95% CI 6.8-11.4) patients; no significant difference in prevalence was observed across genders ($\chi^2 = 3.63$, $p=0.057$).

Table 4-10: White coat phenomena observed in the sample of patients accessing the ABPM service

	White Coat Effect*		White Coat Hypertension*	
	%	95% CI	%	95% CI
Gender				
Male (n=273)	14.4	10.2-18.6	6.6	3.7-9.5
Female (n=307)	21.6	17.0-26.2	11.3	7.8-14.8
Total (n=580)	18.2	15.1-21.3	9.1	6.8-11.4
Age Range				
18-44 (n=109)	19.4	12.0-26.8	14.8	8.1-21.5
45-49 (n=44)	16.7	5.7-27.7	11.9	2.3-21.5
50-64 (n=237)	18.1	13.2-23.0	9.3	5.6-13.0
65-74 (n=146)	18.8	12.5-25.1	3.8	0.7-6.9
≥75 (n=44)	15.0	4.4-25.5	7.5	-0.3-15.3
Total (n=580)	18.2	15.1-21.3	9.1	6.8-11.4

*observation missing for 31 patients

4.5.2.6 Masked phenomena

Masked hypertension was observed in 6.9% of patients (95% CI: 4.8-9.0) and masked uncontrolled hypertension in 3.6% of patients (95% CI: 2.1-5.1). There were no significant differences in the prevalence of masked hypertension by gender.

4.5.2.7 Night-time dipping patterns

A non-dipping pattern was observed in 33.3% of patients (95% CI: 29.5-37.1). 50.2% (95% CI: 46.1-54.3) of patients were classed as dippers with 11.2% (95% CI: 8.6-13.8) and 5.3% (95% CI: 3.5-7.1) exhibiting patterns of extreme and reverse dipping respectively.

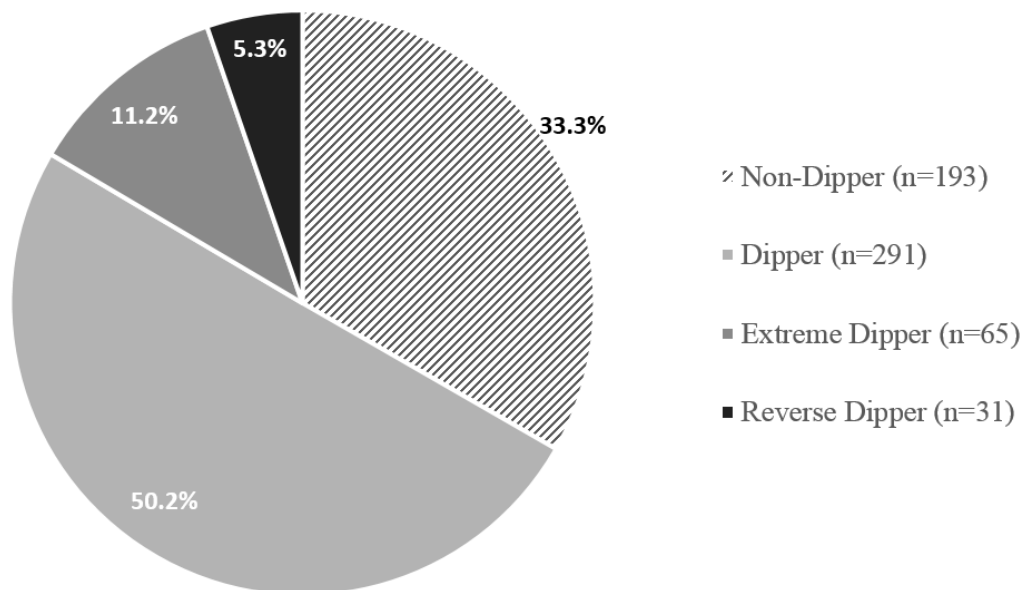


Figure 4-6: Prevalence of night-time dipping patterns in the sample of patients accessing the ABPM service

4.5.3 Medication usage

Information on whether the patient was taking anti-hypertensive medication was available for 90% (n=522) of the sample. Of these 522 patients, 38.5% (n=201) noted (either by naming the medication or stating they were taking a BP tablet) that they were taking antihypertensive medication at the time of ABPM assessment and thus could be considered to have a pre-existing diagnosis of hypertension. 61.2% (95% CI: 54.5-67.9) of patients taking antihypertensive medication were found to have uncontrolled hypertension. 123 patients with a blood pressure profile indicating the presence of some form of hypertension were taking one or more anti-hypertensives at the time of assessment (123/373; 33.0% of the hypertensive sample).

Table 4-11: Prevalence of hypertension in the sample of patients accessing the ABPM service classified by medication status

	Taking Antihypertensive Medication (n=201)			Not Taking Antihypertensive Medication (n=321)		
	<i>n</i>	<i>%</i>	<i>95% CI</i>	<i>n</i>	<i>%</i>	<i>95% CI</i>
<i>Blood Pressure Classification</i>						
24-hour hypertension	89	44.3	37.4-51.2	166	51.7	44.8-58.6
Daytime hypertension	98	48.8	41.9-55.7	171	53.3	46.4-60.2
Nocturnal hypertension	105	52.2	42.3-59.1	168	52.3	45.4-59.2
Any hypertension	123	61.2	54.5-67.9	212	66.0	59.5-72.5

4.5.4 Screening for atrial fibrillation

27.3% (158/580) (95% CI: 23.6-30.9) of patients exhibited some form of irregular pulse patterns. Seventy-four patients over the age of 50 exhibited such patterns, giving a prevalence of irregular pulse patterns potentially indicative of atrial fibrillation of 12.8% (74/580) (95% CI: 10.1-15.5). The average percentage of readings where irregular pulse patterns were observed in this group was 2.4% (SD:23.6; range: 15-97). No significant difference in prevalence between the genders was observed.

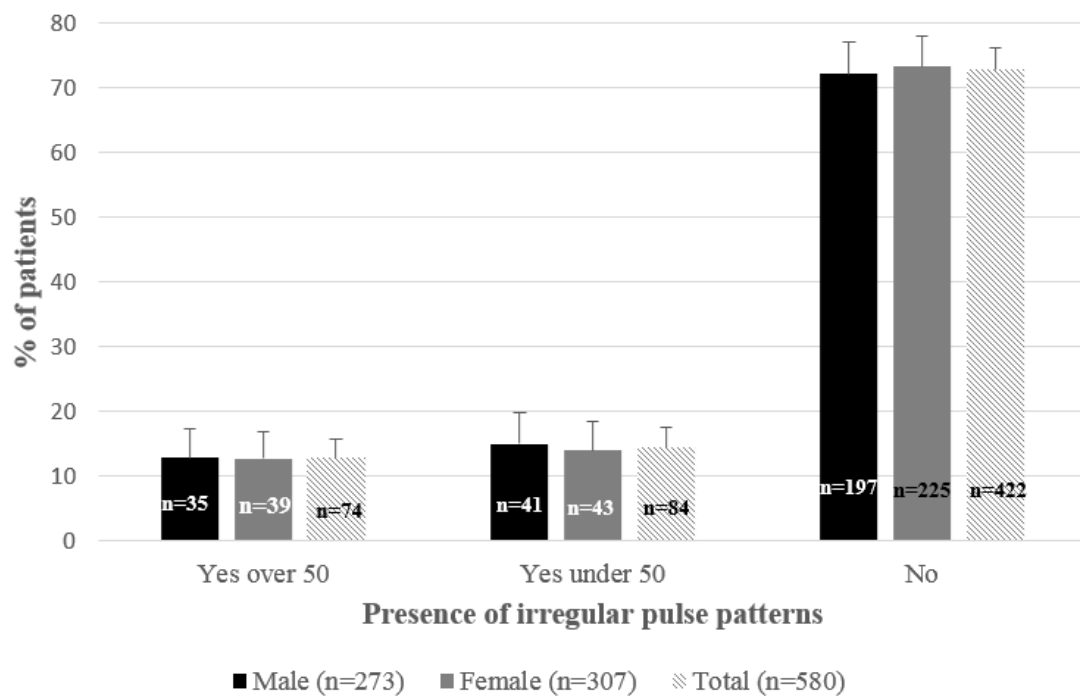


Figure 4-7: Prevalence of irregular pulse patterns in the sample of patients accessing the ABPM service

A sub sample of patients who completed the post-service follow up survey (n=95 respondents) were asked if they had received any new diagnosis post attending for ABPM. Of the 92 patients who answered this question, 10 had pulse patterns potentially indicative of AF. A pre-existing diagnosis of AF was noted on the CRF for 3 patients. When surveyed three patients indicated that they had received a new diagnosis of atrial fibrillation post ABPM assessment. Of these three patients, 2 were on anti-coagulant medication at the time of ABPM assessment so could potentially have had pre-existing atrial fibrillation. The third patient exhibited abnormal pulse patterns during 52.9% of ABPM readings and was subsequently diagnosed with atrial fibrillation. Four patients had pulse patterns indicative of AF but did not indicate that they had been diagnosed with AF post consultation.

4.5.5 Patient profiles by sub-group

No significant differences in risk factor profile were observed across the different sub-groups. Patients with masked uncontrolled hypertension had a higher mean age (62.4 yrs \pm 12.0 yrs) than those with other blood pressure profiles. Similarly, patients with pulse patterns indicative of atrial fibrillation also had a higher mean age (63.1 yrs \pm 9.8 yrs).

Table 4-12: Demographic characteristics of patients classified as normotensive, hypertensive or white coat hypertensive on ABPM assessment

Characteristic	Total sample (n=580)	Hypertensive (n=373)	Normotensive (n=207)	White Coat Hypertension (n=50)
Sex				
Male (n, %)	273 (47.1%)	201 (53.9%)	72 (34.8%)	17 (34.0%)
Female (n, %)	307 (52.9%)	172 (46.1%)	135 (65.2%)	33 (66.0%)
Mean age in years at enrolment (SD)	57.3 (13.3)	57.9 (12.9)	56.2 (14.0)	52.2 (13.4)
BMI (kg/m ²)				
<18 kg/m ² , underweight (n, %)	1 (0.2%)	1 (0.3%)	0 (0%)	0 (0.0%)
18-24.9 kg/m ² , normal (n, %)	103 (17.8%)	59 (15.8%)	44 (21.3%)	13 (26.0%)
25-29.9 kg/m ² , overweight (n, %)	204 (35.2%)	143 (38.3%)	61 (29.5%)	10 (20.0%)
≥30 kg/m ² , obese (n, %)	130 (22.4%)	83 (22.3%)	47 (22.7%)	11 (22.0%)
Smoking status (%)				
Current	53 (9.1%)	39 (10.5%)	14 (6.8%)	3 (6.0%)
Ex - smoker	150 (25.9%)	94 (25.2%)	56 (27.1%)	14 (28.0%)
Never smoker	368 (63.4%)	236 (63.3%)	132 (63.8%)	32 (64.0%)
Weekly alcohol intake				
Rarely/never drink (< 1 sd*)	172 (29.7%)	103 (27.6%)	69 (33.3%)	14 (28.0%)
Low risk female (1-11 sd, % females)	151 (49.2%)	84 (48.8%)	67 (49.6%)	19 (38.0%)
Low risk male (1-17 sd, % males)	159 (58.2%)	118 (58.7%)	41 (56.9%)	10 (20.0%)
Increased risk female (12-28 sd, % females)	21 (6.8%)	16 (9.3%)	5(3.7%)	2 (4.0%)
Increased risk male (18-40 sd, % males)	39 (14.3%)	30 (14.9%)	9 (12.5%)	2 (4.0%)
High risk female (>28 sd, % females)	2 (0.7%)	1 (0.6%)	1 (0.7%)	1 (2.0%)
High risk male (>40 sd, % males)	1 (0.4%)	1 (0.5%)	0 (0%)	1 (2.0%)
Previous cardiovascular event				
Ischaemic stroke (n, %)	6 (1.0%)	3 (0.8%)	3 (1.4%)	0 (0.0%)
Trans Ischaemic Attack (n, %)	11(1.9%)	8 (2.1%)	3 (1.5%)	0 (0.0%)
Haemorrhagic Stroke (n, %)	1 (0.2%)	0 (0.0%)	1 (0.5%)	0 (0.0%)
Heart Attack (n, %)	3 (0.5%)	1 (0.3%)	2 (1.0%)	1 (2.0%)
Atrial Fibrillation (n, %)	26 (4.5%)	15 (4.0%)	11 (5.3%)	1 (2.0%)
Heart Failure (n, %)	6 (1%)	4 (1.1%)	4 (1.9%)	0 (0.0%)
Vascular Disease (n, %)	14 (2.4%)	9 (2.4%)	5 (2.4%)	1 (2.0%)
Other conditions				
Type 1 diabetes (n, %)	7 (1.2%)	5 (1.3%)	2 (1.0%)	1 (2.0%)
Type 2 diabetes (n, %)	17 (2.9%)	8 (2.1%)	9 (4.3%)	0 (0.0%)
Hypercholesterolemia (n, %)	150 (25.9%)	93 (24.9%)	57 (27.5%)	4 (8.0%)
Health pay status +				
Medical Card (n, %)	101 (17.4%)	70 (18.8%)	31 (15.0%)	4 (8.0%)
Private Health Insurance (n, %)	338 (58.3%)	212 (56.8%)	126 (60.9%)	28 (48.3%)

Table 4-13: Demographic characteristics of patients classified as having masked hypertension, masked uncontrolled hypertension or pulse patterns indicative of atrial fibrillation on ABPM assessment

Characteristic	Total sample (n=580)	Masked Hypertension (n=38)	Masked Uncontrolled Hypertension (n=20)	Atrial Fibrillation & Over 50 (n=74)
Sex				
Male (n, %)	273 (47.1%)	16 (42.1%)	8 (40.0%)	35 (47.3%)
Female (n, %)	307 (52.9%)	22 (57.9%)	12 (60.0%)	39 (52.7%)
Mean age in years at enrolment (SD)	57.3 (13.3)	54.9 (13.5)	62.4 (12.0)	63.1 (9.8)
BMI (kg/m ²)				
<18 kg/m ² , underweight (n, %)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
18-24.9 kg/m ² , normal (n, %)	103 (17.8%)	16 (42.1%)	2 (10.0%)	8 (10.8%)
25-29.9 kg/m ² , overweight (n, %)	204 (35.2%)	12 (31.6%)	9 (45.0%)	29 (39.2%)
≥30 kg/m ² , obese (n, %)	130 (22.4%)	6 (15.8%)	5 (25.0%)	21 (28.4%)
Smoking status (%)				
Current	53 (9.1%)	6 (15.8%)	1 (5.0%)	6 (8.1%)
Ex - smoker	150 (25.9%)	10 (26.3%)	7 (35.0%)	16 (21.6%)
Never smoker	368 (63.4%)	22 (57.9%)	12 (60.0%)	51 (68.9%)
Weekly alcohol intake				
Rarely/never drink (< 1 sd*)	172 (29.7%)	10 (26.3%)	8 (40.0%)	28 (37.8%)
Low risk female (1-11 sd, % females)	151 (49.2%)	10 (26.3%)	7 (35.0%)	15 (20.3%)
Low risk male (1-17 sd, % males)	159 (58.2%)	8 (21.1%)	3 (15.0%)	19 (25.7%)
Increased risk female (12-28 sd, % females)	21 (6.8%)	3 (7.9%)	0 (0.0%)	4 (5.4%)
Increased risk male (18-40 sd, % males)	39 (14.3%)	2 (5.3%)	2 (10.0%)	5 (6.8%)
High risk female (>28 sd, % females)	2 (0.7%)	2 (5.3%)	0 (0.0%)	0 (0.0%)
High risk male (>40 sd, % males)	1 (0.4%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
Previous cardiovascular event				
Ischaemic stroke (n, %)	6 (1.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)
Trans Ischaemic Attack (n, %)	11(1.9%)	0 (0.0%)	1 (5.0%)	3 (4.1%)
Haemorrhagic Stroke (n, %)	1 (0.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Heart Attack (n, %)	3 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Atrial Fibrillation (n, %)	26 (4.5%)	1 (2.6%)	2 (10.0%)	6 (8.1%)
Heart Failure (n, %)	6 (1%)	1 (2.6%)	0 (0.0%)	1 (1.4%)
Vascular Disease (n, %)	14 (2.4%)	2 (5.3%)	2 (10.0%)	1 (1.4%)
Other conditions				
Type 1 diabetes (n, %)	7 (1.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Type 2 diabetes (n, %)	17 (2.9%)	1 (2.6%)	0 (0.0%)	2 (2.7%)
Hypercholesterolemia (n, %)	150 (25.9%)	10 (26.3%)	6 (30.0%)	15 (20.3%)
Health pay status +				
Medical Card (n, %)	101 (17.4%)	8 (21.1%)	3 (15.0%)	15 (20.3%)
Private Health Insurance (n, %)	338 (58.3%)	20 (52.6%)	16 (80.0%)	39 (52.7%)

4.5.6 Access to the service

4.5.6.1 Timing of ABPM assessment

Patients availed of ABPM assessments on all seven days of the week. Tuesday was the most popular day to have the device fitted (17.6%) followed closely by Friday (17.4%). The pattern of attendance on weekdays was very similar. 33.6% of patients chose to have their assessment (*i.e.* attended for either a fitting or results consultation) at the weekend.

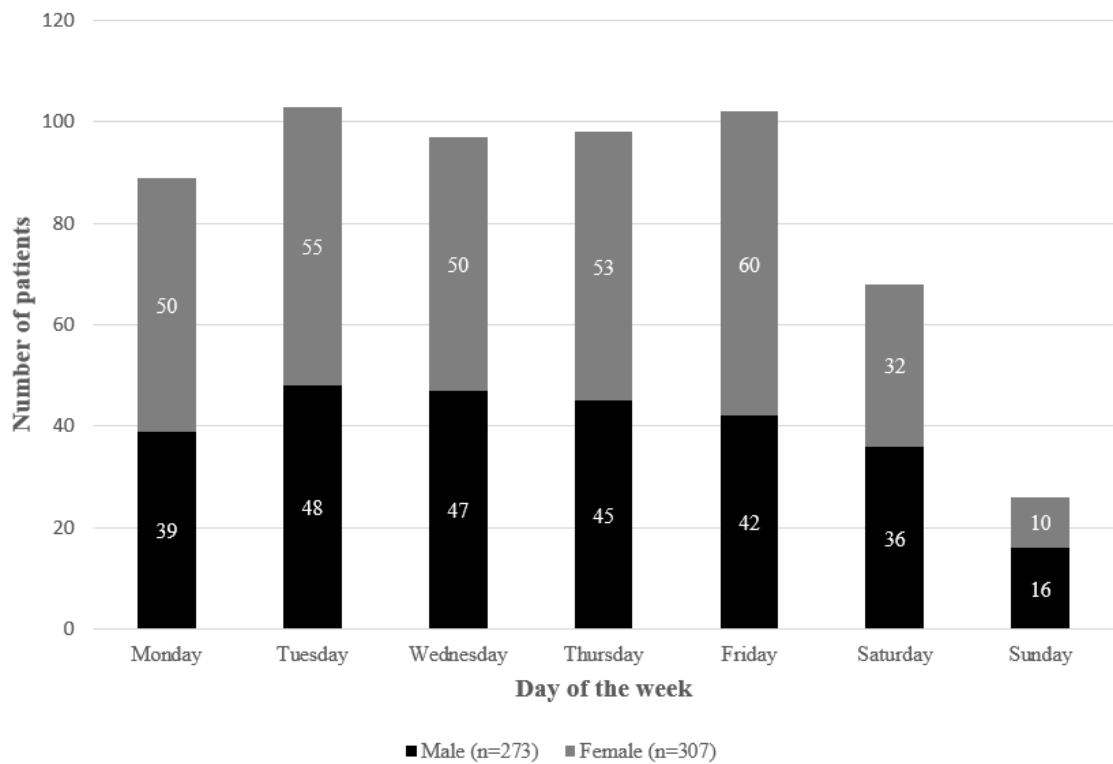
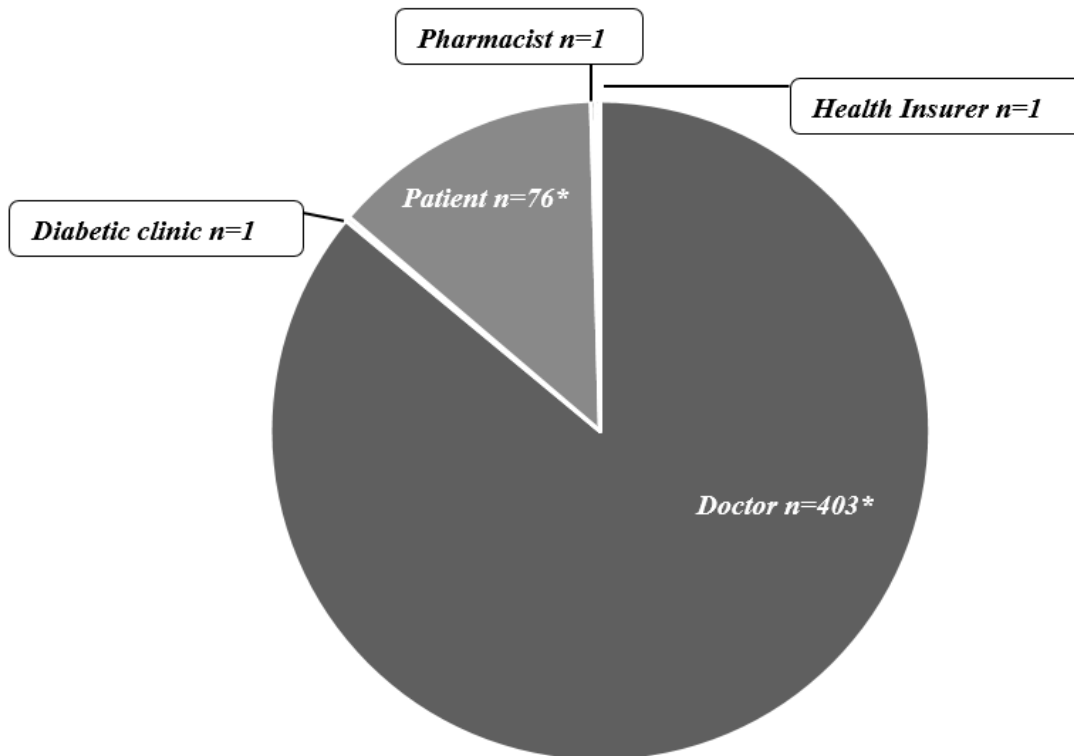


Figure 4-8: Day of ABPM Assessment classified by gender

4.5.6.2 Referral to the service

Information on who requested the service was available for 466 (80.3%) patients. Of these 466 patients, the majority 86.4% were referred for an assessment by their doctor. The referral pathway into the service is outlined in Figure 4.11.



*16 patients indicated that they made the decision in conjunction with their GP

Figure 4-9: Method of referral to the service

4.5.6.3 Reason for availing of the service

Information on the reason(s) why the patient chose to avail of the service was collected via the post-service follow up survey (number of respondents =95). 94 patients answered this question and their reasons for availing of the service are outlined in Figure 4.12.

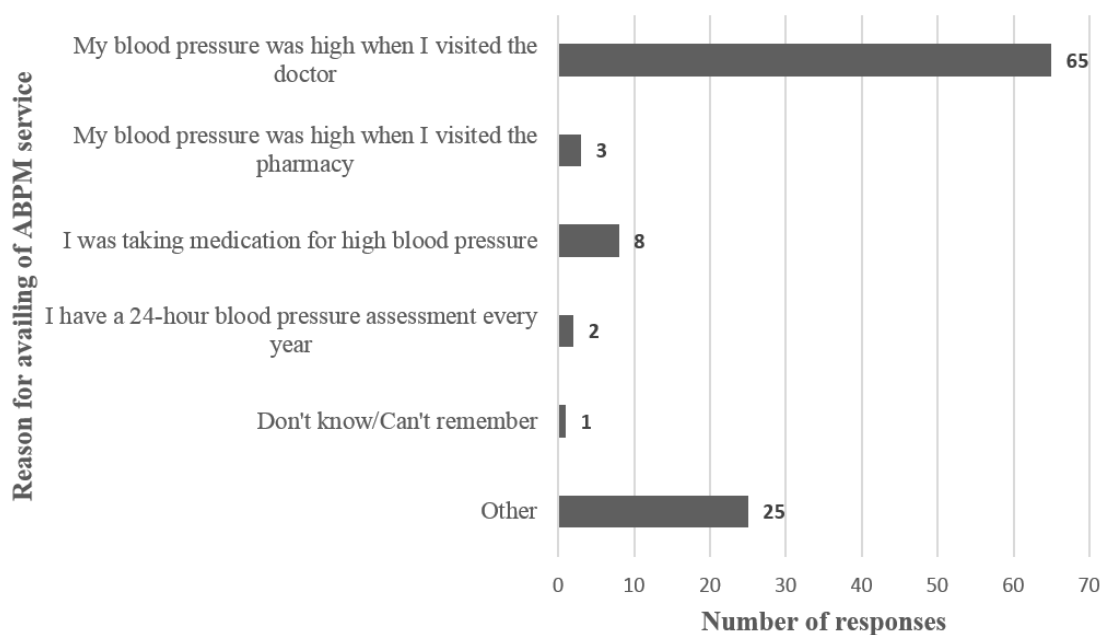


Figure 4-10: Reason for availing of the service (note that more than one reason could be given)

The majority of patients availed of the service because their blood pressure was high on clinic assessment (either in GP surgery or in the pharmacy). Of the 25 patients who answered “other” to this question on the follow up survey the types of reasons given for availing of the service were because the patients wanted to avail of the service themselves (n= 6), their GP recommended it (n=4), a cardiologist recommended it (n=2), the hospital referred them (n=2), their GP wanted to investigate the possibility of masked hypertension (n=1), their GP wanted to investigate the possibility of nocturnal hypertension (n=1), the patient was suffering from stress (n=2), the patient was experiencing nose-bleeds (n=2), wanted to check blood pressure prior to starting antihypertensive medication (n=1), blood pressure was erratic (n=2), patient had just started on new medication post cardiac surgery (n=1), patient was experiencing headaches (n=1) and patient required a 24 hour assessment prior to undergoing surgery(n=1).

4.5.6.4 Reasons for choosing a pharmacy based service

Patients were also questioned as to their reasons for choosing pharmacy as the location for the ABPM assessment. 94/95 patients who completed the survey answered this question and their responses are outlined in Figure 4.13.

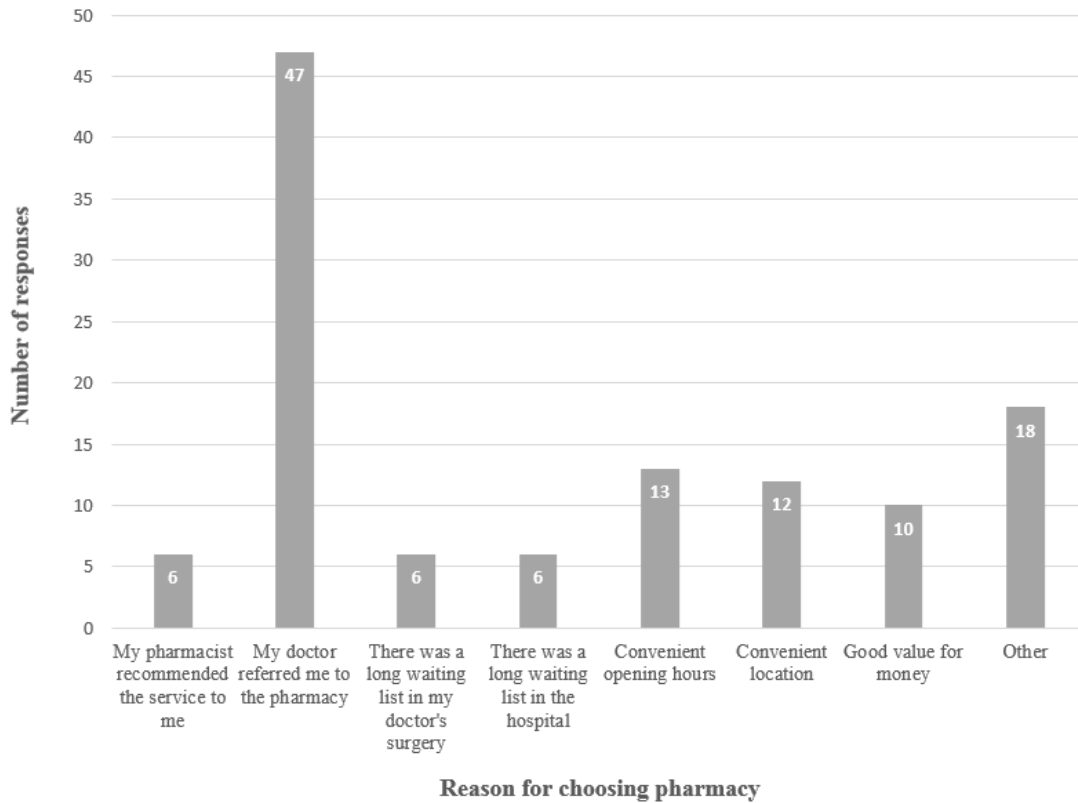


Figure 4-11: Patients' responses to query as to their reason for choosing to have ABPM in community pharmacy (more than one response was possible)

4.5.6.5 Post consultation follow up

Patients also indicated their willingness to allow the pharmacist to share the results of their assessment with their GP (82.6% (479/580) willing to share, 3.8% unwilling (22/580), 13.6% (79/580) did not indicate a preference).

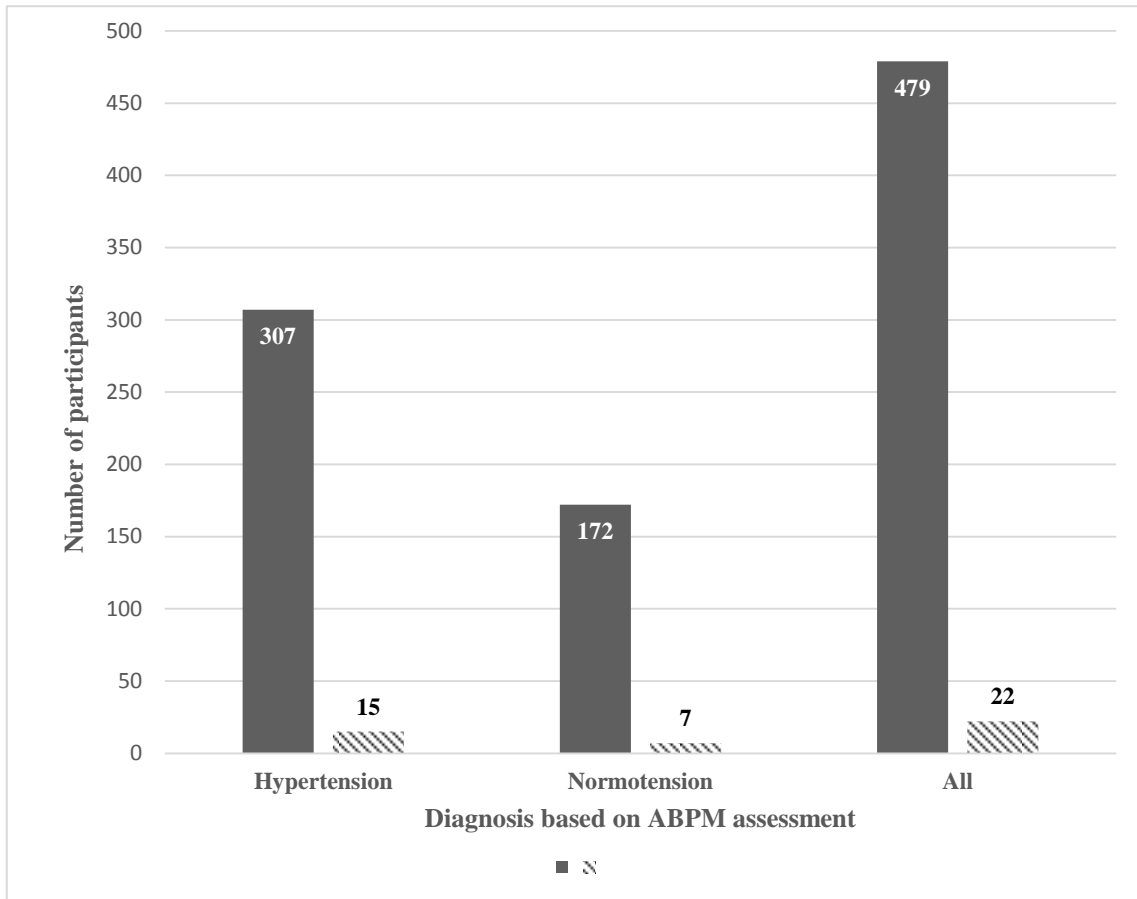


Figure 4-12: Willingness of participants to allow the pharmacist to share results of their ABPM assessment with their GP

4.5.6.6 Medication adjustment post ABPM assessment

Patients who completed the follow up survey (n=95) were asked to provide information on their medication management post ABPM assessment. 39 patients answered the question “Were any changes made to your blood pressure medication following the 24-hour assessment?” Of these 39 patients, the majority experienced no change to their antihypertensive therapy (20/39; 51.3%), 10.3% (4/39) of patients experienced an increase in dosage, the same percentage indicated that they had stopped taking antihypertensive therapy. Figure 4.15 outlines the pattern of therapy adjustment post ABPM assessment.

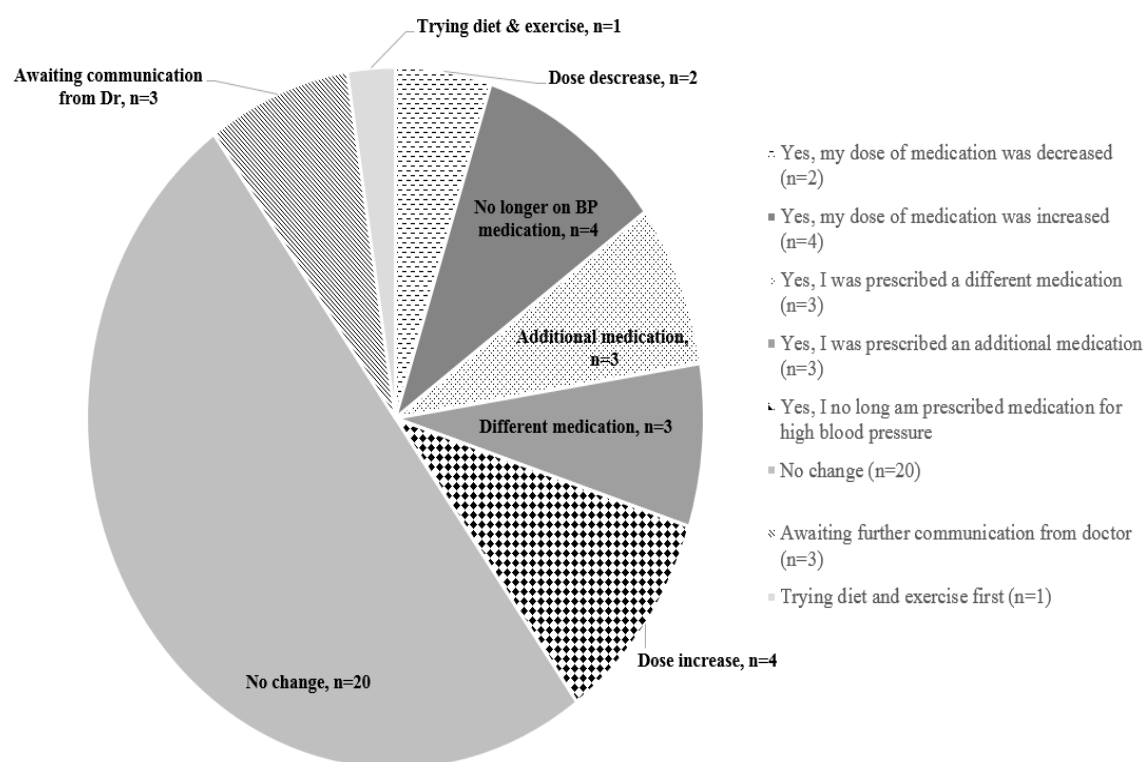


Figure 4-13: Patients' responses to query whether any changes were made to their blood pressure medication after ABPM assessment (number of patients). Note: 1 patient provided 2 answers to the question so total response %=102.6).

4.6 DISCUSSION

4.6.1 Key findings of the study

The results of this study show that it is feasible for patients to undergo a 24-hour blood pressure assessment in their local community pharmacy setting and that such a service can support the diagnosis of different types of hypertension in community dwelling patients. The results indicate a prevalence of overall (i.e. both existing and newly identified) hypertension of 64.3% (95% CI: 60.4-68.2), a prevalence that is in line with recent estimates in the Irish context [348, 368, 369]. Prevalence of white coat hypertension was found to be 9.1% and of masked hypertension 6.9%. Pulse patterns potentially indicative of atrial fibrillation were detected in 12.8% of patients over the age of 50 but a low level of atrial fibrillation diagnosis post consultation was observed.

Amongst those with hypertension, 33.0% were on anti-hypertensive medication at time of ABPM measurement. The percentage of people presenting for assessment with a pre-existing diagnosis points to the fact that patients (and their referring doctors) consider the service useful both in terms of secondary and tertiary prevention. A suboptimal level of hypertension control was observed in those taking anti-hypertensives with 38.8% exhibiting 24 hour, daytime and night-time blood pressure profiles which were below recommended thresholds.

A high level of GP referral to the service (403/466; 86.4%) and willingness on the part of the patient to share results of the assessment with their doctor (479/580; 82.6%) was evident. Access to the service at times when no other service provider was accessible (i.e. at weekends) was high (33.6% of all consultations).

4.6.2 Comparisons with other studies

4.6.2.1 Prevalence of hypertension

Comparing this study to others conducted in primary care in Ireland, James *et al.* [348] showed a prevalence of hypertension of 60.7% and 62.8% of patients attending primary care and pharmacy respectively for ABPM. Classification of hypertension in their study was made with reference to mean daytime blood pressure and if compared to the prevalence of daytime hypertension observed in this study (51.6%, 95% CI: 47.5-55.7) prevalence of hypertension was somewhat higher in their sample. Uallachain *et al.* [369] observed a prevalence of hypertension (based on assessment of both day and night blood pressure profiles but not 24 hour averages) of

62% in a sample of Irish adults attending general practice in the West of Ireland, again similar to this study.

Looking at population based studies the Slán 2007 [370] showed a hypertension prevalence of 60% in a subsample of adults aged 45 years and older taken from a nationally representative sample of Irish adults. More recently Murphy *et al.* [368] reported a hypertension prevalence of 63.7% (95% CI: 62.3-65.1%) in community dwelling Irish adults aged 50 years and older. Prevalence in both of these studies was based on an average of 2 clinic measurements and hypertension was defined as systolic BP \geq 140 mm Hg or diastolic BP \geq 90 mm Hg (Murphy *et al.*[368] extended the definition to include patients below those thresholds who were taking antihypertensive medication). Given the higher cut off points for diagnosis in these studies it is possible that the prevalence figures reported could be underestimates, although this may be confounded by the fact that clinic blood pressures often over-estimate blood pressure due to the white coat effect. In common with other studies in Ireland [348, 368, 370] hypertension in this study was more prevalent in males than females ($\chi^2 = 19.50$, $p < 0.001$).

4.6.2.2 Prevalence of white coat hypertension

One of the advantages of ABPM is the ability to detect white coat hypertension [322]. Without incorporating ABPM into the diagnostic pathway patients with white coat hypertension may go undetected thus leading to potential prescribing of unnecessary antihypertensive therapy at a cost to the patient and the healthcare payer. Unnecessary expenditure on potentially lifelong therapy, penalties on insurance and pension policies and adverse events of medication are some of the consequences of such inappropriate prescribing [322].

Prevalence estimates for white coat hypertension typically range between 20-30% [345, 371] but lower levels (9-12%) have been reported [372]. White coat hypertension in this study was detected at a prevalence of 9.1% (95% CI 6.8-11.4) which is lower than most estimates including that of a sample of patients attending Irish community pharmacies for ABPM [348]. That study reported a prevalence of white coat hypertension of 20.8% but it should be noted that the treatment status of patients in that cohort was unknown meaning that both treated and untreated patients were included in the prevalence estimate for white coat hypertension, making it more representative of the white coat effect than true white coat hypertension. Indeed the white coat effect observed in this study, 18.2% (95% CI: 15.1-21.3), is much closer to the estimate reported by James *et al.* [348]. Additionally, white coat hypertension in that study was calculated with reference to a mean daytime blood pressure of \geq 140 mm Hg systolic and/or \geq 90

mm Hg diastolic, whereas this study reports a prevalence with reference to 24-hour, daytime and night-time readings as per ESC guidelines [322]. Calculating white coat phenomena with reference to mean daytime ambulatory blood pressure of ≥ 135 mm Hg systolic and ≥ 85 mm Hg diastolic in this study gives a higher prevalence of 22.6% (95% CI: 19.1-26.1) for the white coat effect and 14.0% (95% CI: 11.1-17.0) for white coat hypertension.

It has been reported that prevalence of white coat hypertension is higher in those of female gender, older age and who do not smoke [322]. Whilst the proportion of women (0.66) with white coat hypertension was higher than that of males (0.34) and the difference was close to statistically significant ($\chi^2 = 3.63$, $p=0.057$) no significant correlation between these characteristics and a blood pressure profile indicative of white coat hypertension was observed. However, the number of patients with white coat hypertension in this study sample was small ($n=50$) so it may be that larger sample sizes are needed to detect such associations.

4.6.2.3 Prevalence of masked hypertension

Masked hypertension occurs where an untreated patient exhibits normal blood pressure readings in the clinic but high blood pressure readings outside this setting [322]. Where this occurs in patients taking antihypertensive medication it is known as masked uncontrolled hypertension. In this study masked hypertension was observed in 6.9% of patients (95% CI: 4.8-9.0) and masked uncontrolled hypertension in 3.6% of patients (95% CI: 2.1-5.1).

Whilst no definitive data on prevalence of masked hypertension are available it is thought to occur in about 10-30% [322] of individuals with varying prevalence rates reported depending on the population of study and the diagnostic criteria used to identify the condition [372-376]. With no data on the prevalence of masked hypertension in the Irish population available, comparisons were made with international estimates. A study in the pharmacy setting in Switzerland detected masked hypertension in 12 % of patients [377] but the sample size was low ($n=50$ patients). A recent US study puts the prevalence of masked hypertension at 12.3 % (95% CI: 10-14.5) [375], and one in Korea noted a prevalence of 16.2 % (SE 2.16) [376]. The prevalence of masked hypertension in this study sample thus appears somewhat lower than that observed in other studies. Given that the majority of patients in this study were referred for ABPM by their general practitioner, it is perhaps not surprising that a somewhat lower prevalence of masked hypertension would be observed. It is likely that patients are most often referred for ABPM assessment based on the presence of high clinic blood pressure readings and/or a previous diagnosis of hypertension, factors which are not relevant in patients with masked hypertension.

It has been reported that the condition appears to be more prevalent in males and younger age groups [322], two cohorts who may not attend primary care for blood pressure assessment as often [378]. A higher prevalence of masked hypertension was observed in females (7.6% females versus 6.2% males) in this study, although the difference between the genders was not statistically significant. Given that the sample was not a random one the prevalence in this sample cannot be considered to be representative of the general population. An on-going challenge for clinical practice is the identification and management of patients with masked hypertension.

The prevalence of masked uncontrolled hypertension is more difficult to determine with some studies reporting such values being restricted to treated hypertensives and others including both treated and untreated subjects [379]. Studies restricted to treated hypertensives have reported prevalence figures between 9% [380] and 23% [381] and those with mixed samples have reported figures ranging from 12% [382] to 19% [383]. The prevalence of masked uncontrolled hypertension observed in this study is much smaller at 3.6% (95% CI: (2.1-5.1)). Given that the sample was mixed with respect to anti-hypertensive usage, with 201 patients noting that they were taking anti-hypertensives at the time of ABPM assessment, and with level of anti-hypertensive usage being based in patient self-report, caution must be used in interpreting the prevalence estimate due to this small sample size.

4.6.2.4 Night-time blood pressure profiles

It has been suggested that the most important parameter for predicting cardiovascular outcome is the level of night-time blood pressure [322]. Reproducibility of daytime readings is limited by individual daytime activities and thus consideration of the night time blood pressure profile is important. Indeed some 7% of patients with hypertension may have isolated night-time hypertension [322]. Review of nocturnal blood pressure patterns is thus an important advantage of ABPM. It is expected that blood pressure will fall on moving from waking to sleeping and the majority of people exhibit a difference between daytime and night-time BP of between 10 - 20%, known as “dipping” [342]. A reduced nocturnal fall in blood pressure is associated with poor cardiovascular outcomes and reverse dippers are thought to have the worst prognosis [356].

Night to day ratio of SBP was used for dipping status as systolic rather than diastolic blood pressure is the predominant risk factor in adults over the age of 50 [384]. Given the mean age of

57.8 years in our sample this seemed appropriate and mirrors the approach taken in a large 2007 meta-analysis [385]. 50.2% (95% CI: 46.1-54.3) of patients in this study were classed as dippers which is much lower than that reported in either pharmacy or primary care in the James *et al.* study [348] (84.7% and 79.4% respectively, calculated as percentage decrease in SBP or DBP from daytime to night-time) but more in line with that observed in a cohort of Spanish patients at low-to moderate cardiovascular risk (44.8%) [386].

It was not possible to compare the three other dipping patterns with similar studies in the Irish setting as no such observations were noted in the studies retrieved. Non-dipping was observed in 33.3% of patients, a finding within the range of 25-35% reported for studies conducted in a general population [387]. Patients exhibiting patterns of reverse dipping accounted for 5.3% (95% CI: 3.5-7.1) of patients in this sample, a prevalence similar to that observed in a large international database (6.1%) [388].

It is important to note that poor sleep quality has been associated with elevated nocturnal BP and non-dipping BP profiles [389, 390]. Patients are instructed to record sleep quality in the BP diary they are given to complete while undergoing their 24-hour assessment and pharmacists are trained to discuss this with patients and take it into account when providing an overview of ABPM results. However, no information on sleep quality is recorded on the patient record form so it is not possible to say if sleep quality may have had an effect on the dipping patterns observed in this study.

4.6.2.5 Prevalence of pulse patterns indicative of atrial fibrillation

A number of studies have reported on the prevalence of atrial fibrillation detected via screening in a primary care setting [331, 351, 391-393]. The majority of these studies have been conducted in general practice [331, 391-393] with one conducted in the pharmacy setting [351]. Prevalence estimates in these studies varied from 4.5% [392] to 11% [393]. All involved patients over the age of 65 with two restricting the sample size to those over the age of 75 [392, 393]. Where reported, prevalence was higher in males than in females [331, 391]. None of the studies specifically excluded patients with a history of atrial fibrillation and as a result the prevalence estimates include both pre-existing and new detections. For example Kearly *et al.* noted a prevalence of 11% in a sample of patients aged over 75 attending UK general practice clinics with a much lower prevalence (1.4%) noted for those patients with no pre-existing AF

diagnosis at the time of screening [393]. A similar prevalence of newly detected AF was found in the pharmacy population (1.5%) [351].

The prevalence of irregular pulse patterns in patients over the age of 50 in the current study was 12.8% (95% CI: 10.1-15.5), a higher prevalence than that reported in the primary care screening studies noted above. However, it is important to remember that these are irregular pulse patterns which have the potential to be attributable to AF but are not in themselves enough to say with certainty that the patient exhibiting the patterns has AF. Screening for atrial fibrillation in a primary care setting is a two-step process with irregular pulse patterns in asymptomatic patients first identified and then AF either confirmed or excluded by 12 lead electrocardiography (ECG) [325]. Modified blood pressure monitors such as the Microlife ® Watch BP ® O3 AFib device used in this study have been shown to be effective in detecting irregular pulse patterns and have demonstrated a greater accuracy for detecting pulse irregularities caused by AF than pulse palpation [394], the current standard practice. Sensitivity and specificity are important when considering the clinical utility in order to minimise false positives resulting in unnecessary ECGs and false negatives resulting in missed diagnoses. The current study was not set up to determine the sensitivity/specificity of the AF screening but some observations from the post consultation follow up provide a degree of insight into role of the service in detecting AF. Of the 10 patients exhibiting pulse patterns indicative of AF in the post consultation follow up group, 5 had pre-existing AF and 1 new case of AF was detected. Four patients had pulse patterns indicative of AF but indicated that they had received no new diagnosis. It is not possible to ascertain what type of conversation the pharmacist had with the patient about this finding, whether these patients spoke to their GPs about their pulse pattern finding on their ABPM report, if the GPs took this into consideration when considering the need to perform further tests or if AF was ruled out on ECG. Future studies should seek to gain greater insight on the patient follow up post ABPM consultation in the pharmacy setting.

4.6.3 Ambulatory blood pressure monitoring with pulse screening as a community pharmacy based service

Delivery of ABPM services in the community pharmacy setting is a relatively new phenomenon but expanding the service to this setting has many advantages. These include greater accessibility and convenience, reduced waiting lists and provision of a less costly service for patients [322]. All of these advantages were noted by patients in this study as reasons for choosing to have their assessment in the pharmacy. A preference for ABPM assessment at the

weekends was observed in a third of patients in our study thus strengthening the view that weekend availability of ABPM in the pharmacy setting is popular with patients [348]. The prevalence of hypertension is growing in tandem with increases in longevity. With the vast majority of hypertensive patients being managed in primary care [322], ready access to ABPM in that setting is important. Addition of a pharmacy model thus complements existing service provision removing barriers to screening by providing a service when others are inaccessible. Indeed, adoption of a shared care model where patients receive ABPM in their local community pharmacy with onward referral to their GP for diagnosis and therapy initiation may facilitate more appropriate use of resources in primary care. The high level of GP referral to the pharmacy service described in this study coupled with a strong willingness on the part of the patient to share the results of their assessment with their GP suggests a willingness amongst the key parties to work collaboratively.

36.3% (201/553) of patients in this study, for medication information was available, were taking anti-hypertensive medication at the time of ABPM assessment thus pointing to its being used as a method of assessing response to therapy and therefore supporting better tertiary prevention activities. ABPM provides a better assessment of the response to treatment than office BP [322] and a significant amount of uncontrolled hypertension was identified in this study; 61.2% (95% CI: 54.5-67.9). Pharmacists observing such patterns have the opportunity to engage patients in a conversation to determine if the suboptimal control is due to lack of adherence to prescribed treatment or as a result of suboptimal response to treatment. Targeted interventions can then address the relevant factor(s) and more accurately inform future care plans.

The majority of hypertensive patients exhibit additional cardiovascular risk factors which can potentiate one another when present concomitantly, leading to greater overall risk of cardiovascular morbidity and mortality [316]. Cardiovascular risk assessment models such as the Systemic COronary Risk Evaluation (SCORE) [395], QRISK3 [396], ASSIGN [397], Reynolds [398, 399] and Framingham [400] scores allow for risk stratification in practice and support a management approach based on BP levels in the context of overall cardiovascular risk. Such an approach is recommended in a number of international hypertension management guidelines [316, 401] as it facilitates targeted approaches to the reduction of risk factors based on probability of disease, thus maximising cost effectiveness of hypertension management [316, 402]. Cardiovascular risk scores were not calculated as part of the service described in this study but nevertheless a large number of concomitant risk factors were observed in the study

sample. The service thus provides an opportunity to engage patients in the benefits of risk reduction and as such has the potential to support improved outcomes for patients.

4.6.4 Strengths of the study

The study has a number of strengths. It describes a novel service that combines detection of irregular pulse patterns indicative of AF with 24-hour blood pressure assessment, using validated technology [354]. The service described was effective in detecting new cases of both hypertension and atrial fibrillation, national priorities in Ireland [310].

Prevalence of hypertension in this sample is based on the results of ABPM assessment, the most informative method of blood pressure assessment [403]. Patients with white coat hypertension are not included in the prevalence estimates meaning they are less likely to over-estimate true prevalence.

The hypertension prevalence estimates are based on hypertension observed in a daytime, night-time and/or 24-hour window and are thus representative of the many different patterns of hypertension observed in practice. The threshold values employed for classification are more conservative than that routinely employed in clinical practice (140/90 mm Hg) [404], something that is important in light of recent suggestions that achievement of BP levels closer to 120/70 mm Hg may be more appropriate [405].

4.6.5 Limitations of the study

The study was a cross-sectional study conducted in a real-world setting. The group being studied is thus a convenience sample of patients presenting to avail of the service as opposed to a random sample which would be more representative of the general population. An element of selection bias is thus inevitable, especially given the high level of GP referral to the service. In particular patients with masked hypertension may be missed as they are unlikely to be referred for assessment. Additionally, the service is a private service for which a fee of €50 applies. It is thus not fully accessible to all patients who may need the service and as such is not generalisable to the entire population.

Some of the data (e.g. medical history, medication prescribed) were self-reported which has the potential to introduce information bias. Recall bias (e.g. for risk factor reporting such as number of years smoking, previous ABPM assessment) is also a possibility. Information on medical history and post consultation follow up was not confirmed with patients' GPs and thus estimates of newly diagnosed hypertension and atrial fibrillation should be interpreted with some caution. The prevalence of irregular pulse patterns does not provide an accurate assessment of prevalence of AF given the lack of confirmatory ECG data. The patient follow up data coupled with previously reported sensitivity and specificity of the Watch BP device [393] do provide some insights and show that detection of previously undiagnosed AF through this novel pharmacy service is possible.

The study reports blood pressure profiles based on a single ABPM assessment. Although more reproducible than clinic blood pressure measurement, factors such as degree of physical activity, environmental stimuli and duration and quality of sleep lead to an intrinsic variability between 24-hour measurement sessions [371]. This can affect consistency of hypertensive status classification. Indeed, movement from a classification of white coat hypertension on first ABPM to sustained hypertension on second ABPM within a 1-3 month window has been reported in independent studies [406, 407]. Thus, it is recommended that a diagnosis of white coat hypertension be confirmed via a repeat ABPM assessment after 3-6 months [341, 408]. Due to the cross-sectional nature of the study such confirmation was not possible.

Paroxysmal AF (short infrequent episodes of AF [335]) is associated with an increased risk of stroke that is comparable to continuous AF [409]. As patients may not be experiencing an arrhythmia when being screened, paroxysmal AF can be difficult to detect [393]. It is possible that some patients with paroxysmal AF could have been missed in this study due to the timing of assessment.

4.6.6 Implications for practice and future direction

Ready availability of 24-hour blood pressure monitoring for all patients in primary care will ultimately be dependent on reimbursement by the national healthcare system. In line with a number of other countries (e.g. Canada, China, Germany, Greece, Holland, Italy, Switzerland, United States) [322] Ireland has recently approved funding for reimbursement of ABPM in primary care [410]; however this funding is limited to ABPM conducted by GPs only. This study shows that community pharmacists have a role to play in delivery of ABPM in primary care, and for reimbursement of a pharmacist led service to be considered information on the

cost-effectiveness of such an approach would need to be taken into account. Limited studies have been conducted in the pharmacy setting to date [348, 411] and none has reported on the cost effectiveness of ABPM delivered in that setting meaning there is scope for future work in this field.

The role of ABPM in reviewing patients' response to anti-hypertensive treatment has been highlighted [322] as has the role of pharmacists in medication management for patients with hypertension [412]. The results of the current study indicate a high level of suboptimal hypertension control, albeit in patients about whom there was sufficient concern to prompt ABPM. Combining an ABPM service with a pharmacist led medication management programme designed to address issues such as adherence and to provide prescribing support to GPs has the potential to improve care for hypertensive patients. Future studies could explore the feasibility of offering such a service.

Community pharmacy delivered public health interventions such as smoking cessation have been shown to be both effective and cost effective [236]. Given that many health promotion services are directed at addressing risk factors for cardiovascular disease, identification of such risk factors through the ABPM consultation may provide an opportunity for referral to pharmacy delivered public health interventions. Expanding the reach of public health interventions delivered in community pharmacy through cross referral from other pharmacy services is a topic worthy of further exploration.

This study reports on the prevalence of pulse patterns indicative of atrial fibrillation present in a sample of patients attending community pharmacy for 24-hour blood pressure measurement. It employed the Watch BP O3 AFib device to detect these pulse patterns. A number of other screening devices for AF which can be used in primary care have been developed which offer complementary information that may further enhance the detection rate of AF in settings such as community pharmacy [338, 351, 413, 414]. Some work has been done on assessing the relative merits of the different devices [394] but very limited data on their use in the community pharmacy setting have been reported - something which future studies could explore in more detail in order to inform decisions on the most effective and cost effective method(s) of screening for AF in primary care.

Chapter 5: Community Pharmacy Inhaler Adherence Intervention: Inhaler Compliance Assessment (INCA™)

5.1 INTRODUCTION TO THE CHAPTER

Asthma and chronic obstructive pulmonary disease (COPD) are common, chronic respiratory diseases [415, 416]. Both conditions are characterised by symptoms such as wheeze, breathlessness and airflow limitation which vary in intensity from patient to patient [417, 418].

Appropriate pharmacological treatment, used correctly, can help to reduce symptoms and improve quality of life [417, 418]. Inhaled medications are commonly prescribed but can be difficult to use and this can lead to technique errors [419, 420] that may have both direct costs such as medication waste, and indirect costs such as increased use of other healthcare resources as a consequence of poor symptom control [421].

This chapter describes a prospective, cluster randomised, parallel-group, multi-site study comparing two pharmacist-delivered strategies to optimise inhaler technique and adherence in respiratory patients in the community setting. The study is reported using the CONSORT (Consolidated Standards of Reporting Trials) statement checklist as extended for cluster randomised trials [422].

5.2 BACKGROUND

5.2.1 Chronic Respiratory Disease

Chronic respiratory diseases are diseases of the airways and other structures of the lung [423]. Asthma and COPD are two of the most common chronic respiratory diseases with an estimated 235 million people currently suffering from asthma [423] and 65 million suffering from COPD [424] worldwide. Both conditions lead to significant morbidity and mortality with the World Health Organisation reporting that COPD is the third leading cause of death globally [416]. Ireland has the 4th highest prevalence of asthma in the world with prevalence estimates varying between 7 and 15% of the population [425]. European prevalence of moderate to severe COPD

is estimated at 10% with prevalence increasing with age [426]. Ireland has one of the highest standardised death rates for COPD in Europe [427] as well as one of the highest rates of hospital admissions for COPD exacerbations within the OECD [34].

Whilst asthma and COPD are incurable, appropriate pharmacological treatment, used correctly, can help to reduce symptoms and improve quality of life [417, 418].

5.2.2 Inhaler Medication

Inhaled medications such as bronchodilators and inhaled corticosteroids are mainstays of the treatment of both asthma and COPD. Two types of inhaler devices commonly used are metered dose inhalers (MDIs) and dry powder inhalers (DPIs). When used correctly both types of inhaler have been shown to improve patients' clinical outcomes.

Inhaled medications can be difficult to use and this can lead to technique errors [419, 420] that may have both direct costs, such as medication waste, and indirect costs such as increased use of other healthcare resources as a consequence of poor symptom control [421]. Thus inhaler technique education is an important part of the management of patients with respiratory conditions [417, 418].

Adherence to inhaled medication is also critical to achieving best outcomes. Adherence can be defined as 'the extent to which the patient's behaviour matches agreed recommendations from the prescriber'[428]. Suboptimal adherence to inhaled medications for respiratory disease is common [429-431] and is associated with poor clinical outcomes. Non-adherence can be intentional (where the patient chooses not to take their medication) or unintentional (where a patient wants to comply with treatment but is unable to do so for various reasons *e.g.* difficulty remembering the exact instructions for use, problems taking their treatment, problems paying for the treatment or simply forgetting to take the medication) [428].

Supporting the mastery of correct inhaler technique and promotion of on-going adherence to therapy are important treatment goals and should be addressed before stepping up treatment in asthma/COPD [432, 433].

5.2.3 The role of the community pharmacist

Community pharmacist delivered interventions have been shown to improve inhaler technique [434, 435], inhaled medication adherence rates [436] and therapeutic outcomes [159, 188, 437, 438] for adult patients with asthma [159, 188, 434, 435, 437, 438] and COPD [434, 436]. However, adherence rates in reported studies are frequently either based on patient self-report which has been shown to be unreliable [439, 440] or calculated from pharmacy databases containing prescription refill data which provide information on medication obtained but not on how such medication is used in practice [441, 442]. An ability to objectively measure both technique and adherence in practice would lead to more robust studies in this field.

5.2.4 Electronic monitoring of adherence

Electronic inhaler adherence monitors are considered the most accurate practical tool for objectively measuring adherence [443]. A variety of electronic monitoring devices have been developed, predominantly for use with Metered Dose Inhalers (MDIs) [443]. Such devices have been shown to reliably measure [444-447] and in some cases improve [448] adherence but the majority have the limitation of only measuring temporal adherence due to an inability to measure inhalation technique [443]. The INhaler Compliance Assessment (INCA™) device has been designed to overcome these limitations and was utilised in this study to provide an objective assessment of both time and technique of inhaler use [449].

5.2.4.1 The INCA™ device

The INhaler Compliance Assessment (INCA™) device manufactured by Vitalograph Ltd (Vitalograph Ireland Ltd., Ennis, Ireland) was employed in this study. The device, which is battery operated, is activated upon opening of the inhaler in the standard way. It contains a microphone capable of recording the acoustics of inhaler use [450, 451]. Audio files are stored on a micro SD card housed within a small (1cm x 2cm x 2cm) plastic housing which is attached securely to the side of a salmeterol/fluticasone Diskus™ inhaler (Seretide, GlaxoSmithKline (Ireland) Limited) (Figure 5.1) and which does not impact the mechanics of inhaler use. Once uploaded to a computer via a USB connection the audio files can be analysed using an algorithm that allows for automated evaluation of temporal and technique adherence to the Diskus™ inhaler [451]. The technology has been validated and the suitability of audio in identification of inhaler technique errors has been demonstrated [449, 450, 452-454].



Figure 5-1: INCA™ device attached to a Seretide Diskus™ inhaler

Figure 5.2 shows a graph of the times of use of the inhaler by a patient. The graph also shows whether the acoustic analysis of the inhalation followed the correct steps: the inhaler was used correctly when a green dot is presented or incorrectly when there is an orange diamond.

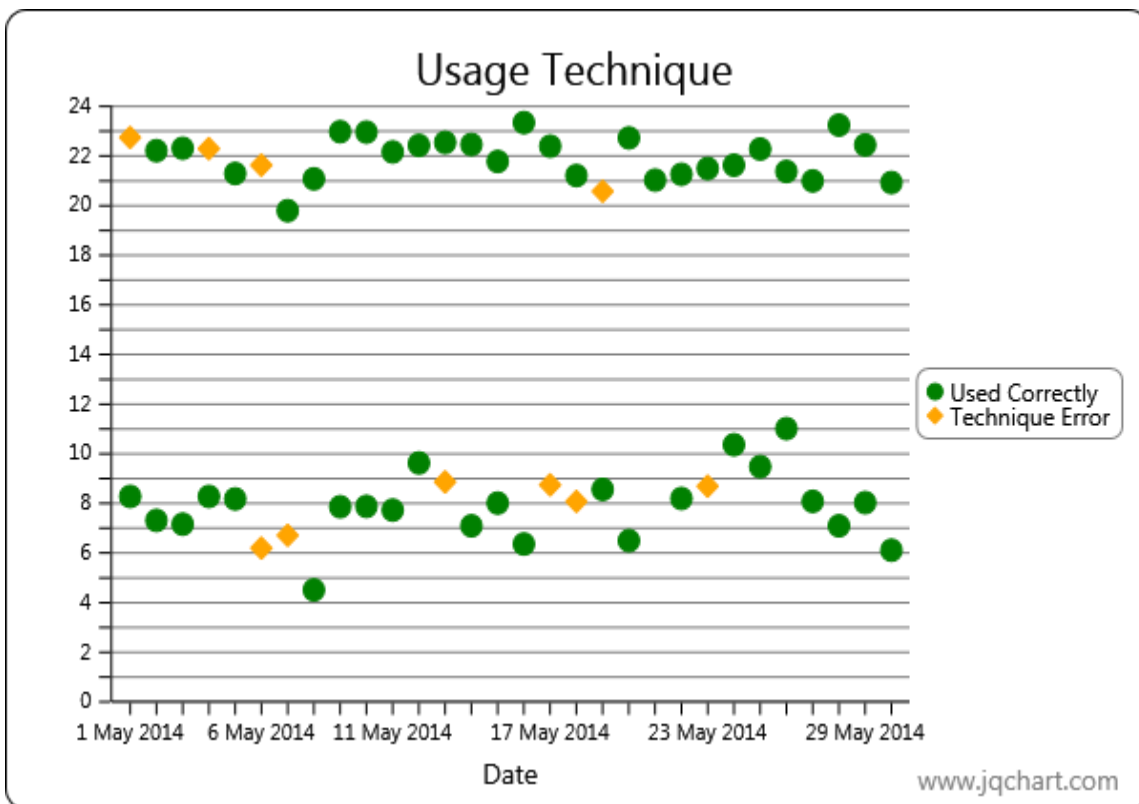


Figure 5-2: Graph of a patient's inhaler usage generated from INCA™ device recordings

5.3 OBJECTIVES

The purpose of this study was to discover whether providing personalised feedback to patients from a device that records when and how well a patient uses an inhaler leads to:

- Improved compliance with prescribed inhaler use;
- Improved technique of inhaler use;
- A reduction in respiratory health related outcomes caused by poor inhaler compliance and usage;
- An improvement in patient quality of life scores.

5.4 METHODS

5.4.1 Study Design

The study was a prospective, randomised, parallel-group, multi-site study incorporating a cluster design and was designed to compare usual mode of care with the use of the INCA™ device for respiratory patients in a community pharmacy setting. A cluster randomised study was chosen in order to minimise the risk of contamination of knowledge by the pharmacists across the three study groups.

Pharmacies operating in a chain of community pharmacies in the Republic of Ireland were eligible for inclusion in the study if they dispensed Seretide Diskus™ inhalers to four or more patients attending their pharmacy per month.

Pharmacies were the unit of randomisation and on enrolment to the study were allocated by the lead researcher to one of the three study groups (intervention, comparator or control group) using a computer-generated list of random numbers with a ratio of 1:1:0.5. Given the nature of the intervention neither pharmacists nor patients could be blinded.

The study flow is indicated in Figure 5.3

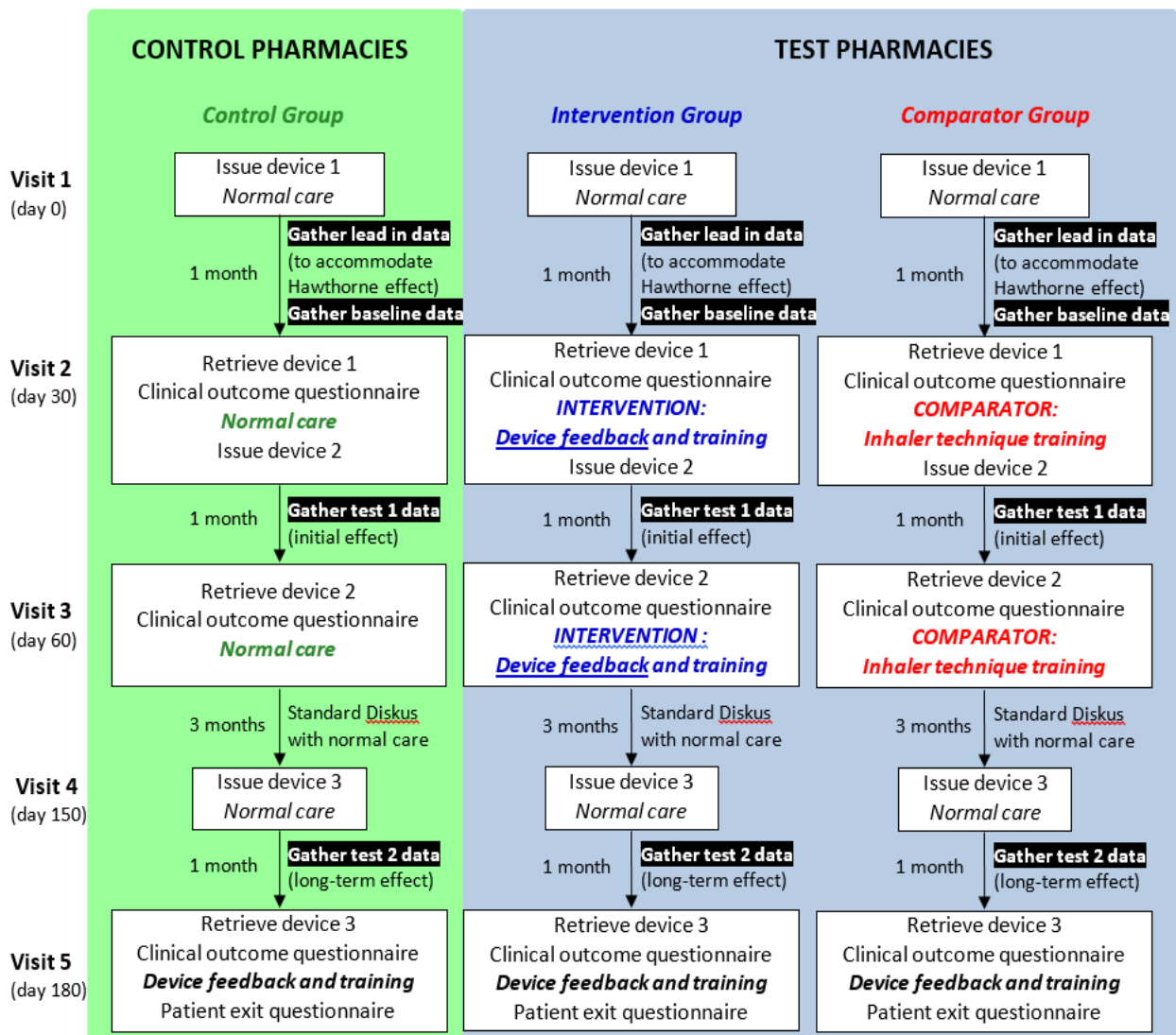


Figure 5-3: Overview of study flow and design

5.4.2 Setting

The study was conducted in a chain of 83 community pharmacies operating in the Republic of Ireland. Pharmacies were eligible for inclusion in the study if they had patients who were prescribed a salmeterol/fluticasone Diskus™ inhaler and if those patients had regularly attended the pharmacy to collect a prescription in the six months prior to enrolment. Regular attendance was defined as having at least 3 prescriptions for any medication filled in the pharmacy in the

six months preceding study enrolment. The study period was from February 2014 to December 2016.

5.4.3 Study Procedures

At the initial visit, each participant's age, sex, dose of salmeterol/fluticasone, duration of taking this dose and details of concomitant medications were recorded on paper based case report forms which were developed specifically for this study and piloted in a sample of 3 pharmacies. The pharmacist recorded the Peak Expiratory Flow Rate (PEFR) as measured by an electronic peak flow meter (eMini-Wright[®], Clement Clarke International, Harlow, England). The St. George's Respiratory Questionnaire (SGRQ) [455], a validated tool used to assess quality of life in patients with diseases of airway obstruction, was completed by the participant. History of inhaled therapy (salmeterol/fluticasone and short acting beta agonists), steroid and antibiotic usage over the prior six months was obtained from the participant's patient medication record in the pharmacy. Participants were asked to identify an aspect of their life affected by their respiratory condition that they would like to improve. This "breathing related goal" was recorded and improvement was monitored through the study period. The purpose of this was to provide an additional focus for the participant via which a tangible and personalised measure of any symptom improvement could be noted. Patient reported clinical diagnosis (asthma or COPD), smoking status and health pay status were also recorded for all participants.

The participants received a salmeterol/fluticasone Diskus[™] inhaler with an INCA[™] device attached for use twice per day as prescribed. This inhaler was provided free of charge to all participants, regardless of their health pay status, with the relevant professional service fee being paid by the patient in the usual manner. For all participants, the INCA device was used to capture data on adherence and inhaler technique. Participants in the intervention and comparator groups were asked to record their peak expiratory flow with the eMini-Wright[®] electronic monitor twice daily. In the intervention and comparator groups participants were also provided with a paper based diary for recording daily symptoms, medication usage and health care utilisation. This diary, based on the Asthma Society of Ireland's peak flow diary [456], was developed specifically for this study and piloted in a sample of 7 patients. An extract of the diary is provided in Figure 5.4.

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Did you cough today?							
Did you wheeze today?							
Were you short of breath today?							
Did your chest trouble/ breathing wake you up during the night?							
Were you off school/ work today because of chest trouble/breathing?							
Has your chest trouble/ breathing caused you to avoid other activities?							
How often did you take your reliever inhaler today?							

Figure 5-4: Extract of participant respiratory diary

Participants were instructed to note the symptoms experienced by them on a daily basis by ticking the relevant section in the table above. For the question relating to reliever use a numerical answer, indicating the number of times the reliever inhaler was used that day, was required.

After the initial visit (visit 1), follow up visits were scheduled 30 (visit 2), 60 (visit 3), 150 (visit 4) and 180 (visit 5) days later. At visits 2, 3 and 5 the participants returned their inhalers with the INCA™ devices. Visit 4 was a dispensing visit. At each of these visits, for control group participants, changes in medications (including new medications) were recorded as was progress towards the participant's breathing related goal. For intervention and comparator group participants, this information was also noted along with the SGRQ responses. Assessment of inhaler technique using an inhaler technique checklist and inhaler technique training based on assessment observations was given to intervention and comparator participants also.

An overview of the procedures at each study visit is provided in Table 5.1.

Table 5-1: Study procedures observed for INCA study

Study Procedure	Visit 1 Day 0	Visit 2 Day 30	Visit 3 Day 60	Visit 4 Day 150	Visit 5 Day 180
Informed Consent	X				
Demographics	X				
Inclusion & exclusion Criteria	X				
Current medications	X				
Quality of Life measurement (only at visit 1 and visit 5 for control group)	X	X	X		X
Dispense peak flow meter and respiratory diary (not for control group)	X				
Record peak flow measurement	X				X
Review improvement in breathing related goal		X	X		X
Review respiratory diary (not for control group)		X	X		X
Dispense adapted inhaler	X	X		X	
Download device readings (feedback group only)		X	X		X
Inhaler use education, as required by cluster group (feedback and demonstration groups only)		X	X		X
Review of adverse events, if any		X	X		X
Concomitant medications		X	X		X
Review steroid and antibiotic use					X

5.4.4 Participants

Adult patients of both sexes aged 18 years or older using, or capable of using, a salmeterol/fluticasone Diskus™ inhaler and in possession of a current valid prescription for same were eligible to enrol on the study.

5.4.4.1 Inclusion criteria

In order to meet inclusion criteria for the study patients needed to:

- be capable of understanding, and willing to provide, voluntary informed consent before any protocol specific procedures were performed;
- be capable of understanding and complying with the requirements of the study protocol;
- demonstrate a willingness to attend for all required visits;
- be able and willing to use inhaled medication;
- have had a history of regular attendance at the pharmacy in which they were recruited as demonstrated by having at least 3 prescriptions for any medication filled in the prior six months.

5.4.4.2 Exclusion criteria

Patients were excluded from the study if they had a known sensitivity to salmeterol/fluticasone, if their physician had indicated that they would not be continuing to receive salmeterol/fluticasone Diskus™ over the six-month study period or if they had used any investigational product or device within the 3 months prior to enrolment.

5.4.4.3 Recruitment

Patients attending the study pharmacies who were prescribed a salmeterol/fluticasone Diskus™ inhaler were identified via prescription medication records. On attendance to collect their medication in the pharmacy patients were invited to participate in the study. Interested patients were screened for eligibility by the pharmacist and if eligible were provided with information about the study and a copy of the patient information leaflet. Voluntary informed consent was obtained for all recruited participants.

5.5 OUTCOMES

The objective of this study was to assess whether providing personalised feedback on adherence and technique errors leads to better adherence and clinical outcomes for participants than current best practice.

5.5.1 Primary outcome

The primary study objective was to determine whether there was at least a 20% greater rate of actual adherence in the INCA™ feedback group (“Intervention Group”) compared with the current best practice group (“Comparator Group”) post intervention. Thus, the primary outcome measure was the rate of participant adherence to their inhaled medication, defined as the proportion of correctly taken drugs at the correct time relative to the prescribed interval. To accommodate for potential Hawthorne effect comparisons of the rate of actual adherence at two months and at six months were performed.

5.5.2 Secondary outcomes

Comparison of the proportion of patients in each group who achieved good actual adherence (defined for this study as $\geq 80\%$) as well as the number progressing to good technique ($\geq 80\%$ of all doses attempted by the patient classified as correct technique) at both two and six months was assessed. Changes in patterns of adherence in the intervention and comparator groups was also reviewed by looking at error rates, overdose rates, and attempted rates of adherence.

The SGRQ responses and rescue medication (inhaler, steroid, antibiotic) use of the intervention and comparator groups were compared, as were levels of reported symptoms (as noted in the participants’ respiratory diaries) and improvement in participants’ breathing related goals. It was also intended to compare PEFr between groups.

Prescription medication dispensing records were reviewed to provide a further assessment of adherence (as defined by the proportion of days covered method) pre and post the study, and adherence measured in this way was compared across the intervention and comparator groups.

5.5.3 Randomisation and allocation

Pharmacies were the unit of randomisation and on enrolment to the study were allocated by the lead researcher to one of the three study groups (intervention, comparator or control group) using a computer-generated (Microsoft Excel[®] 2013) list of random numbers. In order to control for trial participation effects 10 pharmacies were randomly allocated to the control group. It was intended to then randomly allocate the remaining pharmacies to either the intervention or comparator group in a 1:1 ratio. Initially, 50 pharmacies were allocated to the 3 groups (10 control and 20 each to the comparator and intervention groups). Recruitment rates were lower than expected and were not consistent across pharmacies with a lower number of participants recruited per pharmacy in the comparator group and greater number of comparator pharmacies failing to recruit participants. Therefore, a further two recruitment phases were conducted in an effort to both boost and balance participant recruitment, resulting in a total of 27 pharmacies being allocated to the intervention group and 37 pharmacies being allocated to comparator group. Given the nature of the intervention neither pharmacists nor participants could be blinded. All participants were aware that data on adherence was being collected for analysis and a lead in period was incorporated into the study design to account for a potential Hawthorne effect.

5.5.4 Data collection

Pharmacists completing data collection were trained to understand the importance of robust data collection, were provided with a study guidance pack outlining all relevant data collection procedures and signed a declaration indicating their agreement to keep complete and accurate records. The accuracy, completeness and progress of data were overseen by a lead researcher in the pharmacy chain where the study was conducted. This researcher, who had no role in participant recruitment or in conducting any study related procedures, conducted visits to the study pharmacies to check compliance with the protocol.

Every reasonable effort to follow up all enrolled participants for the entire six-month study period was employed. At each study visit an appointment for the next visit was scheduled and non-attenders were contacted to re-schedule as required. The lead pharmacist researcher monitored recruitment and retention and targeted counselling and training interventions were

provided to pharmacy sites where retention was a challenge. At any point in time, study participants were free to withdraw their consent from the study. It was also possible, although it did not occur, for a participant to be withdrawn from the study by the investigator if necessary, based on clinical assessment of adverse events, or in the event of early discontinuation of the study. In the case of withdrawing from the study, a final study consultation was completed where possible and the participant's adapted inhaler, peak flow meter and diary were collected if available.

5.5.5 Data Management

Paper based case report forms were pseudonymised with a unique patient identifier code. On study completion or withdrawal, data from these report forms was input by the lead researcher into an electronic, password protected database. Participant files remain locked in a secure and accessible place, in a manner consistent with local data protection requirements, and will be maintained in storage for a period of three years post termination of the study.

Audio data was uploaded to a secure server, access to which is by individual user name and password. Individual pharmacists did have access to this database. The tool has an inbuilt audit trail that records and can display, details of additions or changes made to data, either on a by user or by patient basis.

1.1.1 Interventions

5.5.5.1 Intervention Group: Feedback using recordings from the INCA® device

Participants in the intervention group received the INCA™ intervention. These participants received feedback on their own inhaler use, with personalized information on their technique and timing of use of the salmeterol/fluticasone Diskus™ inhaler as recorded on the INCA™ device at day 30 (visit 2), day 60 (visit 3) and day 180 (visit 5). Utilising a structured review, the pharmacist identified barriers to good adherence and supported patients to improve habit of use where necessary. Remediation of errors of inhaler use identified through assessment of participants' inhaler technique using a Diskus™ inhaler technique checklist, the "Inhaler Proficiency Schedule" (IPS) [457] (Appendix 6), was also conducted.

5.5.5.2 Comparator Group: Inhaler technique education

The comparator for this study was current best practice in the community pharmacy setting, defined for this study as an assessment of the participant's inhaler technique using a Diskus™ inhaler technique checklist (IPS) [457] and a physical demonstration of optimal technique by the pharmacist followed by demonstration of same by the participant until device mastery was achieved.

5.5.5.3 Control Group: Usual care

In order to control for trial participation effects a control group was included in the study design. Participants in the control group did not receive any intervention other than usual care (*i.e.* the safe supply of medicines and advice on their use). Review of inhaler technique, as initiated by the pharmacist where deemed necessary, or as requested by the participant, was a feature of usual care but its provision was not a standard or structured intervention in the control group.

Upon exiting from the study at visit 5, all participants were provided with the option to receive personalised feedback on their Diskus™ use based on the INCA™ device recordings.

5.5.6 Pharmacist training

Pharmacists delivered the intervention allocated to the pharmacy in which they practised and received training specific to that intervention. Training consisted of one 1.5-hour face to face workshop with a respiratory physician, nurse specialist and pharmacist educator/researcher where they were provided with an overview of the study and trained to provide education on inhaler technique and medication adherence. A distance learning study guide specific to each study arm and outlining all study related procedures was also completed. Throughout the study pharmacists were supported by the lead pharmacy researcher who was available via phone or email to answer any queries they had.

5.5.7 Ethics

The use of the INCA™ device in clinical investigation trials has been approved by the Irish Medicines Board (now Health Products Regulatory Authority) and the device is CE marked

(CE0086). The study was approved by Royal College of Surgeons in Ireland Ethics committee (REC712b) and is registered as NCT02203266 on Clinicaltrials.gov (27 July 2014).

5.5.8 Sample size

Studies in the pharmacy setting have identified baseline rates of attempted adherence amongst asthma patients of < 0.6 [437]. In the primary care setting poor inhaler technique amongst patients with respiratory disease has been identified in preliminary studies conducted using the INCA™ device (0.47 ± 0.33). A pre-intervention actual adherence rate of 0.5 at the end of the first month was therefore assumed. The primary endpoint was the rate of actual adherence post intervention and comparison between adherence rates in the intervention and comparator groups was to be conducted at the end of months one, two and six. The sample size was dictated by comparisons to be made between these two groups.

It was hypothesised that the intervention group would get closer to the commonly reported level of “good” adherence (≥ 0.8) [458] improving by 0.2. Adherence in the comparator group had the potential to improve as a result of the educational intervention received and an assumed improvement of 0.05 in this group over the study period was incorporated into the sample size calculation. An intra-class correlation coefficient of 0.025 and a loss to follow up of 10% (as observed in a recent similar study conducted in the pharmacy setting [438]) were assumed. With a power of 0.85 at the 0.05 significance level to detect a 0.2 difference in actual adherence between the two groups, a sample size of 75 participants across 25 clusters in each of the intervention and comparator groups was required.

5.5.9 Data analysis

5.5.9.1 Analysis of the audio data

The INCA™ device is a CE marked device which is manufactured by Vitalograph Ireland Ltd, Ennis, Ireland. Digital recordings from the INCA™ device were analysed by the INCA™ algorithm as previously described [449]. For each audio file, the algorithm firstly identifies the piercing of the medication blister, it then identifies breath sounds, differentiating between inhalations and exhalations and calculates a score of user technique based on whether the inhaler was (a) used correctly, (b) used incorrectly or (c) not used [451]. If used incorrectly the algorithm checks the events that have taken place to provide a classification of the error type

[451]. The files are uploaded to a secure server and analysed using signal processing methods. The sensitivity and specificity details of the signal processing algorithm have been published [459]. The algorithm identifies each audio file as one representing either correct or incorrect inhaler use as well as automatically classifying any technique errors identified. To validate the data human raters also over-read all files from all participants. Comparison was made between the automated and human classification. In the event of any disagreement, review by an additional independent over-reader yielded the final classification. The human raters were independent of any patient care during the trial.

The original classification, based on the INCA™ algorithm, was used in the calculation of the actual adherence for this study. The reason for this was because this was the classification that was available to the pharmacists delivering the study intervention and therefore any adherence counselling provided to patients would have been based on that classification.

Calculation of the rate of actual adherence was completed using the method proposed by Sulaiman et al [460]. With this method, errors of inhaler use are combined with observations relating to the timing of the dose to provide a single measure of adherence calculated as an area under the curve [460].

Inhaler errors which can occur include failure to prime the inhaler with drug, failure to hold the inhaler in a vertical position post priming with drug and prior to inhalation, exhalation into or near the mouthpiece after priming but before inhalation, failure to achieve an adequate flow rate and presence of multiple inhalations indicating inadequate breath-holds. The INCA™ device is capable of identifying all such errors except correct (vertical) positioning post priming with drug.

5.5.9.2 Analysis of additional measures

Quality of life

Quality of life was measured for participants in the intervention and comparator groups using the St. George's respiratory questionnaire (SGRQ), a disease-specific instrument suitable for use in patients with asthma and COPD [461]. It consists of 50 items divided into three components: symptoms, activity and impact [462]. A total score is also calculated. Scores range from 0 to 100 with lower scores indicating better quality of life [462]. A change in the total score of 4 units is considered the minimal clinically important difference (MCID) [463].

Breathing related goal

At visit 1 patients were asked to identify an aspect of their daily life affected by their respiratory condition that they would like to improve. This breathing related goal was recorded and improvement was monitored at subsequent visits by reminding the patient of the goal and asking them to grade the improvement, if any, on a scale of 0-10 (with 0 being no improvement). Thematic analysis was conducted in order to identify top-level goal domains and goals were classed as being “specific”, “moderately specific” or “non-specific”; an approach employed in a previous study involving asthmatic patients attending community pharmacy [464]. Themes were derived inductively from the responses provided. Improvement status at each visit was classed as “good” (improvement score of 7-10), “moderate” (4-6) or “poor” (0-3).

Adherence as measured by proportion of days covered

Two common methods of calculating adherence from prescription refill databases are the medication possession ratio (MPR) and the proportion of days covered (PDC) methods [465, 466]. The PDC method was used to calculate adherence to the salmeterol/fluticasone Diskus® inhaler from prescription refill records in this study. The PDC is calculated as the number of days a medication is available to a patient (i.e. the days “covered”) divided by the total number of days in the data analysis period [466]. The PDC was chosen over the MPR method as it is a more conservative approach to adherence estimation from refill records [467], whereby each prescription is considered as an array of days supplied and overlapping arrays are moved forward to the first day that the patient would not have medication from the previous dispensing (array) prior to calculating the PDC [467, 468]. Thus, the patient is assumed to have finished one fill of medication before starting the next and the maximum possible value of the PDC is 1.

The PDC was calculated for the 6-month period prior to enrolment on the study (calculated as the 180 days prior to the first recorded use of the INCA™ device) as a measure of lead in adherence and for the 6-month period post study completion (calculated as 180 days post the date of the last recorded use of the INCA™ device) as a measure of on-going adherence post study completion. As it was not a requirement of study enrolment that the participants have a history of regularly taking a salmeterol/fluticasone Diskus® inhaler in the six months prior to enrolment it could not be assumed that this was the case. Thus, in determining the denominator for the PDC calculation the number of days to first refill was subtracted from 180 to allow for the fact that that first refill date may have been the initiation date of the medication. For the post

study PDC the denominator was 180 for all participants as all had been taking the medication through the study period.

Rescue medication use

Details on short acting beta agonist, steroid and antibiotic usage over an up to 18-month period (six months pre study enrolment, duration of study participation and six month post study completion) were obtained from the participant's patient medication record in the pharmacy. Changes in patterns of use were examined as a marker of respiratory disease exacerbation.

Peak expiratory flow rate

All participants in the intervention and comparator groups were provided with an electronic peak flow meter (eMini-Wright[®], Clement Clarke International, Harlow, England) and asked to record their peak flow twice daily throughout the study period. This electronic meter is capable of storing 4 months of electronic recordings. To ensure recording for the entire six study period was collected data from the peak flow meter was downloaded at visit 3 for intervention participants and the meter returned to participants for use in the final three months of the study. Comparator pharmacies did not have a facility whereby data could be downloaded from the devices and thus comparator participants were given a new peak flow meter midway through the study and the first meter collected. Participants in the control group had their peak flow measured in the pharmacy at visit 1 and visit 5 only.

Respiratory symptoms

For participants in the intervention and comparator groups respiratory related symptoms were recorded in the paper diary described previously. Participants were asked to note the number of days per week that they experienced a range of symptoms such as cough, shortness of breath and wheeze. The number of days with reported symptoms per four-week period was calculated and changes in the level of reported symptoms across the four-week blocks were assessed.

5.5.10 Statistical Methods

Statistical analysis was conducted using Stata Statistical Software: Release 14. (StataCorp, College Station, TX: 2015). Descriptive statistics were used to evaluate differences in demographic characteristics, clinical condition, medication profile, exacerbation history and

quality of life scores between study groups. Categorical variables were expressed as frequencies or percentages and quantitative variables as means and standard deviations.

Participants' adherence to their inhaled medication is described in terms of both attempted and actual adherence rates. Where the participant opens their Diskus[®] inhaler, initiating an audio recording, this is classed as an attempt to take the inhaled medication. The pattern of attempts relative to the dosing interval over a defined period provides an "attempted" rate of adherence. Analysis of the associated acoustic recordings allows for detection of correct inhaler technique, which is taken to indicate that the participant actually received the dose they attempted to take. Thus, the pattern of attempted doses with correct technique yields the "actual" rate of adherence.

All consenting participants who completed at least one month of the study were included in an intention-to-treat (ITT) analysis of the primary outcome, rate of actual adherence at month 2 and month 6. Multiple imputation techniques were employed to include participants with missing data [469]. Multiple complete data sets were imputed using Stata's mi command (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). A secondary, per-protocol analysis was also conducted. This form of analysis includes only those participants who completed the treatment protocol originally allocated, providing results on the efficacy of the trial.

The rate of actual adherence and changes in the rate over time were compared between and within groups with the "vce" command in Stata being used to account for the effects of clustering by pharmacy.

Differences in proportion of patients achieving good actual adherence ($\geq 80\%$) and the proportion progressing to good technique ($\geq 80\%$ of all doses attempted by the patient classified as correct technique) were analysed using a clustered Chi squared analysis where possible or Fishers exact test where sample sizes were too small for a clustered Chi squared analysis.

Changes in patterns of adherence were investigated. Rescue medication use and reported symptoms are described and were compared between the groups. Rescue medication use was assessed before and after study enrolment. Reported symptoms were assessed in four weekly blocks and changes in the level of reported symptoms across the four-week blocks were assessed. Additionally, differences in the SGRQ responses were examined. It was intended to

compare changes in PEFr over time but due to a large number of device failures in the field this was not possible.

Statistical analysis was supported by the INhaler Compliance Assessment (INCA™) study team statistician.

5.6 RESULTS

5.6.1 Participants

5.6.1.1 Recruitment and study participation

74 pharmacies were recruited and randomised (27 to intervention, 37 to comparator and 10 to control) between January 2014 and December 2016. 56 (75.7%) pharmacies recruited at least one participant with a total of 152 participants were recruited (74 to intervention, 56 to comparator and 22 to control). 149 participants (98%) completed visit 1 and received one INCA device, 133 (87.5%) received two INCA devices and 86 (61.8%) received all 3 INCA devices.

The flow of both clusters and participants is shown in Figure 5.5 overleaf.

A drop out of 10% was assumed at the outset. Whilst this was broadly in line with the actual 12.5% drop out observed between enrolment and attendance at the third study visit (i.e. post-intervention short term follow-up), the drop-out rate at the six-month mark was much larger at 38.8%. Drop-out rates were similar in both the intervention (41.9%) and comparator groups (42.9%). The reasons for drop out were varied with the majority (39.7% of drop outs) as a result of the participant being lost to follow up within the six-month study period. A further 25.9% withdrew their consent to continue with the study citing reasons such as being unable/unwilling to make the time commitment for completion of study paperwork and having a preference for using a Seretide that did not have an INCA™ device attached. Three participants changed drug therapy mid-way through the trial and a further two moved house making them ineligible to continue with the study post enrolment.

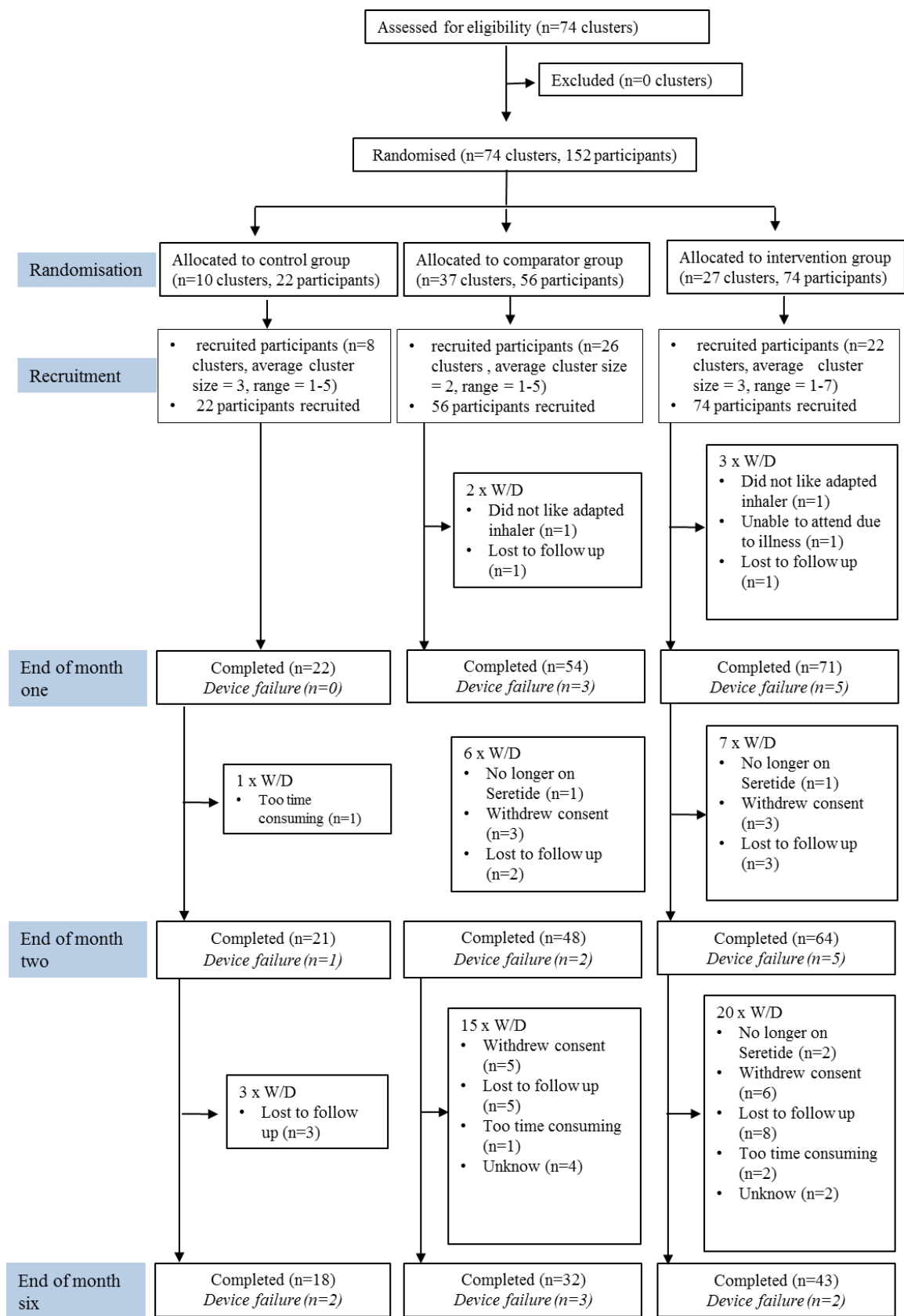


Figure 5-5: CONSORT flow diagram of participant flow through the INCA study

5.6.1.2 Demographic profile of the participants

The baseline characteristics of participants in all three groups are presented in Table 5.2. Please note this table is spread over two pages.

Table 5-2: Baseline characteristics of study participants

<i>Characteristic</i>	Control Group	Comparator Group	Intervention Group	All participants
	N= 22	N=56	N=74	N=152
Mean age at enrolment (SD; range)	55.4 (13.4; 32-76)	53.1 (15.2; 27-78)	53.5 (15.3; 22-92)	54.1 (14.9; 22-92)
<i>Gender</i>				
Male (n, %)	11 (50)	32 (57.1)	31 (41.9)	74 (48.7)
Female (n, %)	11 (50)	24 (42.9)	43 (58.1)	78 (51.3)
<i>Diagnosis</i>				
Asthma (n, %)	13 (59.1)	25 (44.6)	35 (47.3)	73 (48.0)
COPD (n, %)	1 (4.5)	4 (7.1)	8 (10.8)	13 (8.6)
Asthma & COPD (n, %)	4 (18.2)	1 (1.8)	3 (4.1)	8 (5.3)
Other (n, %)	0 (0)	1 (1.8)	0 (0)	1 (0.7)
Missing (n, %)	4 (18.2)	25 (44.6)	28 (37.8)	57 (37.5)
Mean number of years since diagnosis (SD; range)	24.9 (19.7; 3-61)	21.1 (13.1; 3-50)	19.9 (13.5; 1-45)	21.6 (15.0; 1-61)
<i>Smoking Status</i>				
Current smoker (n, %)	3 (13.6)	3 (5.4)	7 (9.5)	13(8.6)
Ex-smoker (n, %)	8 (36.4)	8 (14.3)	13 (17.6)	29 (19.1)
Never smoked (n, %)	7(31.8)	18 (32.1)	12 (16.2)	37 (24.3)
Missing (n, %)	4 (18.2)	27 (42.6)	42 (56.8)	73 (48.0)

Health pay status

Medical Card (n, %)	7 (31.8)	20 (35.7)	29 (39.2)	56 (36.8)
Drug Payment Scheme (n, %)	11 (50)	17 (30.4)	26 (35.1)	54 (35.5)
Private (n, %)	4 (18.2)	19 (33.9)	19 (25.7)	42 (27.6)

Respiratory Medication

SABA (n, %)	15 (68.2)	41 (73.2)	43 (58.1)	97 (63.8)
LAMA (n, %)	3 (13.6)	8 (14.3)	12 (16.2)	23 (15.1)
Oral corticosteroids (n, %)	2 (19.1)	3 (5.4)	2 (2.7)	7 (4.6)
Nasal corticosteroid (n, %)	5 (22.7)	11 (19.6)	14 (18.9)	30 (19.7)
Anti-leukotriene (n, %)	3 (13.6)	10 (17.9)	12 (16.2)	25 (16.4)
Nebules, any (n, %)	1 (4.5)	3 (5.4)	3 (4.1)	7 (4.6)
Mean number of concomitant medications (SD, range)	7.1 (4.0, 2-15)	4.9 (3.7, 1-16)	4.5 (3.6, 0-16)	4.9 (3.8; 0-16)

Seretide Diskus Dosage

Seretide 250 (n, %)	14 (63.6)	26 (46.4)	28 (37.8)	68 (44.7)
Seretide 500 (n, %)	8 (36.4)	30 (53.6)	46 (62.2)	84 (55.3)

Rescue medication use pre-enrollment

Mean canisters of salbutamol (SD; range)	2.8 (3.0; 0-8)	2.1 (2.3; 0-7)	2.1 (2.5; 0-8)	2.2 (2.5; 0-8)
Mean courses of antibiotics (SD; range)	0.9 (1.5; 0-5)	0.9 (1.5; 0-6)	0.7 (1.1; 0-4)	0.8 (1.3; 0-6)
Mean courses of oral steroids (SD; range)	0.4 (0.7; 0-2)	0.4 (0.7; 0-3)	0.4 (0.9; 0-5)	0.4 (0.8; 0-5)

5.6.1.3 Audio recordings for analysis

A total of 379 devices were distributed to study participants of which 347 (91.6%) yielded audio data for analysis. 5 (1.3 %) were not returned by participants and 26 (6.9%) of devices failed in the field yielding no audio recordings for analysis. Included in this number of devices which failed in the field were 8 devices where one or two audio files were retrieved which may have occurred where the patient left their device open between dosing thus inactivating the recording mechanism (which commences on opening of the inhaler). The device failure rates across the intervention, comparator and control groups were 7.8%, 6.5% and 4.9% respectively.

5.6.2 Inhaler adherence

5.6.2.1 Rates of adherence

Adherence rates were calculated via a variety of methods and these are summarised in Table 5.3

Table 5-3: Inhaler Adherence Calculations

<i>Adherence Rate</i>	Control Group N=22	Comparator Group N=56	Intervention Group N=74
Month 1			
Dose Counter Rate	92.67±14.2, n=22	93.1±13.8, n=52	92.3±17.6, n=68
Attempted Rate	51.7±33.0, n=22	62.5±30.9, n=51	72.2 ±27.5, n=64
Actual Rate	34.6± 31.0, n=22	41.0±32.6, n=51	55.3±31.3, n=64
Over Doses	4.9±4.9, n=22	5.2±5.4, n=51	6.2±11.8, n=64
Missed Doses	34.0±25.7, n=22	23.1±20.9, n=51	15.8±17.9, n=64
Technique Error Rate	20.1±31.56, n=22	30.6±37.0, n=51	24.0±32.9, n=64
Critical Technique Error Rate	10.3±16.9, n=22	19.0±30.7, n=51	14.8±22.9, n=64
Month 2			
Dose Counter Rate	94.1±11.9, n=21	95.9±10.6, n=48	94.5±9.8, n=58
Attempted Rate	51.4±32.3, n=20	64.7±32.3 n=46	75.0±23.3, n=58
Actual Rate	31.2±30.4, n=20	39.3±31.3, n=46	61.0±26.4, n=58
Over Doses	6.9±8.7, n=20	6.6±10.2, n=46	3.0±3.1, n=58
Missed Doses	31.7±24.8, n=20	25.0±21.8, n=46	15.1±15.7, n=58
Technique Error Rate	32.7±36.3, n=20	29.89±36.9, n=46	19.5±29.1, n=58
Critical Technique Error Rate	22.8±29.3, n=20	19.4 ±30.0, n=46	14.6±24.7, n=58
Month 6			
Dose Counter Rate	98.1±7.5, n=16	95.8±9.2, n=31	95.5±9.4, n=43
Attempted Rate	52.1±32.6, n=16	62.5±27.5, n=28	76.7±22.9, n=41
Actual Rate	30.5±27.6, n=16	40.2±29.2, n=28	61.7±27.3, n=41
Over Doses	8.4±9.3, n=16	8.6±14.4, n=28	3.7±4.5, n=41
Missed Doses	30.9±20.5, n=16	23.1±18.3, n=28	12.7±13.8, n=41
Technique Error Rate	43.1±35.6, n=16	34.6±36.1, n=28	23.1±30.6, n=41
Critical Technique Error Rate	36.1±33.0, n=16	21.9±28.8, n=28	17.5±26.8, n=41

5.6.2.2 Comparison of rate of actual adherence

Including all consented participants with at least one month of calculated adherence an intention to treat analysis (ITT) was conducted to compare the rate of actual adherence between the intervention and comparator groups at month 2 and month 6. In this analysis, a statistically significant difference in the rate of actual adherence between the intervention and comparator groups was observed at month 2 and month 6. At month two the intervention group had a mean actual adherence that was 19.5% (95% CI: 9.7 – 29.3) higher than that of the comparator group ($p < 0.0005$) and at month six the difference was 16.4 % (95% CI: 1.2 – 31.0), $p = 0.036$.

The difference between groups remained significant when the rate of actual adherence in month 1 was added to a linear regression model as a predictor of adherence in month 2 ($p = 0.012$) but not at month 6 ($p = 0.249$). The model statistically significantly predicted actual adherence in month two, $F(2, 41.1) = 64.59$, $p < 0.0005$ and month six, $F(2, 27.8) = 13.2$, $p < 0.0005$.

Multiple linear regression analysis, accounting for clustering and with month 1 actual adherence included as a predictor variable was also conducted to assess differences between the intervention and control group and the comparator and control groups respectively. Statistically significant differences between each pairwise group were observed at month two and month 6 but randomisation group only added significantly to the prediction when comparing the intervention and control groups at month 2 ($p = 0.001$) and month 6 ($p = 0.006$).

It was intended to conduct a per protocol analysis which excluded all participants with missing data as well as those participants who completed either two (short term adherence) or three (longer term adherence) study visits but at incorrect timings as per the pre-defined time limits per visit (*i.e.* timing of V1-V2 and/or V2-V3 outside of a 30 ± 7 day window, and/or V3-5 outside of a 90 ± 7 day window). Analysis of the timing of attendance for each study visit revealed a low level of adherence to study timings amongst participants. Conducting such an analysis would have resulted in a month 2 comparison for 29 intervention and 18 comparator participants and a month 6 comparison for 20 intervention and 9 comparator participants. As the study was conducted in a real world setting, where participant presentation to collect their inhaled medication was likely to be more reflective of their need for a new supply of medication (and as such related to their actual medication adherence) rather than attendance for a study visit it was decided that the secondary analysis would include all consented patients who completed, and had INCA adherence data available, for two (short term adherence) or all three (longer term

adherence) study visits, but where these visits occurred outside of the pre-defined protocol timings.

In this “per protocol” analysis, the mean actual adherence of participants in the intervention group in month two was 61.0 (± 26.4), $n=58$ participants and that of the comparator group was 39.3 (± 31.3), $n=40$ participants. There was a statistically significant relationship between actual adherence and randomisation group ($p<0.0005$) with randomisation group accounting for 21.72% of the variability in actual adherence observed between the two groups at month two. However, as mean actual adherence was higher in the intervention group than the comparator group at month 1, a multiple regression which accounted for clustering was run to predict actual adherence in month 2 from randomisation group and actual adherence in month 1. These variables statistically significantly predicted actual adherence in month 2, $F(2,41) = 83.93$, $p<0.0005$. Both actual adherence in month 1 ($p<0.0005$) and randomisation group ($p=0.014$) added statistical significance to the prediction.

Comparing the two groups at month six the mean actual adherence of participants in the intervention group at the end of month six was 61.7 (± 27.3), $n=41$ participants and that of the comparator group was 40.2 (± 29.2), $n=29$ participants. There was a statistically significant relationship between actual adherence and randomisation group ($p=0.007$) with randomisation group accounting for 21.4% of the variability in actual adherence observed between the two groups at month six. The multiple linear regression was also conducted as per month two analysis and the variables statistically significantly predicted actual adherence in month six, $F(2, 38) = 20.00$, $p<0.0005$ with actual adherence in month 1 ($p<0.0005$) adding statistical significance but not randomisation group ($p=0.096$).

Multiple linear regression analysis, accounting for clustering and with month 1 actual adherence included as a predictor variable was also conducted to assess differences between the intervention and control group and the comparator and control groups respectively. Statistically significant differences between each pairwise group were observed at month two and month 6; randomisation group added significantly to the prediction when comparing the intervention and control groups (month 2 $p=0.001$, month 6 $p=0.013$) and the comparator and control groups at month 6 ($p=0.009$).

5.6.2.3 Comparison of change in the rate of actual adherence

It was only possible to compare the change in rate of adherence for the per protocol population. Looking at the change in actual adherence between month 1 and month 2 and between month 1 and month 6 and comparing this for the intervention and comparator groups in the “per protocol” participants there was no statistically significant difference observed between the two groups for either measure ($p=0.341$ and $p=0.759$ respectively). A mean improvement in the rate of actual adherence of $5.7 (\pm 24.8)$ was observed in the intervention group between month 1 and month 2 ($n=58$ participants). Comparing month 1 to month 6 a mean improvement of $6.4 (\pm 30.0)$ was observed. For the comparator group the rate of actual adherence decreased by $1.7 (\pm 16.2)$ between month 1 and month 2 ($n=44$ participants) and by $0.8 (\pm 28.3)$ between month 1 and month 6 ($n=28$ participants).

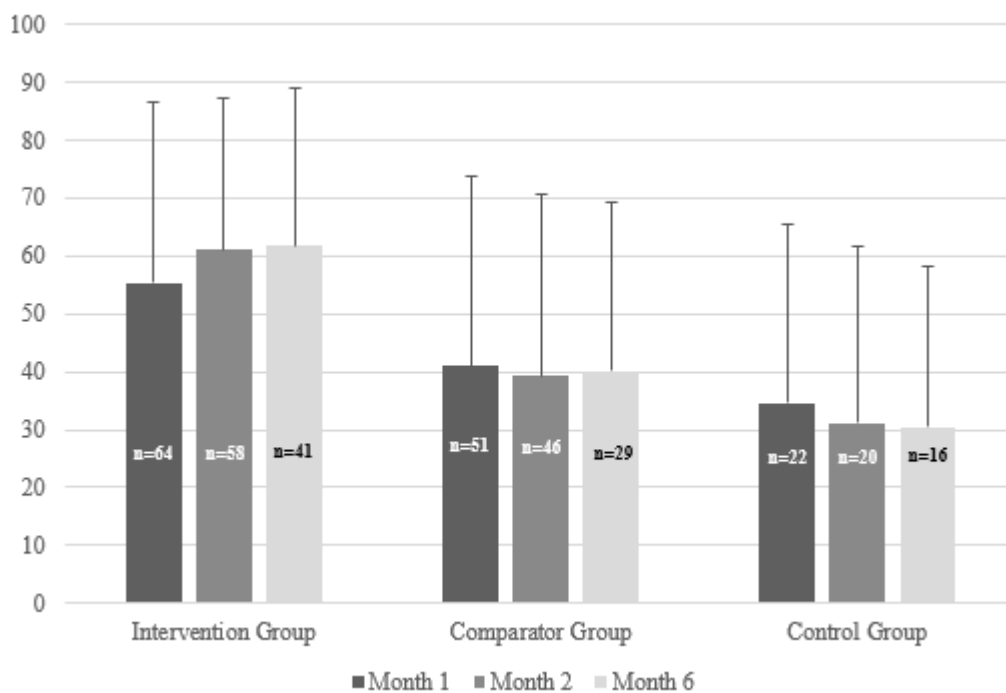


Figure 5-6: Rate of actual adherence observed in the per-protocol population across study visits

5.6.2.4 Rate of attempted adherence

For the ITT population a multiple linear regression analysis, accounting for clustering and with month 1 attempted adherence included as a predictor variable, statistically significantly predicted attempted adherence in month 2 ($F(2, 36.4) = 41.05, p < 0.0005$). Attempted adherence at month 1 added statistically to the prediction ($p < 0.0005$) whereas randomisation group did not ($p = 0.336$). A similar analysis looking at rate of attempted adherence in month 6 statistically significantly predicted attempted adherence in month 6 ($F(2, 22.7) = 9.77, p < 0.0005$). Again, attempted adherence at month 1 added statistically to the prediction ($p < 0.0005$) whereas randomisation group did not ($p = 0.78$).

The per protocol analysis demonstrated that the mean attempted adherence of participants in the intervention group in month two was 75.5 (± 24.34), $n = 58$ participants and that of the comparator group was 63.37 (± 31.8), $n = 46$ participants. Multiple linear regression analysis, accounting for clustering and with month 1 attempted adherence included as a predictor variable statistically significantly predicted attempted adherence in month 2 ($F(2, 41) = 57.3, p < 0.0005$). Attempted adherence at month 1 added statistically to the prediction ($p < 0.0005$) whereas randomisation group did not ($p = 0.467$). The mean attempted adherence of participants in the intervention group in month 6 was 78.61 (± 21.08), $n = 41$ participants and that of the comparator group was 60.83 (± 31.17), $n = 30$ participants. Multiple linear regression analysis, accounting for clustering and with month 1 attempted adherence included as a predictor variable, statistically significantly predicted attempted adherence in month 6 ($F(2, 38) = 17.83, p < 0.0005$). Attempted adherence at month 1 ($p < 0.0005$) added statistical significance whereas randomisation group did not ($p = 0.117$).

5.6.2.5 Proportion of patients with good actual adherence

The proportion of patients with good actual adherence at month 1, 2 and 6 was compared across the groups for the per protocol population. No statistically significant difference in the observed proportions of good actual adherence (*i.e.* actual adherence $\geq 80\%$) in each study group was observed at month 1 (Fisher's exact test, $p = 0.375$) or at month 6 (Fisher's exact test, $p = 0.06$). A significant difference existed at month 2 (Fisher's exact test, $p = 0.001$).

The proportion of patients with good actual adherence in the intervention group increased from 0.22 (95% CI 0.13 - 0.34) at month 1 to 0.36 (95% CI 0.25 - 0.49) at month 2, a statistically significant increase (Fisher's exact test $p = 0.004$). At month 6 an increased proportion of

adherent patients versus baseline (0.34; 95% CI 0.21 - 0.50) continued to be observed (Fishers exact test, $p=0.016$).

A statistically significant difference between the proportion of patients with good actual adherence at month 1 and month 2 was observed in the comparator group (Fisher’s exact test, $p<0.0005$) where the proportion in month 2 was smaller than that in month 1; no significant difference was observed between month 1 and 6. No significant differences were observed in the control group (Fisher’s exact test, $p=0.15$) for any of the time points.

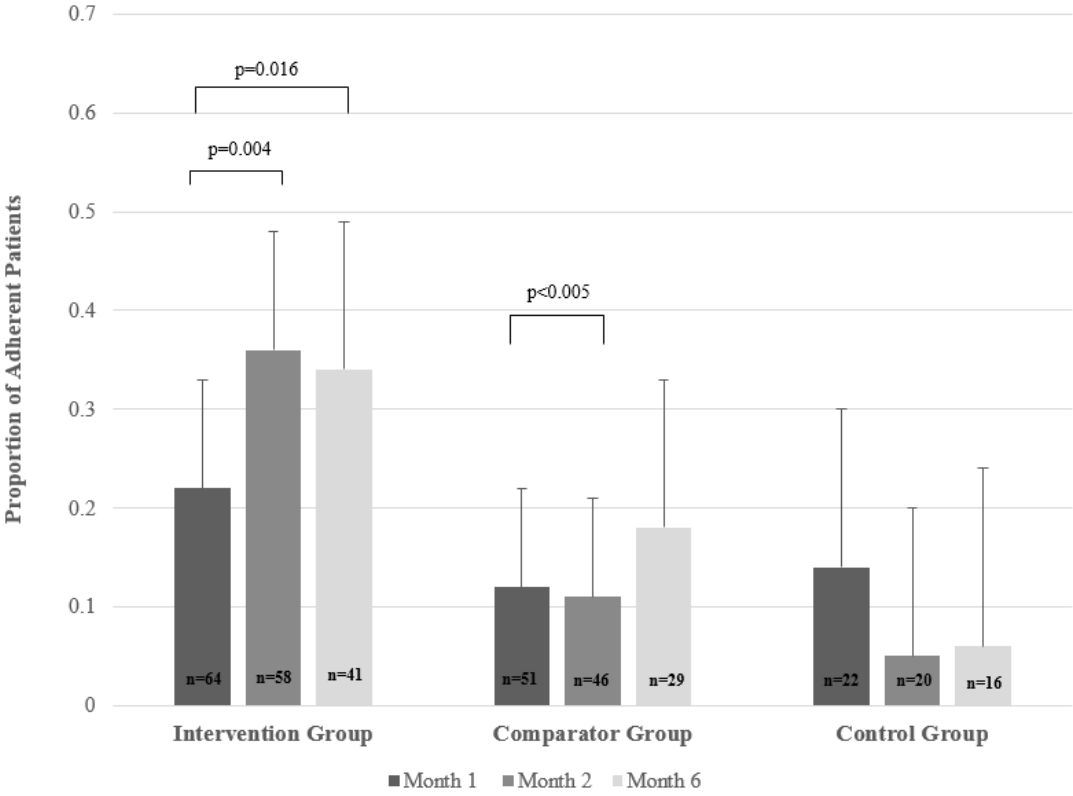


Figure 5-7: Proportion of patients with good actual adherence by randomisation group

A random effects logistic regression which accounted for clustering was conducted to analyse the proportion of patients progressing to good technique in the intervention and comparator group. Both randomisation code ($p=0.003$) and good actual adherence ($\geq 80\%$) in month 1 ($p<0.0005$) predicted the likelihood of being adherent in month 2.

A total of 8 (15.1%) participants in the intervention group progressed from poor actual adherence ($<80\%$) in month 1 to good actual adherence in month 2; in the comparator group 0

(0.0%) participants improved in this manner. Three (5.6%) intervention and one (2.3%) comparator participants changed from good to poor adherence over the same period.

5.6.2.6 Patterns of adherence

Visual representation of electronically monitored dosing histories was available for all devices uploaded to the INCA™ server. Different patterns of adherence were observed and some examples of these patterns are shown below.

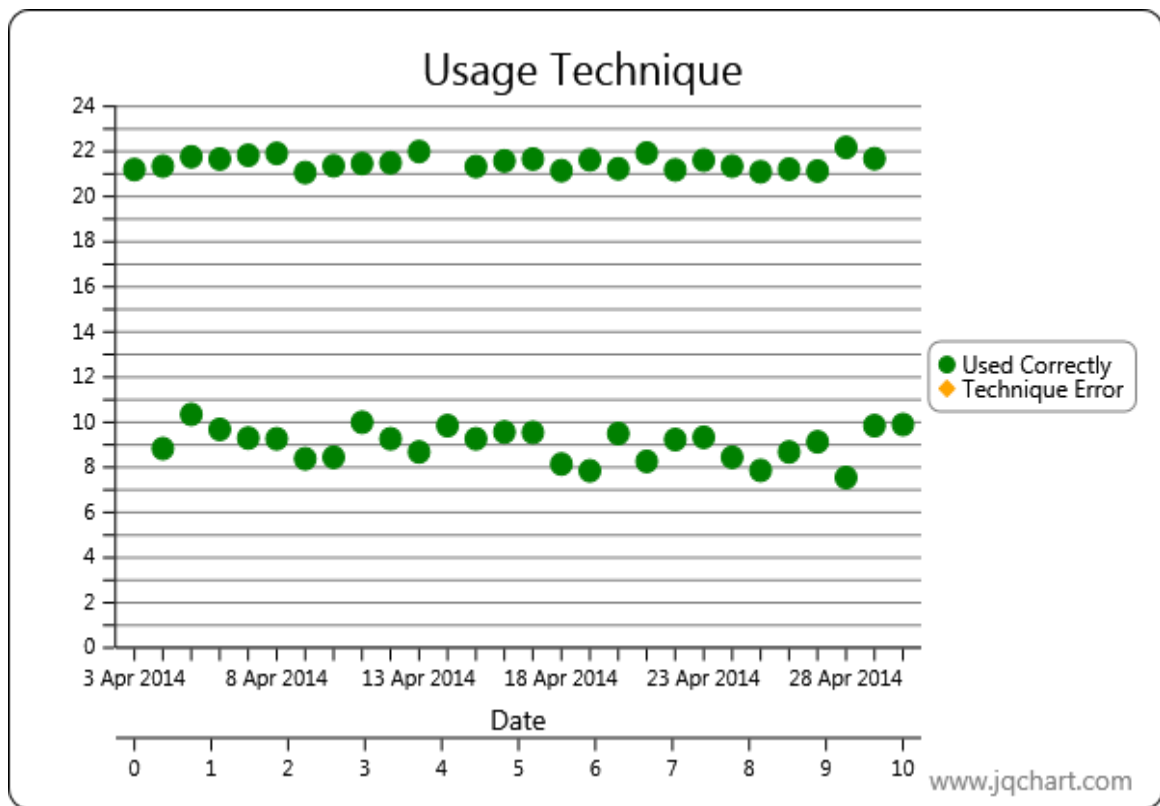


Figure 5-8 INCA™ graphical output for participant A: an example of good timing and good technique

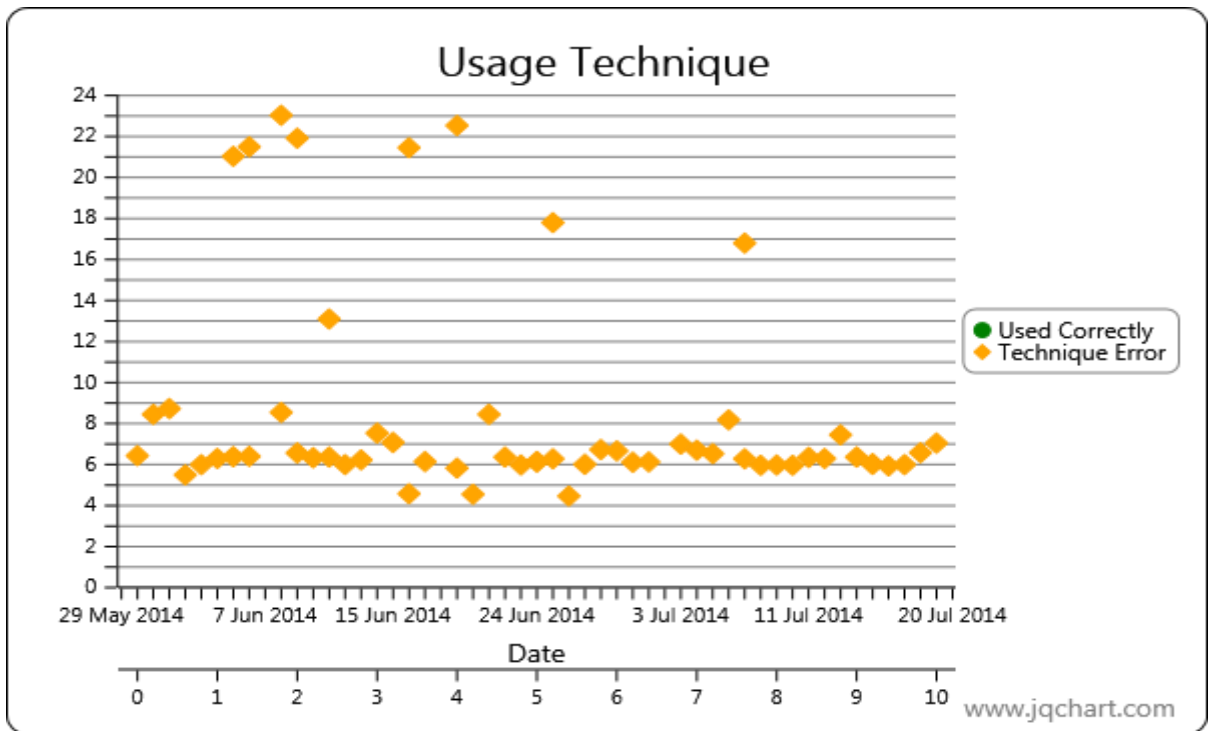


Figure 5-11 INCA™ graphical output for participant D: an example of poor timing and poor technique

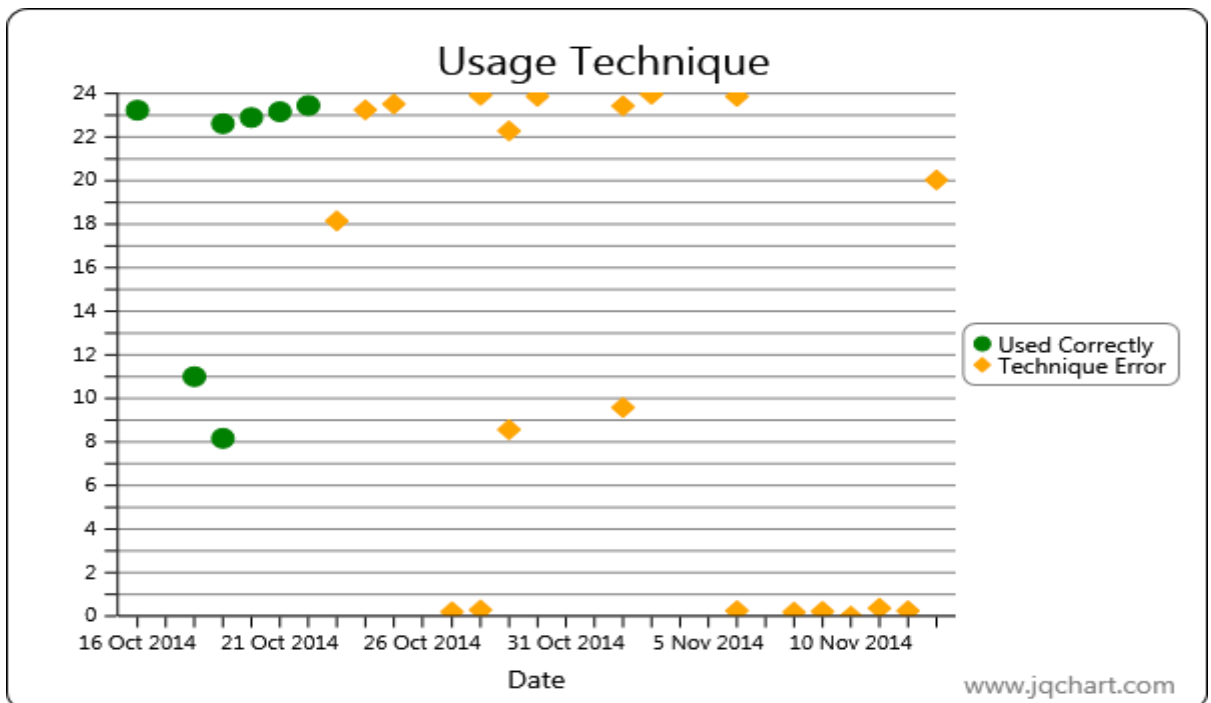


Figure 5-12 INCA™ graphical output for participant E: an example of erratic use with poor technique

5.6.2.7 Adherence as measured by the PDC method

The PDC for salmeterol/fluticasone Diskus® inhaler was calculated from prescription refill records for all participants. The mean pre-study and post study PDC for all groups are shown in Figure 5.13 below.

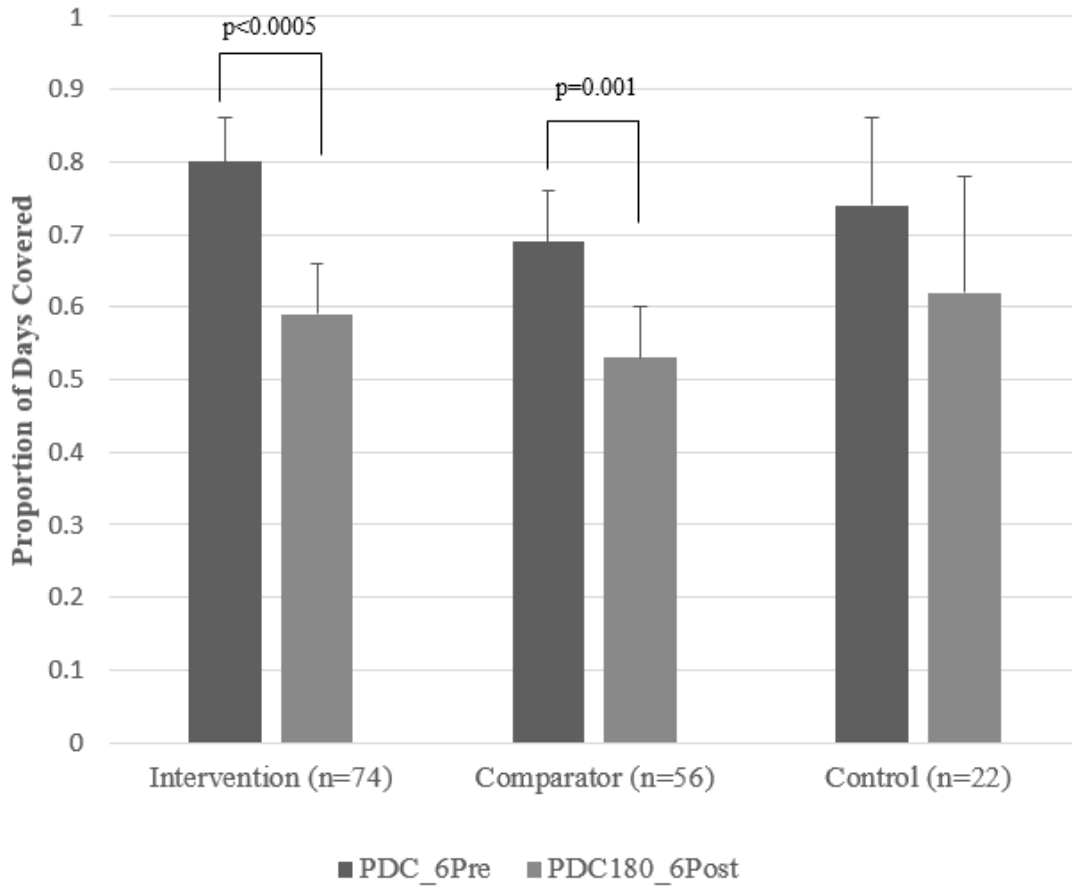


Figure 5-13: Adherence as measured by PDC pre and post for all study participation

Participants in the intervention group had a statistically significantly higher mean PDC than those in the comparator group pre-study enrolment ($p=0.023$). A mean $20.8 \pm 32.1\%$ reduction in the PDC was observed for the intervention group, with a $15.1 \pm 31.5\%$ and $11.3 \pm 39.5\%$ reduction seen in the comparator and control groups respectively. There was no statistically significant difference in PDC observed between groups post study completion.

PDC observations were also carried out on the cohort of patients who completed the trial. The same patterns of decreasing rates of adherence as calculated using the PDC method were observed in this cohort and the only statistically significant between group difference observed was that for PDC in month 1 (PDC intervention = 0.82 ± 0.25 , PDC comparator = 0.68 ± 0.30 ; $p=0.039$). The mean pre-study and post study PDC for participants who completed the six months of the study are shown in Figure 5.14 below.

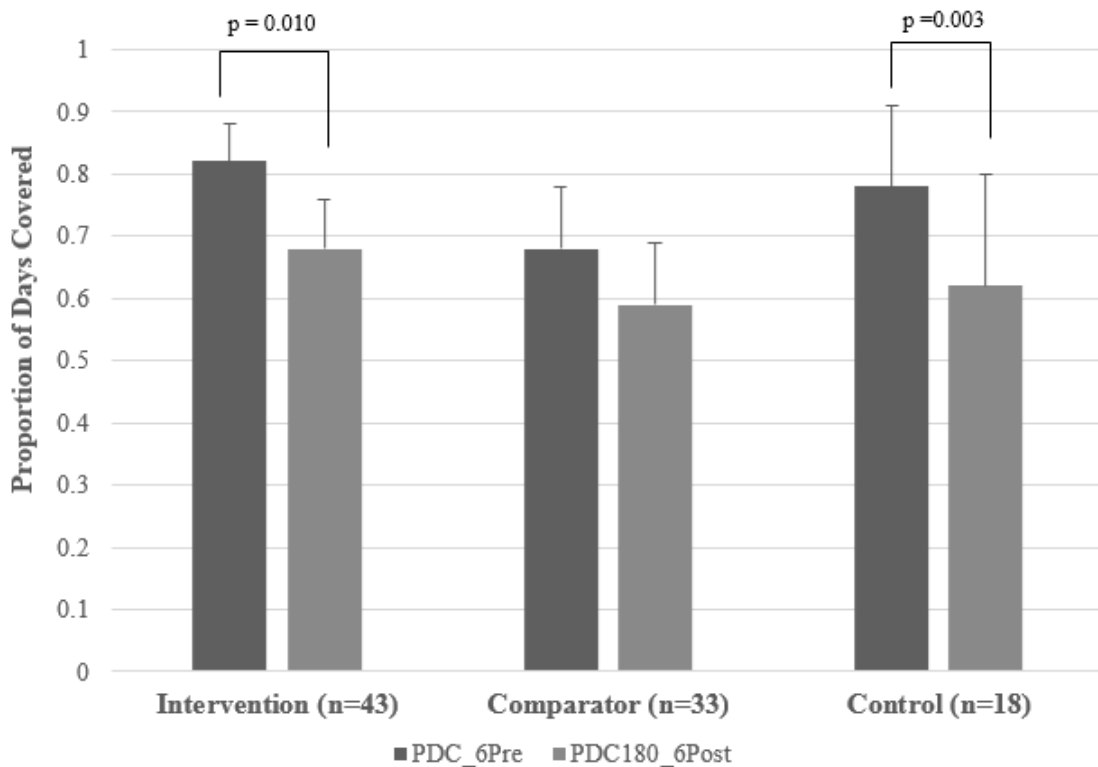


Figure 5-14: Adherence as measured by PDC pre and post study participation for participants who completed the study

5.6.3 Inhaler technique

5.6.3.1 Inhaler technique as measured by the Inhaler Proficiency Schedule

Errors in inhaler technique were assessed manually using the IPS [457] at visit 2, visit 3 and visit 5 for participants in the intervention and comparator groups only. The mean IPS scores per group at each of the three time points are presented in Table 5.4. No statistically significant relationship between IPS score and randomisation group was observed.

Table 5-4: Inhaler Proficiency Scores across the study

<i>Inhaler Proficiency Score</i>	Intervention Group	Comparator Group	p value
End month 1 (V2)	7.61 ± 1.8	8.16 ± 1.8	0.197
End month 2 (V3)	9.44 ± 1.1	9.36 ± 0.9	0.683
End month 6 (V5)	9.63 ± 0.6	9.46 ± 1.2	0.560

Looking at the within group differences (as presented in Figure 5.15), a statistically significant difference in IPS scores between visit 2 and 3, and between visit 2 and 5 was observed in both groups.

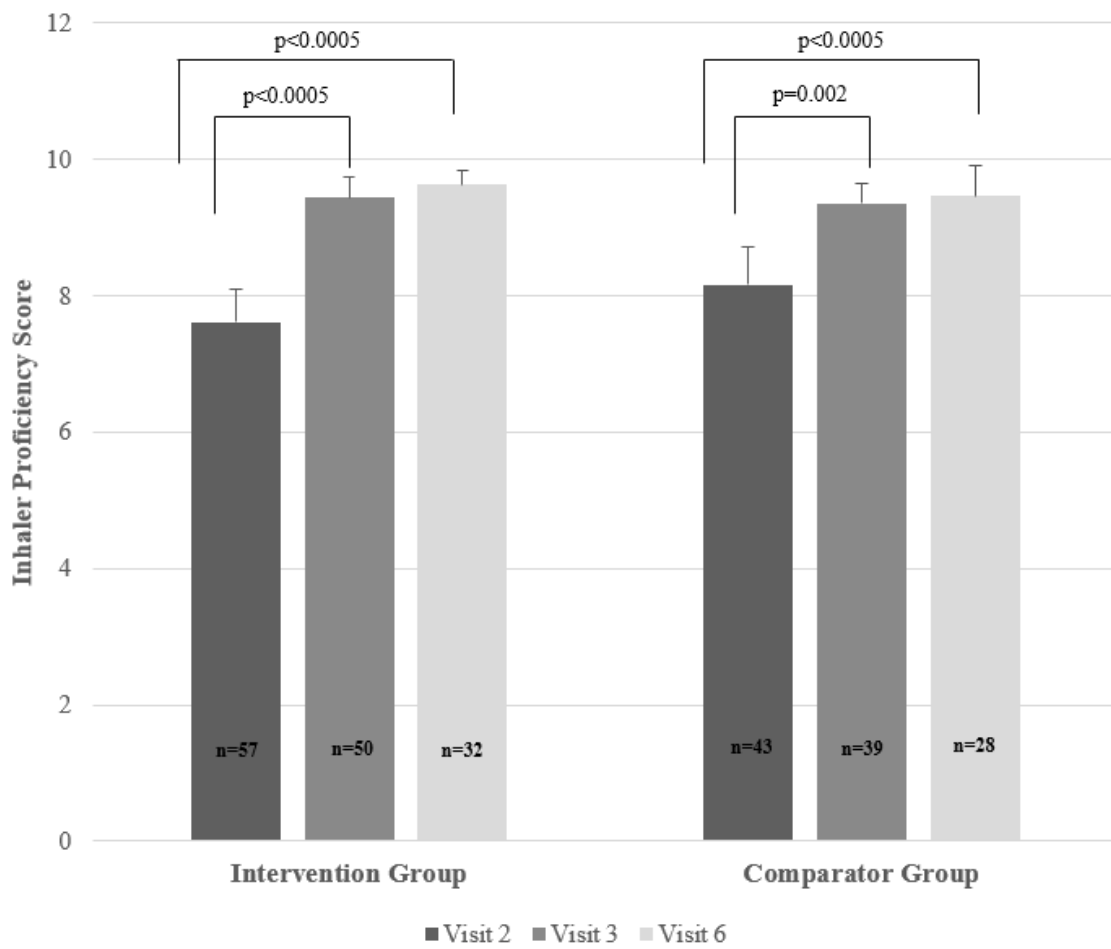


Figure 5-15: Mean Inhaler Proficiency Scores across the three study visits for the intervention and comparator groups

5.6.3.2 Rate of inhaler technique errors as classified by the INCA device

The mean technique error rates over time are shown in Figure 5.16

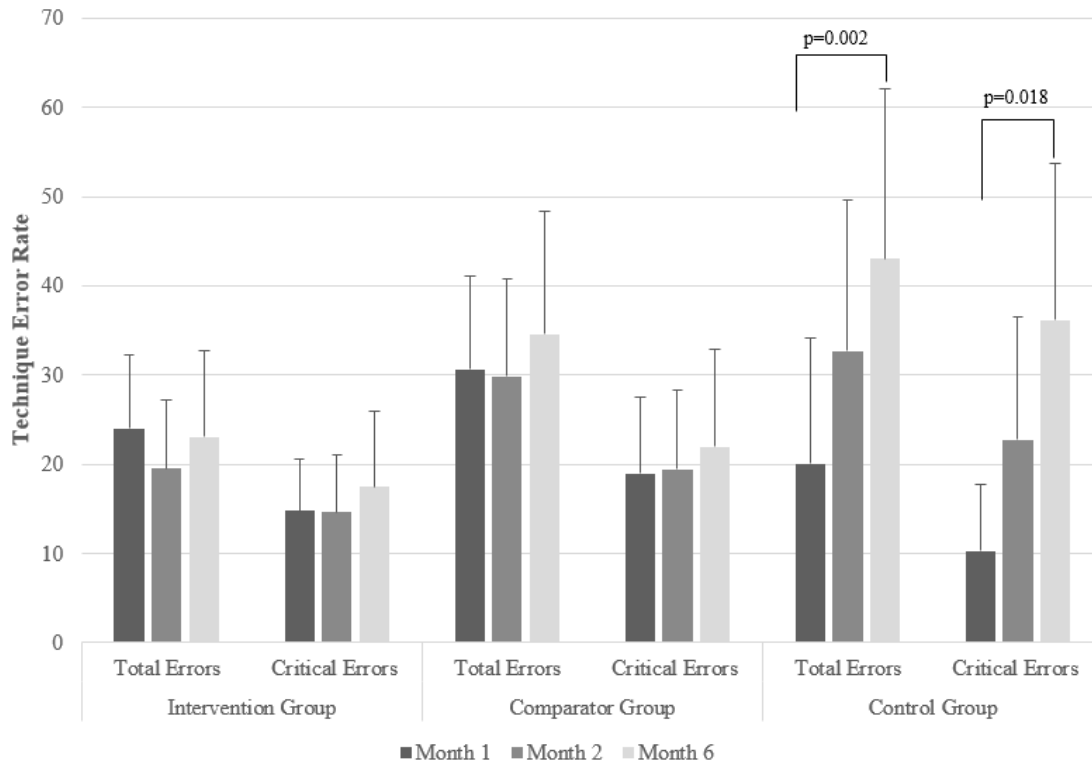


Figure 5-16 Technique errors classified as total and critical errors and sorted by randomisation group over time

Whilst the rate of total and critical errors decreased more in the intervention group than the comparator group between month 1 and month 2, no statistically significant differences in the technique error rates were observed between groups over time. The decreases in technique error rate observed at month 2 for the intervention and comparator groups were not sustained over the six-month study period. The only within group differences that reached statistical significance were the increase in both total and critical errors between month 1 and month 6 in the control group.

5.6.3.3 Inhaler technique errors observed on analysis of audio files

Once all bookmarking files were removed from the audio data a total of 19,033 audio files were available for analysis. Analysis of the audio data identified that 12,335 (64.8%) of the audio recordings followed the correct Diskus™ inhaler technique. 5,588 files were noted as being associated with an error, of these files 39 had no error type reported leaving 5,549 (29.15%) of files reporting an error which was possible to classify as a particular error type. For 1,071 (5.63%) files, no blister or inhalation was detected in the audio file meaning either that the patient opened their inhaler and did not use it or there was a processing error associated with the file.

The most common errors observed were lack of an audible inhalation, multiple inhalations and lack of blistering medication prior to inhalation, accounting for 44.76%, 26.26% and 19.12% of all errors respectively. Errors within the audio files as identified by the INCA algorithm are outlined in Table 5.5.

Table 5-5: Inhaler technique errors as classified by INCA algorithm

Instruction	<i>Audio Error</i>	<i>Frequency (% of all files)</i>	<i>Frequency (% of all errors)</i>
BLISTER	No blister, inhale detected	1,061 (5.57)	1,061 (19.12)
	Multiple blisters	172 (0.90)	172 (3.10)
	Dose Dumping	36 (0.19)	36 (0.65)
BREATHE OUT DEEPLY AWAY FROM INHALER	Exhaling into the mouthpiece	261 (1.37)	261 (4.70)
INHALE DEEPLY	Blister Present, No Inhale	2,484 (13.05)	2,484 (44.76)
HOLD BREATH FOR > 5 SEC	Multiple inhalations	1,457 (7.66)	1,457 (26.26)
	Multiple blisters + multiple inhalations	78 (0.41)	78 (1.41)

Human over-readers also reviewed the audio files. Moderate agreement [470] was observed for the classification of the audio file as being associated with an error or not ($\kappa=0.53$, $p<0.0005$) and moderate agreement between the original (algorithm) opinion and the final (human over-reader) was observed ($\kappa=0.43$, $p<0.0005$). Human over-reading changed the error type classification for a large number of files. Post over-reading 4,802 files were noted as being associated with an error, of these files 66 had no error type reported leaving 4,736 (24.88%) of files reporting an error which was possible to classify as a particular error type. In this analysis 507 (2.66%) files were classified as having no blister or inhalation detected.

The most common errors observed post human over-reading were multiple inhalations, exhaling into the mouth piece and lack of an audible inhalation, accounting for 32.57%, 29.8% and 27.84% of all errors respectively. With human over-reading it was possible to further classify the lack of audible inhalation error type into “blister present, no inhalation detected” (13.35% of all errors) and “Low PIFR <35L/min” (14.49% of all errors). Errors within the audio files as classified by the human over-readers are outlined in Table 5.6

Table 5-6: Inhaler technique errors as classified by human over-readers

Instruction	<i>Audio Error</i>	<i>Frequency (% of all files)</i>	<i>Frequency (% of all errors)</i>
BLISTER	No blister, inhale detected	213 (1.12)	213 (4.44)
	Multiple blisters	142 (0.75)	142 (3.02)
	Dose Dumping	10 (0.05)	10 (0.21)
BREATHE OUT DEEPLY AWAY FROM INHALER	Exhaling into the mouthpiece	1,431 (7.52)	1,431 (29.8)
INHALE DEEPLY	Blister Present, No Inhale	641 (3.37)	641 (13.35)
	Low PIFR (<35 L/min)	696 (3.66)	696 (14.49)
HOLD BREATH FOR > 5 SEC	Multiple inhalations	1,564 (8.22)	1,564 (32.57)
	Multiple blisters + multiple inhalations	77 (0.40)	77 (1.60)

5.6.4 Clinical outcomes

5.6.4.1 Rescue medication usage

The mean number of salbutamol inhalers dispensed in the six months pre-study enrolment, during the study and during the six-month period post study completion were analysed for all participants. No significant difference in refills obtained was observed between the groups for any period. Looking at within group differences in refill rate no significant differences were seen in reliever usage pre and post study.

Table 5-7 Salbutamol using pre, during and post study compared across the randomisation groups

<i>Group</i>	Canisters Pre Study	Canisters During Study	Canisters Post Study
	Mean ± SD (range)	Mean ± SD (range)	Mean ± SD (range)
Intervention	2.1±2.5 (0-8)	1.4±2.0 (0-7)	1.7±2.3 (0-7)
Comparator	2.1±2.3 (0-7)	1.6±2.2 (0-7)	1.8±2.3 (0-7)
Control	2.8±3.0 (0-8)	2.2±2.4 (0-7)	2.0±2.4 (0-7)

Mean number of courses of antibiotics and steroids were compared within and between groups for all participants and for those who completed all study visits. Comparator and control group participants had a greater mean number of antibiotic and steroid courses during the study period than those in the intervention group but the between group differences were not significant. No significant differences in the rates of antibiotic or steroid use pre or post enrolment were observed.

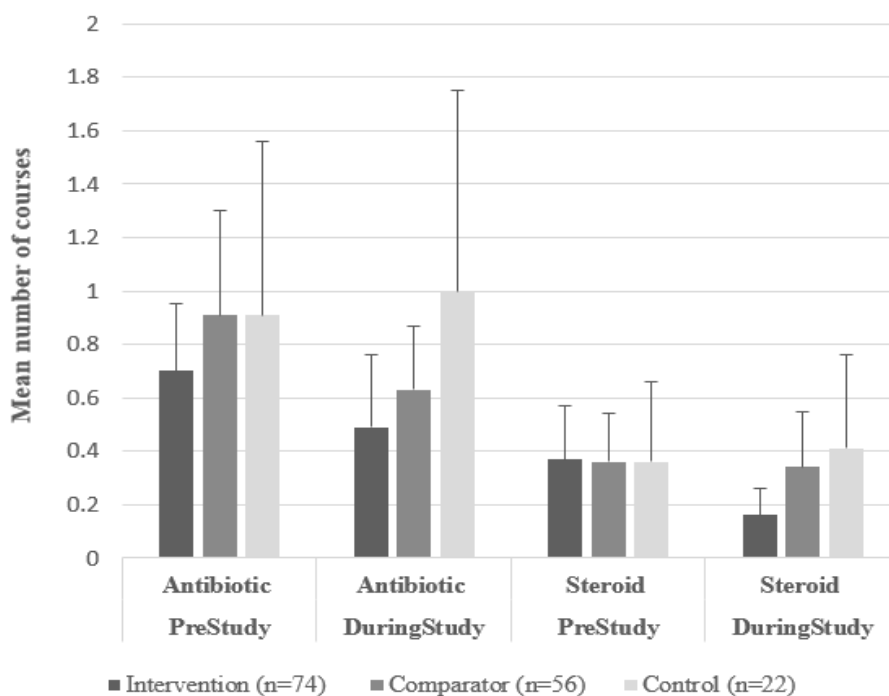


Figure 5-17 Mean number of antibiotic and steroid courses pre and during study classified by randomisation group for all participants

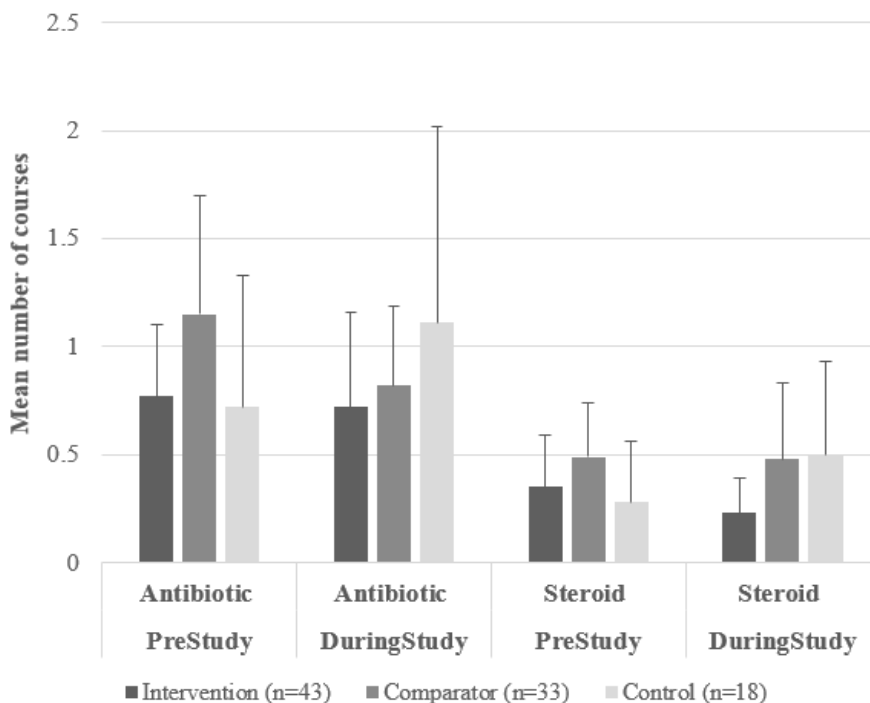


Figure 5-18 Mean number of antibiotic and steroid courses pre and during study classified by randomisation group for participants who completed the study

5.6.4.2 Patient reported symptoms

Participants in the intervention and comparator groups were asked to record daily symptoms in their respiratory diary. A total of 57 diaries were returned, 29 from intervention participants (39.2% return) and 22 from participants in the comparator group (39.3% return).

Number of days with cough

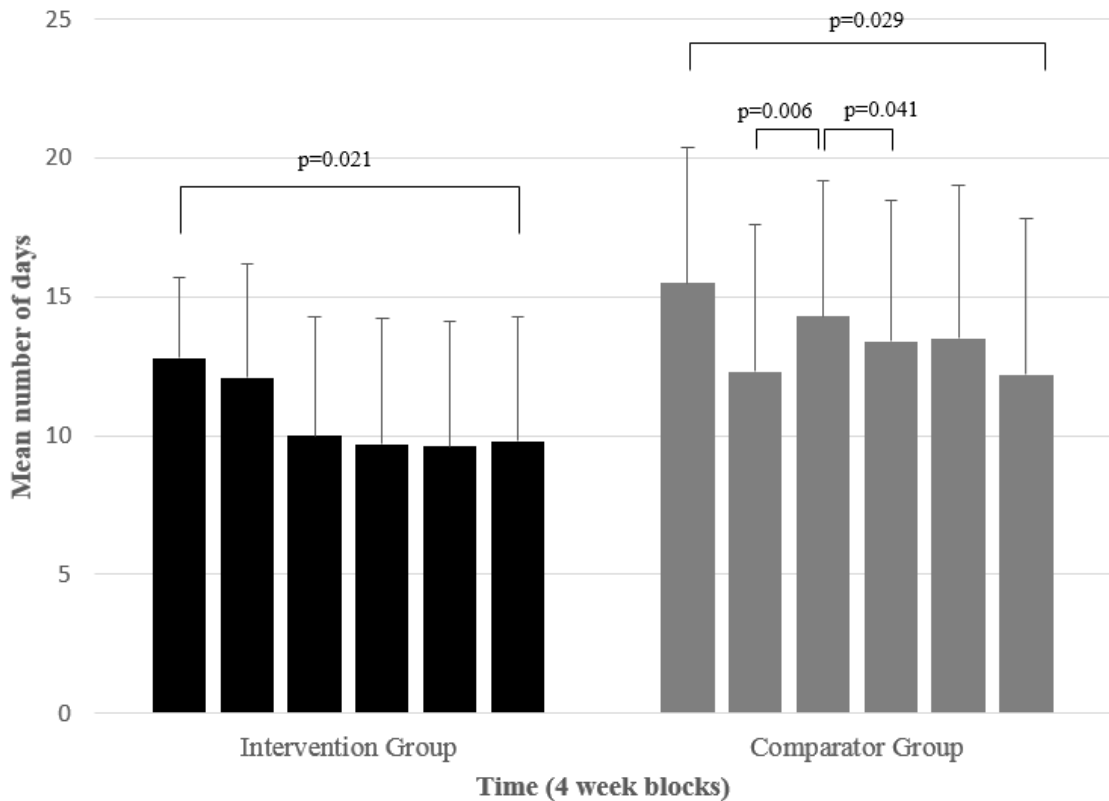


Figure 5-19 Mean number of days with cough per four-week block by randomisation group

The mean number of days where cough was reported as a symptom was highest in the first four-week block for participants in both the intervention (mean number of days = 12.76 ± 10.44) and comparator group (mean number of days = 15.45 ± 11.06). The mean number of days when cough was reported decreased significantly between block one and block six for both groups (intervention $p=0.021$, comparator $p=0.029$). No statistically significant between group differences in the mean number of days with cough were observed for any of the six four-week blocks.

Number of days with shortness of breath

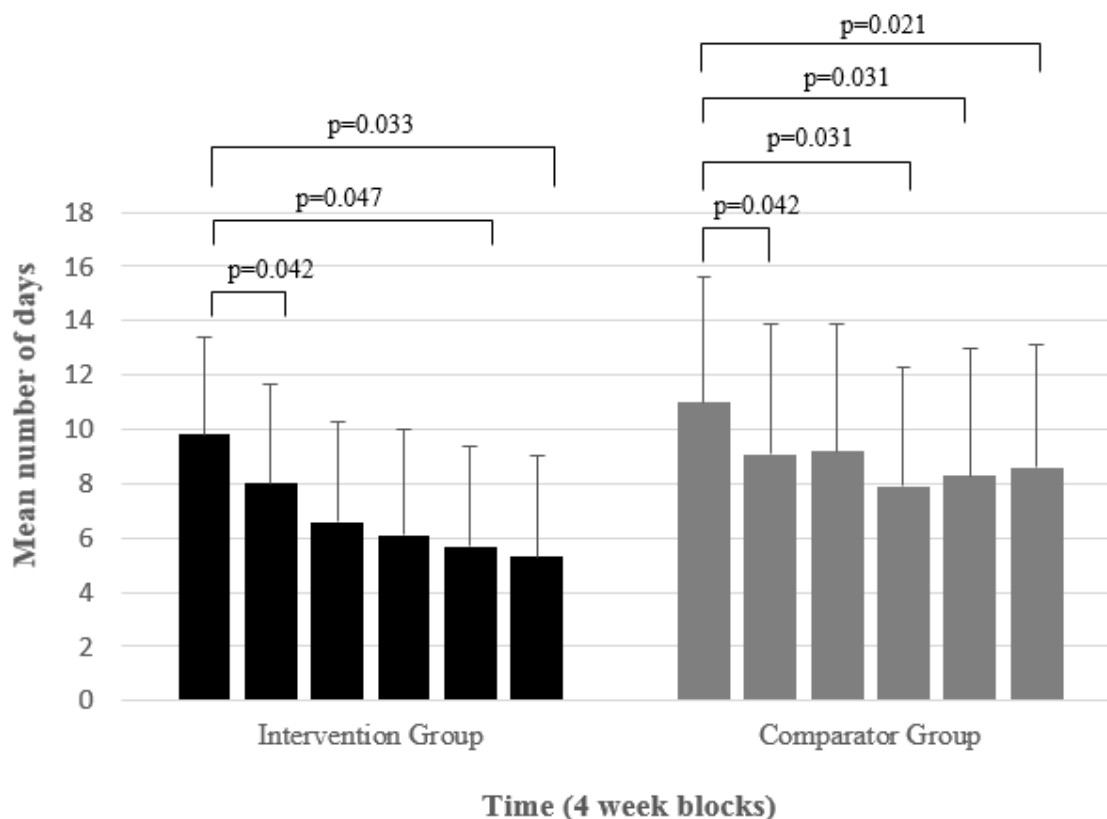


Figure 5-20 Mean number of days with shortness per four-week block by randomisation group

The mean number of days where shortness of breath was reported as a symptom was highest in the first four-week block for participants in both the intervention (mean number of days = 9.75 ± 9.68) and comparator groups (mean number of days = 11.00 ± 10.40). The mean number of days when shortness of breath was reported decreased significantly between block one and block two ($p=0.042$), five ($p=0.047$) and six ($p=0.033$) for participants in the intervention group. For participants in the comparator group there were statistically significant differences between block one and block two ($p=0.042$), four ($p=0.015$), five ($p=0.015$) and six ($p=0.031$). No statistically significant between group differences in the mean number of days with shortness of breath were observed for any of the six four-week blocks.

Number of days with wheeze

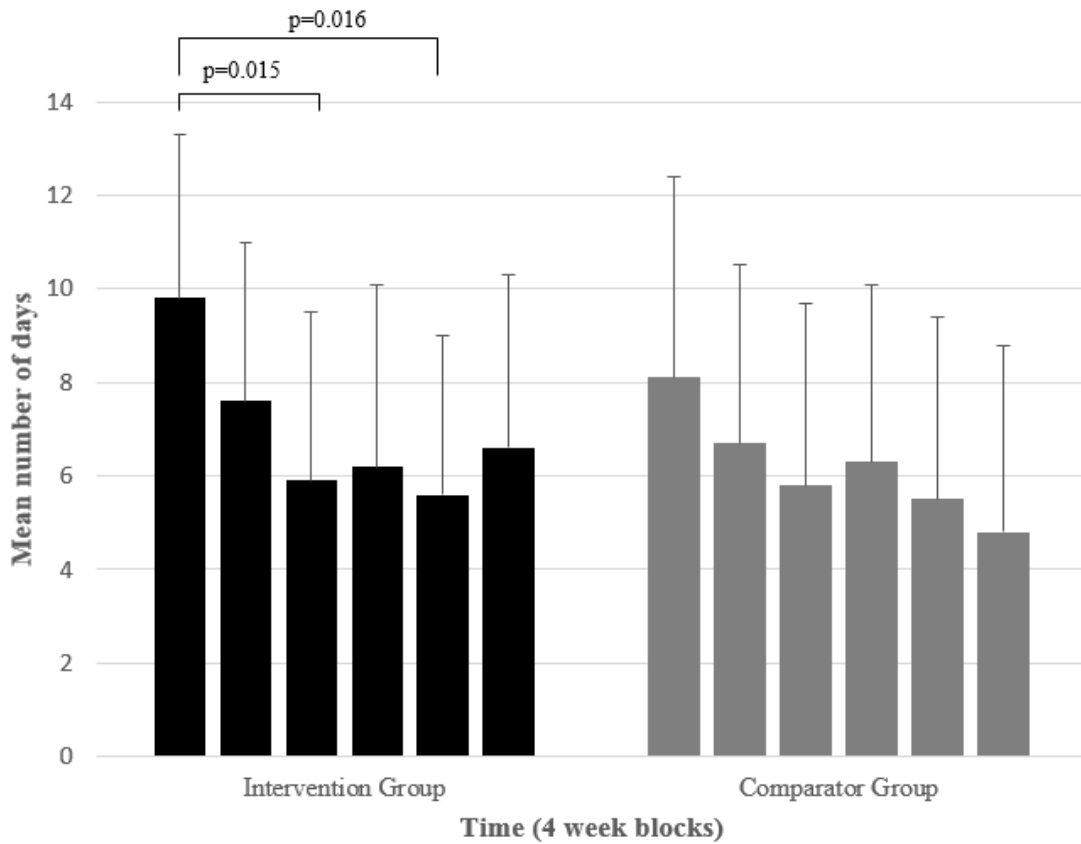


Figure 5-21 Mean number of days with wheeze per four-week block by randomisation group

The mean number of days where wheeze was reported as a symptom was highest in the first four-week block for participants in both the intervention (mean number of days = 9.79 ± 9.38) and comparator group (mean number of days = 8.14 ± 9.64). The mean number of days when wheeze was reported decreased significantly between block one and block three ($p=0.015$) and between block one and block five ($p=0.016$) for participants in the intervention group. For participants in the comparator group there were no statistically significant within group differences over time. No statistically significant between group differences in the mean number of days with wheeze were observed for any of the six four-week blocks.

Number of days with nocturnal symptoms

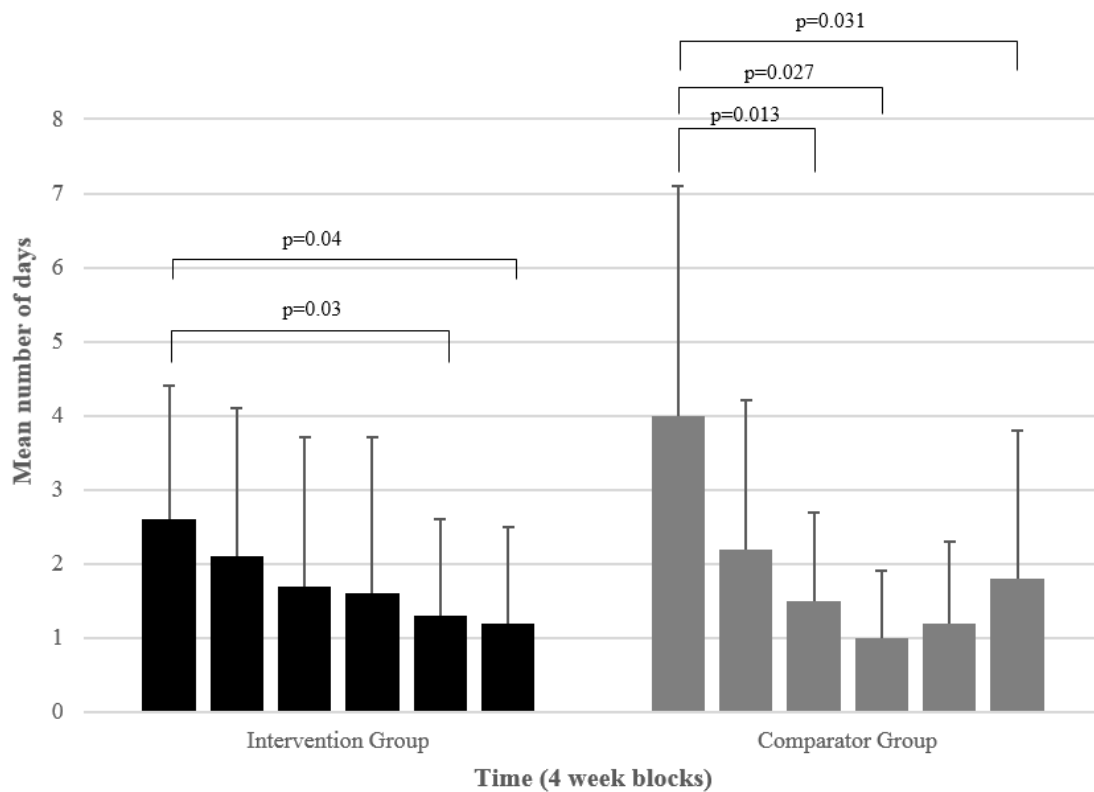


Figure 5-22 Mean number of days with nocturnal symptoms per four-week block by randomisation group

The mean number of days where nocturnal symptoms were reported as a symptom was highest in the first four-week block for participants in both the intervention (mean number of days = 2.76 ± 4.77) and comparator groups (mean number of days = 4.00 ± 6.92). The mean number of days when nocturnal symptoms were reported decreased significantly between block one and block five ($p=0.03$) and between block one and block six ($p=0.04$) for participants in the intervention group. For participants in the comparator group there were statistically significant differences between block one and block three ($p=0.013$), four ($p=0.027$) and six ($p=0.031$). No statistically significant between group differences in the mean number of days where nocturnal symptoms were reported were observed for any of the six four-week blocks.

5.6.4.3 Quality of life

In a per protocol analysis mean total SGRQ scores of 30.73 ± 15.52 (range 159-67.57), 32.66 ± 19.02 (4.31-84.21) and 27.42 ± 16.88 (4.69-59.27) were observed for participants in the intervention, comparator and control groups respectively. The SGRQ score decreased over time for participants in the intervention group and comparator group with statistically significant within group differences shown in Figure 5.23. A decrease in SGRQ score greater than the MCID of 4 units was observed when comparing month 1 to month 3 and month 1 to month 5 for both the intervention (-5.34 ± 11.79 and -6.01 ± 13.56) and comparator groups (-5.72 ± 10.80 and -4.66 ± 11.41).

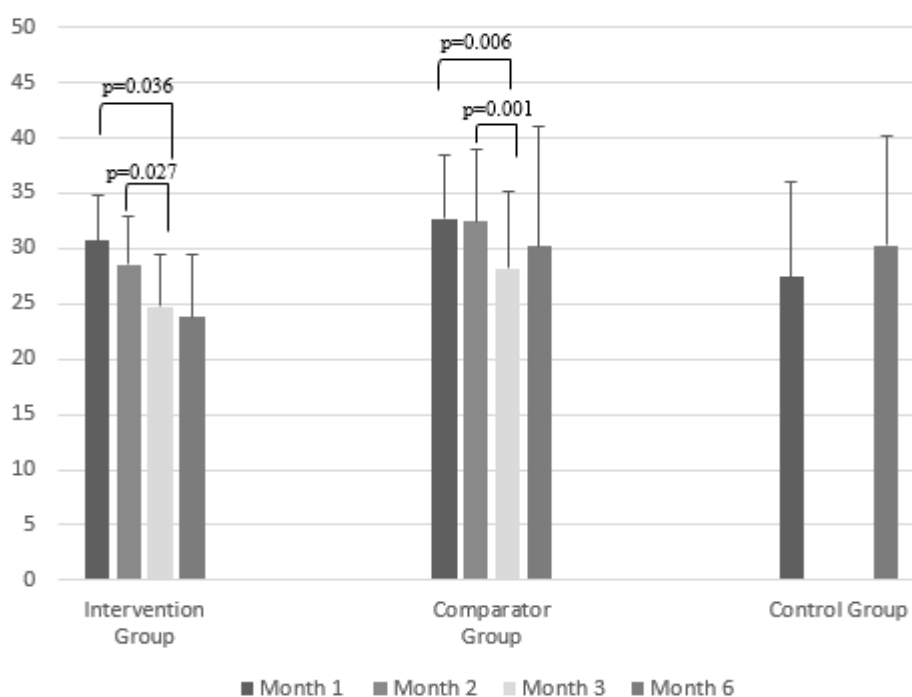


Figure 5-23: Mean SGRQ total scores per group across study visits

Decreases in the scores for the Symptom, Activity and Impact components of the SGRQ showed a general pattern of decreasing over time in both intervention and comparator participants. No statistically significant between group differences were observed for any of the domains at any time point. Compared to baseline, symptoms in the intervention group were lower at month 3 ($p=0.048$) and month 5 ($p=0.021$). The impact score for intervention patients was lower at month 3 than at baseline line (12.89 ± 13.18 versus 21.81 ± 16.5 ; $p=0.012$). For comparator patients, the month 3 and month 5 impact scores were significantly lower than baseline ($p=0.004$ and $p=0.017$ respectively).

5.6.4.4 Breathing related goal

Breathing related goals were recorded for 128 participants (84.21%). Thematic analysis of goal content mapped goals to 13 breathing related goal domains as outlined in Table 5.8. The majority of participants (112, 87.5% of participants with recorded goals) had a goal that mapped to a single domain; the remainder had more compound goals that could be mapped to two or more domains. No goals were classed as specific as none of them contained an inbuilt strategy for goal attainment, specific actions to be carried out or specific timeframes for achievement. 75 participants set what were classed as moderately specific goals where a specific reference point for improvement/achievement could be identified, with the remainder, 53 participants (41.4%), setting unspecific goals with abstract outcomes and/or ambiguous reference points for improvement.

Table 5-8: Goal domains for participants' self-reported breathing related goal

Goal domain	<i>Example</i>	<i>Goals set, n (% of participants)</i>
Activity	“Would like to be able to paint the flat” “Playing with grandchildren in the garden”	8 (7.14)
Adherence	“To discover if the use of my inhaler is optimal” “Symptoms worsen quickly when miss a few days doses”	5 (3.91)
Allergy/trigger management	“Cutting grass” “Solid pollution causes breathing irritation”	2 (1.56)
Anxiety/stress control	“Worried about breathing deteriorating as I age” “Dread going up the stairs at night”	5 (3.91)
Avoidance of other illness	“To suffer less from infections” “Prevent chest infections”	6 (4.69)
Exercise	“Get fitter” “To be more active”	25 (22.32)
Exercise tolerance	“Walking the dog without being breathless” “Breathing currently interfering with golfing”	39 (30.47)
Medication reduction	“Not to have to use Ventolin regularly” “Like to be off inhaler altogether”	5 (3.91)
Overall health and energy	“Would like to have more energy” “Feeling less tired”	16 (12.5)
School/work	“Return to work” “Manual work for long periods of time”	2 (1.56)
Symptom	“I would like to be less wheezy in the morning” “Not to feel congestion in the chest”	25 (19.53)
Other	“Most areas” “To be able to have a normal life”	2 (1.56)
None	“Nothing comes to mind, currently not affecting any aspect of life”	5 (3.91)

Changes in the mean improvement score for breathing related goals are shown in Figure 5.24. Statistically significant differences in the mean improvement score for the PP population were seen between month 2 and month 3 ($p < 0.005$), month two and month six ($p < 0.005$) and between month three and month six ($p = 0.038$) for participants in the intervention group. For participants in the control group the increase in improvement score from month two to month three and from month three to month six ($p = 0.033$ and $p = 0.024$ respectively) were significant. A statistically significant between group difference in mean improvement scores for the intervention and control groups was seen at month three (PP analysis, $p = 0.032$, ITT analysis, $p = 0.032$) and at month six (PP analysis, $p = 0.021$, ITT analysis, $p = 0.022$).

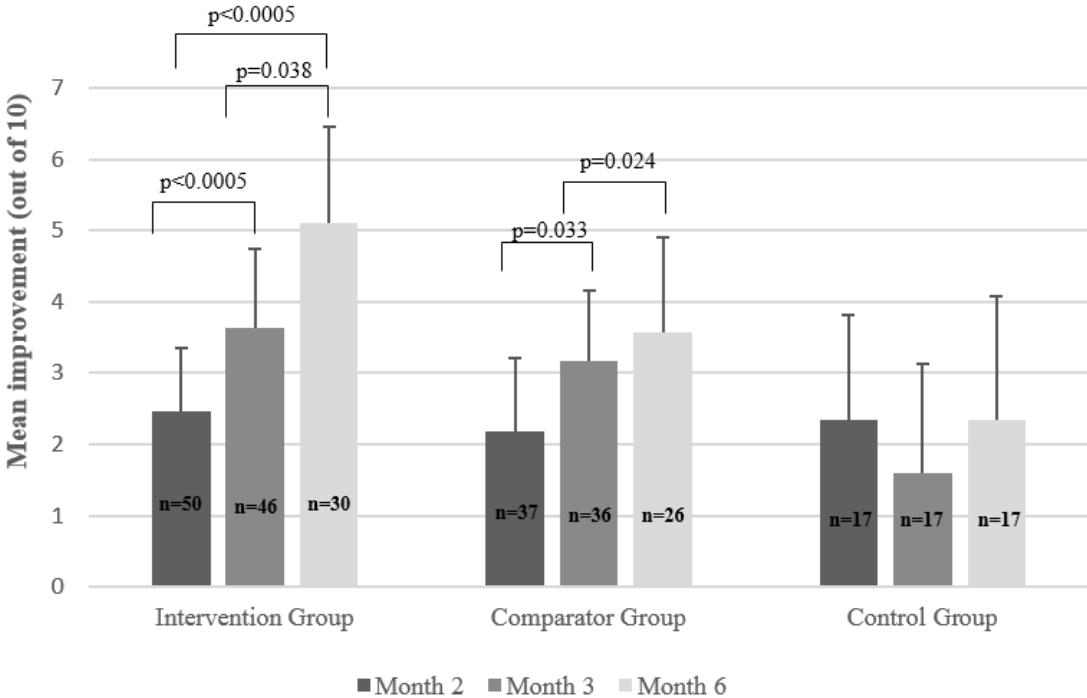


Figure 5-24: Mean breathing related goal improvement score over time by randomisation group

5.7 DISCUSSION

The results of this study show that a community pharmacist delivered intervention combining monitored adherence with repeated personalised education is feasible and can improve inhaler technique and adherence in patients with respiratory disease. Participants receiving feedback on their adherence as measured by an electronic monitor demonstrated improved inhaler technique and adherence which was maintained over time. However, baseline differences in adherence between study groups, difficulties in recruiting a sample of sufficient size and a high drop-out rate mean that it is difficult to fully determine the contribution of the intervention to improved adherence.

5.7.1 Effect of the intervention

Considering the primary outcome, a comparison of the rate of actual adherence, a significantly higher rate of actual adherence was seen in the intervention group versus the comparator group during months two and six in both the intention to treat and per protocol analyses. For both the per protocol population and the more conservative ITT both adherence in month 1 and randomisation group were significant predictors of adherence in month 2 but this was not the case in month 6 where only month 1 adherence was of significance. Whilst the mean adherence increased throughout the study for the intervention group and decreased for the comparator group there were no significant between group differences observed in the rate of change in actual adherence over time. The comparator in this study reflects current best practice as opposed to usual care. The fact that there were statistically significant differences between intervention and control participants (who received no education or feedback) points to a benefit of the INCA™ intervention over the usual care currently provided in the community pharmacy setting.

The intervention was successful in increasing the proportion of adherent patients post feedback and education. In common with other adherence studies a cut off of 80% was used to classify patients as adherent. Given that improving adherence to fluticasone propionate to > 50% is likely to have major clinical benefit in the long term management of asthma [471] it is possible that this cut off underestimated the effect of the intervention.

Improvements were noted in reported quality of life scores and for participants who completed the study diary there was a suggestive trend of improvement in the level of daily symptoms such as cough and shortness of breath although these were not statistically significant. Breathing related goal themes were derived inductively from the responses provided by participants and

progress towards these goals was observed for participants in the intervention and comparator groups over time.

The higher rate of actual adherence observed in the intervention group in the first month pre-intervention is suggestive of bias of some kind. One possibility is that pharmacists in the intervention group invited more adherent patients to take part in the study. Whilst a statistically significant difference in PDC between the intervention and comparator groups pre study enrolment was observed this was not something the pharmacists would have been aware of when approaching patients to take part in the study. Pharmacists were trained to approach, in consecutive order, all patients with a valid prescription for a salmeterol/fluticasone Diskus® inhaler and invite them to take part in the study. Due to the nature of the study design randomisation occurred at the level of the pharmacy and thus participants were aware of the study group they would be assigned to prior to enrolment. Thus, it is possible that patients who were more adherent to begin with were more likely to agree to participation in the intervention arm of the study.

Change in participant behaviour as a result of monitoring with the INCA™ device is another possibility. Whilst a one-month lead in was incorporated into the study design to minimise any potential Hawthorne effect it is possible that participants in the intervention group modified their behaviour to a greater extent than any other group due to the fact that they knew they would be discussing the results of any observation with the pharmacist at the end of the observation month. The possibility of this type of behaviour change has been identified previously [472] and observed in patients for whom adherence to inhaled corticosteroids measured by an electronic monitor [473] suggesting that this is not a unique phenomenon.

5.7.2 Observed levels of adherence

In common with other observational studies in primary care [474, 475], suboptimal levels of adherence were observed in all groups throughout the study period. This is reflective of the real world setting in which the study took place and supports previous observations that patients in research [471] settings often exhibit higher levels of adherence than community dwelling patients.

Previous studies using electronic monitors to measure adherence to inhaled corticosteroid treatment in asthmatic populations have demonstrated adherence levels of between 21% [474]

and 66% [471] with the mean adherence pooled across studies estimated at 53.27% [476] in non- intervention participants. This is in line with attempted adherence observed in control patients in our sample. Of note is that adherence as measured by the dose counter and medication records was much higher and that defined as true actual adherence combining both timing and technique adherence was lower than 35% throughout the study period. This demonstrates the variability of reported adherence levels by classification type; an important consideration when deciding how best to accurately determine adherence in patients. Thus, the results of this study show that errors in inhaler handling are common and more prevalent than is suggested by more common methods of adherence estimation such as calculation of the dose counter rate.

5.7.3 Comparisons with other studies and reviews

A number of electronic monitoring devices for inhalers have been developed [445, 448, 477, 478]. Studies with such devices have utilised electronic adherence trackers with in-built reminder alarms and tested the impact of the automated reminder system on patient adherence to their inhaled medication [471, 475, 479] but not all have involved the provision of feedback to patients. The results of those studies, involving tailored feedback from a healthcare professional based on adherence data as recorded via an electronic monitoring device for patients with asthma [474, 475, 480-482], have been collated in a recent Cochrane review [476]. Some of these studies involved childhood populations but overall results for adults and children were similar [476] and thus provide a reasonable comparator to the current study. Mean adherence of patients using electronic trackers or reminders was found to be 20% better than those in the control group (Mean difference 19.86, 95% CI; 14.47 – 25.26, n=555 participants across 6 studies of moderate quality) [476]. This is similar to the magnitude of the difference in attempted adherence observed between intervention and control group participants post intervention in this study. Whilst this difference was not found to be significant, a statistically significant difference in actual adherence between intervention and control participants post intervention was observed (31.2 ± 30.4 vs. 61.0 ± 26.4 ; $p < 0.0005$).

Subgroup analysis in the Cochrane review provided weak evidence that inhaler reminders combined with individual feedback may be more effective than reminders alone [476]. A similar observation pointing to the provision of feedback to patients on their electronically compiled dosing histories as the biggest factor influencing adherence has been observed in a meta-analysis of 79 randomized clinical trials utilising electronic monitors to improve adherence to chronic medication [483]. Given that statistically significant differences in

adherence were only observed between intervention and control participants in the current study there is a suggestion that the individualised feedback element of the INCA™ intervention is of importance.

Studies utilising electronic monitoring for the measurement of adherence with oral medications for the treatment of chronic diseases have shown different general patterns of adherence ranging from “perfect” adherence (taking all doses at the correct time) through occasional timing irregularity, sporadic or regular dose holidays (omission of medication on three or more sequential days [484]) to non-adherence where few or no doses are taken [472, 485, 486]. In common with these studies, different patterns of adherence behaviour were observed for patients using the INCA™ device further demonstrating that non-adherence is multi-faceted in nature. Future work with the INCA device will seek to explore whether classification of patient by adherence pattern exhibited can allow for targeting of adherence interventions to better meet the needs of individual patients.

5.7.4 Proposed clinical utility of the INCA™ device

No single “gold standard” intervention targeting improved adherence has been identified [487]. Both single and multi-component interventions have demonstrated effectiveness [487-489] but this is usually modest in size and can be expensive. Coupled with the fact that non-adherence to medication is a multidimensional one, involving both intentional and un-intentional non-adherence, it could be argued that the limited effectiveness of adherence interventions reported to date may be due to a lack of insight into the underlying reasons for non-adherence in the target population. The results of this study show that the INCA™ device can support in identifying both intentional and unintentional patterns of adherence, a finding that has been replicated in other studies [460, 490]. Given the importance of health care professionals being able to distinguish between the type of non-adherent behaviour when choosing the most appropriate adherence support intervention for their patients [472, 491], this is an important feature of the device and one that points to its clinical utility in the care of patients with respiratory disease.

It is important for clinicians to be able to objectively assess adherence before increasing therapy [432]. The difference between attempted and actual adherence highlights the level of technique errors contributing to sub-optimal adherence. Lack of instruction on inhaler technique by health care professionals is associated with inhaler technique errors something that is not uncommon in

clinical practice [421]. Errors in inhaler technique are typically assessed and corrected with reference to standardised inhaler technique checklists [421] but such checklists are a point prevalence assessment of technique and do not address errors with day to day use. Given that the mean technique error rate did not exceed 35% for intervention or comparator participants at any point in this study it seems reasonable to suggest that patients demonstrate a variable ability to correctly use their inhaler device. Thus, inhaler technique education would benefit from being conducted with reference to actual errors observed in practice over an extended period of time; something that can be facilitated with use of the INCA device TM. Given the moderate correlation between the algorithm and human over-reader error classification, future work will need to be done on refining the algorithm and error classification in order to maximise this potential benefit.

Arguably correction of technique errors could be considered somewhat easier to address than other forms of non-adherence such as non-intentional forgetfulness or indeed intentional avoidance of medication taking. However identification of inspiratory errors is critical given that failure to breathe in deeply and rapidly when using a DPI can lead to a suboptimal inspiratory flow which in turn results in limited or no treatment benefit [492]. It is not always possible to correct such errors with education [493] and for such patients a change to an alternate inhaler device may be preferable. This has important clinical benefit for individual patients but also, in the context of significant government spending on respiratory medications (almost 10% of national drug spending in Ireland) schemes (84), it has the potential to support more rational allocation of limited healthcare resources.

Actual adherence as measured with the INCA device was much lower than that observed via the dose counter which has implications for clinical trials of inhaled medication. Non-adherence to inhaled medication in such trials has the potential to underestimate efficacy, overestimate dosing requirements and distort pharmaco-economic analyses, all of which may result in erroneous conclusions [494]. Utilising electronic monitoring devices such as the INCATM device to more accurately estimate true adherence to inhaled medication has the ability to supported improved analysis could thus be considered.

5.7.5 The role of the pharmacist in management of chronic respiratory disease

Inhaler education studies conducted in the pharmacy setting have demonstrated that pharmacists can support improved outcomes for asthma patients under their care with significant

improvements in inhaler technique [435, 438, 495, 496], adherence [435, 438, 495], quality of life [156, 188, 189, 437] and asthma control [435, 438, 495]. Pharmacist interventions to support improved management of COPD have not been studied as extensively as those for asthmatic patients but they have shown improved inhaler technique [135, 201, 434] and adherence to inhaled medication [201] post pharmacist intervention.

There are some notable differences in the results obtained in the current study and those previously observed in community pharmacy practice. The proportion of patients achieving good actual adherence post intervention in this study (month 2: 0.36; 95% CI 0.25 - 0.49) is much lower than that reported for other pharmacy studies. Giraud et al [495] reported a 0.66 post intervention adherence proportion and Garcia-Cardenas et al [438] 0.78 but adherence in both studies was based on patient self-report which has been shown to be unreliable [439, 440]. Mean percentage of technique errors post intervention of over 90% in intervention patients was observed in multiple studies [159, 201, 496]. Technique errors in all these studies were measured with reference to an inhaler technique checklist similar to the IPS used in this study and indeed similarly high levels of inhaler technique mastery were seen with the IPS. However, error classification with the INCA™ device revealed a higher level of inhaler mishandling, something which has not been identified in pharmacy studies to date.

Pharmacists are increasingly involved in comprehensive medication management [497]. In order to optimise clinical outcomes for their shared patients close collaboration between pharmacists and doctors is likely to be required [498]. Provision of high quality clinical recommendations that improve patient outcomes is important in establishing trust [499], a key component of successful pharmacist/doctor collaboration [498, 500]. Collecting objective longitudinal information on inhaler adherence may support the formulation by the pharmacist of such recommendations thus supporting the collaborative clinical decision-making process. Analysis of objective adherence as measured by the INCA device has the potential to support the inter-professional decision making for individual patients by potentially distinguishing between patients who would benefit from further interventions to promote adherence as opposed to those in whom therapy adjustment or change of inhaler device may be more appropriate.

Enabling the patient with asthma and/or COPD to gain the confidence, skills and knowledge to support the management of their condition in partnership with their health care provider is a cornerstone of effective care [432, 501]. The ability to successfully engage with self-management will vary between individuals, and may be dependent on factors such as literacy,

numeracy, beliefs about their condition and medications and desire for autonomy[432]. However, for the motivated patient providing them with a print-out of the inhaler technique and adherence as recorded by the INCA™ device and discussing strategies for improvement has the potential to empower the patient to take control of their medication management in a more proactive way. For health care professionals gaining insight into the day to day medication habits of patients outside of the clinic setting has benefits. Understanding healthcare professionals can support enhanced adherence with empathetic counselling [502] and thus improving understanding of real life challenges to inhaler mastery may lead to improved care.

5.7.6 Strengths of the study

The study has a number of strengths. It is the first community pharmacy-based study to use a technology that objectively assesses appropriate use of inhalers both in terms of technique of use as well as time of use, permitting longitudinal evaluation of patients' habitual performance when not under direct visual observation. This technology incorporates a novel electronic device, automated algorithms and feedback tools including graphical representations of adherence, facilitating personalised feedback provided by the pharmacist.

The study employed a prospective design and enrolled community dwelling participants meaning it is reflective of "real world" patients. The inclusion of a usual care group allowed for the effects of greater pharmacist/patient engagement to be observed and also controlled for potential temporal improvements in asthma symptoms.

Pharmacists were not paid to deliver the intervention and funding to conduct the study was derived from non-commercial sources.

5.7.7 Limitations of the study

Limitations of the study include the fact that target recruitment was not met thus potentially increasing the risk of Type II statistical error. This was the first study of its kind in terms of design and scale to be conducted in the community pharmacy setting in Ireland and as such the pharmacists involved were unfamiliar with conducting a clinical trial and inexperienced in study recruitment. Whilst training was provided on effective recruitment strategies and support was

provided to encourage teams to reach target recruitment, this inexperience may have contributed to sub-optimal recruitment.

Attrition bias cannot be discounted as whilst the rate of drop out was similar in both the intervention and comparator groups the participants who dropped out of the intervention group post visit 2 exhibited a lower mean adherence score at visit 2 that was close to statistically significant (51.6 ± 29.2 versus 65.6 ± 24.1 , $p=0.057$) than those who completed all three study visits meaning that the effect size in the per protocol analysis may have been somewhat overestimated. However, a more conservative ITT analysis was also conducted to mitigate against this effect.

The high drop-out rate in the second half of the study means it is difficult to determine the effect of the INCA™ device on actual adherence over the longer term. The drop-out rate whilst high (38.15%), is not uncommon for studies conducted in the community pharmacy setting [202, 503]. The timeline of the study – 6 months - is a relatively long time in a busy pharmacy. Patients are not used to taking part in clinical trials in the community pharmacy setting in Ireland and thus the idea of making an appointment to attend study visits, even where this coincided with a visit to collect their medication, was an unfamiliar concept for many patients. A number of patients stated their reason for withdrawing from the study was related to not having sufficient time to attend for study visits.

Patients with asthma and/or COPD were eligible to join the study meaning there is a lack of sample homogeneity with respect to clinical condition. Stratification by condition at point of analysis was considered but due to the small sample size and the large amount of missing data with respect to clinical diagnosis the analysis lacked sufficient power to make valuable inferences. The absence of spirometric confirmation of patients' respiratory condition could also be considered a limitation but as pharmacists do not have access to such information in practice it is reflective of the setting and the pragmatic nature of the trial.

Adapted inhalers dispensed to study participants were provided free of charge and thus there was a potential for participation to be motivated by monetary considerations. Efforts to minimise such motivation included not telling patients that medication would be provided free of charge until after enrolment consent was provided. The anticipated effect was not as significant in practice with 37% of patients entitled to subsidised medication and paying a nominal €2.50 monthly fee for their non-adapted inhalers pre study enrolment and thus unlikely to associate the study with financial reward.

5.7.8 Future direction

Participants in this study did not have to pay for the intervention undertaken. The cost of delivering the intervention was supported through research funding, a source of funding that would not be available if the intervention were to be delivered in clinical practice on an ongoing basis. It is not clear whether patients and/or payers (health insurers or state) would be willing to pay for such an intervention in practice but it is likely that the comparative costs of the intervention versus costs of non-adherence would form the basis of any such decision. Future studies on the utility of the INCA™ device in clinical practice may benefit from the addition of a pharmacoeconomic analysis.

Variability between the errors detected by the INCA algorithm and those classified by human over-readers was observed. In this study, the opinion of the human over-reader had the ability to over-ride the INCA algorithm where disagreement between the two classifications was observed. If the INCA device was to be used in clinical practice a reliable, automated algorithm would be essential and as a result further work on refining the algorithm is currently underway (McNulty J, Reilly RB *et al.* Personal communication: Objective Assessment of Inhaler Adherence within Community Pharmacy Respiratory Patients using Audio-Based Classification: manuscript submitted for review on June 15, 2017).

The INCA™ device used in this study was developed for use with a salmeterol/fluticasone Diskus™ inhaler (Seretide, GlaxoSmithKline (Ireland) Limited). Whilst this medication is still commonly prescribed in Ireland [504] this may not be the situation in other countries. Additionally, as newer inhaler therapies and technologies emerge its use may decline into the future. The development of other INCA™ type devices for use with other inhalers is something that warrants consideration and further research.

Prediction of the risk of future exacerbations is a key issue in respiratory disease management [505]. Linking patterns of adherence to exacerbation profiles of participants has the potential to support the development of models that may help predict the risk of future exacerbations. Further analysis of the INCA™ pharmacy data either alone or in combination with data derived from other studies employing this technology could support such modelling research.

Chapter 6: Summary and Reflection

6.1 INTRODUCTION TO THE CHAPTER

This thesis describes three clinical pharmacy services introduced in a community pharmacy chain setting in Ireland. The results of each intervention, discussion on how reflective the results are of previous research in the field and reflections on implications for practice are discussed in the individual chapters relating to the specific interventions. All the interventions relate to the delivery of clinical pharmacy services in the community pharmacy setting and as such a number of different themes in relation to the provision of such services in the chain setting in Ireland have been identified. What follows is a broader discussion on the overall findings and implications for practice.

6.2 EFFECTS OF THE INTERVENTIONS

6.2.1 Overall findings

The overall results from this thesis show that pharmacists working in the community can provide services designed to support the primary, secondary and tertiary prevention of disease and that these initiatives can be successful in terms of recruiting patients and improving health outcomes for patients enrolled on the programme(s).

The literature review provided insights into a range of clinical pharmacy services being delivered in the community pharmacy setting worldwide and showed that such services can have beneficial outcomes for people's health. The heterogeneity of studies retrieved in terms of services delivered and disease states targeted shows the broad scope of pharmacist delivered services worldwide but mean that a structured meta-analysis of the collated data was not possible.

The provision of a community pharmacy based smoking cessations service was discussed in chapter 3. This primary prevention initiative was successful in recruiting patients and supporting them in commencing a quit attempt. A 12-week CO verified abstinence rate of 5.52% was reported. Given the strong addictive properties of nicotine [506], the behavioural dependence associated with smoking [507], the fact that smokers typically require multiple attempts before successfully quitting [259] and the significant health benefits of cessation [261, 508], a 5.52% quit rate is welcome albeit somewhat lower than desirable.

In chapter 4, an ambulatory blood pressure monitoring service was described. This secondary prevention service was also successful in recruiting patients and a high level of GP referral was noted indicating a demand for the service in primary care in Ireland. This intervention was successful in identifying patients with hypertension who could benefit from commencement of antihypertensive treatment or adjustment of their previously prescribed medication. Through the use of a sophisticated blood pressure monitoring device, it was also possible to detect abnormal pulse patterns in patients undergoing 24-hour BP assessment and refer such patients for further investigation. Previously undetected atrial fibrillation was diagnosed in a subset of patients and coupled with the role of the service in detecting previously undiagnosed hypertension this service has the potential to be important in terms of stroke prevention in primary care, a national health priority [18].

The tertiary prevention initiative explored was a medication management initiative and this was described in chapter 5. The intervention in this case was focussed on improving inhaler usage both in terms of technique of use and adherence to prescribed dosing in patients with asthma and COPD. Significant differences in clinical and humanistic outcomes between intervention and usual care participants were observed. The differences between the INCA™ intervention and current best practice (physical demonstration of optimal technique by the pharmacist followed by demonstration of same by the participant until device mastery is achieved) were significant one month post intervention. These differences did not reach significance at six months meaning the effects of the intervention were not sustained over the longer term. The fact that differences between the intervention and usual care groups remained significant over time suggests that structured engagement with the pharmacist was an important factor in and of itself. The intervention was successful in improving inhaler adherence and technique in certain individuals but the high drop-out rate and lack of sustainability over the longer term highlights the challenges associated with a “one size fits all” medication management approach to chronic disease.

6.3 DELIVERY IN PRACTICE

6.3.1 Implementation of services

The focus of this thesis was on assessing the patient outcomes resulting from participation in clinical pharmacy interventions in the community setting as opposed to conducting a structured review of implementation models related to practice/organisational change. This is not to

downplay the importance of paying careful attention to such models as proper implementation is critical to the success of any such innovation [49]. It is also not to say that they were not considered in the design, development and delivery of the services described in the thesis, rather they were not the main focus of the research. That being said the level of patient and pharmacist engagement with the initiatives described give some insights into the success or otherwise of their implementation in practice.

Incomplete engagement with the initiative from the pharmacy teams was observed in the case of the Stop for Good service with 58 out of a potential 72 (80.6%) pharmacies recruiting patients to the service. There was variation too in the numbers of patients recruited per pharmacy with a median of 21 and an average of 23 patients ($SD \pm 12$, range 1-70) enrolled on the programme over the six-month period. This pattern of incomplete pharmacist engagement and variable patient recruitment was also observed in the INCA study. For the ABPM intervention, all pharmacies delivered at least one consultation but again there was considerable variability in patient recruitment (range 2-84 patients).

In the case of pharmacist engagement, a considerable body of evidence relating to the barriers and facilitators to service development in community pharmacy has been reported in the literature to date. Factors such as lack of time either on the part of the patient [509] or the pharmacist [509-515], inadequate staff resource [511, 513], lack of re-imburement [511, 514, 515], inadequate privacy in the pharmacy [512], insufficient training [512, 514] and lack of support from and/or acceptance by other health care professionals [513, 516] have been cited as barriers to implementation with good relationships with physicians [499, 517], having the correct pharmacy layout [517, 518], adequate resources [40, 517, 519], being remunerated for services provided [517], good communication and team work [40, 517, 520], patient demand [517, 520] and access to external support [40, 517, 521] noted as facilitators.

In the case of barriers, there is some debate as to whether these barriers are perceived or actual. Whilst no structured feedback on the views of pharmacists was collated as part of the interventions described, it is interesting to note that whilst engagement with the initiatives was variable it can still be considered high (77.8% of pharmacies delivering the INCA™ intervention, 80.6% of pharmacies conducting smoking cessation consultations and 100% of pharmacies in which an ABPM service was offered delivering the service). The service in which GP referral was most evident (ABPM) also had the highest rate of service delivery which may point to the importance of acceptance from other health care professionals. Lack of re-imburement was not a clear barrier as neither the smoking cessation service nor the INCA™

intervention resulted in payment for the pharmacy. Structured and comprehensive training was provided for each intervention and pharmacists and pharmacy teams were provided with funded time to complete the relevant training, assessments and authorisation procedures. Given that all community pharmacies in Ireland are required by law to have a private consultation room [38] and as the services described in this thesis were delivered in the consultation room the issue of privacy as a barrier was also addressed and unlikely to have been significant.

Delivery in practice can give some insights into potential facilitators to successful service delivery but seeking the views of pharmacists on their involvement with the delivery of services is also important and it seems likely that it could support service improvement. For this reason, the author has been supervising a pharmacist in the organisation who is conducting some follow-on work on the ABPM service [522]. As part of this work the pharmacist has conducted a survey seeking to assess the views of pharmacists involved in the delivery of the Boots ABPM service. Initial results show that the pharmacists surveyed value the opportunity to be engaged in clinical pharmacy services with 61.8% (52/85; response rate of survey 85/124, 68.5%) of pharmacists stating that involvement with the ABPM service had a major positive effect on their level of job satisfaction [522].

6.3.2 Uptake of services

Of the three interventions described in this thesis insights from the Stop for Good and ABPM services provide the best insights into patient uptake of advanced services into the community pharmacy setting. These were conducted as observational studies, a study design which has the advantage of being able to provide insights into day to day “real world” care and associated patient outcomes [523]. The INCA™ adherence intervention was introduced and presented to prospective patients as a research study as opposed to a structured service. This may have impacted patients’ acceptability of the intervention as it sought to clarify the effectiveness of the INCA™ device in clinical practice meaning it was more exploratory in nature. Whilst some patients agree to take part in clinical trials for altruistic reasons such as helping with research and supporting the care of future patients [524] many expect personal benefit which cannot be assumed given the investigational nature of randomised controlled trials [525].

Information on patient uptake as a percentage of the total number of eligible patients attending the pharmacy is not routinely recorded for pharmacy services delivered in the community pharmacy chain described in this thesis. As a result, no information on access percentages is

available meaning that the insights on patient access are limited to a discussion on the numbers of patients accessing the services. It is clear that patients did access services in pharmacies throughout the country but that access was variable. For example; looking at the Stop for Good service the numbers of patients availing of the service ranged from 1 to 70 across different pharmacies. For ABPM, a similar pattern of variability was seen with one pharmacy only engaging 2 patients with the service over the 16-month study period whilst at other end of the scale another pharmacy recruited 84 patients in the same time period. It is difficult to say what factors were at play in terms of creating this variance. It is likely that some combination of pharmacist, patient and pharmacy (team, location, format) factors were involved.

All pharmacists received the same training and the same marketing materials were available to all teams for in-store promotion of the service. In the case of Stop for Good, a national television campaign promoted the service and for ABPM some national and regional press coverage was secured. Both were promoted online via the website of the pharmacy chain. Pharmacists were also briefed in a structured way on how best to engage their local doctors with the service offerings; this was particularly true of ABPM due to the fact that referrals would be made to the GP post ABPM assessment.

Socio-economic status can be a barrier to accessing healthcare services [526]. Patients accessed the services in a range of different locations throughout the country and the author, being familiar with the types of pharmacies, can confirm that the pharmacies represent different formats (large urban (*e.g.* city centre), suburban and rural/small town) with different socio-economic population bases. An attempt was made to determine the potential socio-economic status of patients accessing the services described in this thesis by asking patients if they had medical card eligibility. However, this is an imprecise measure as not all patients in possession of a medical card are of reduced means (*e.g.* patients over the age of 70). Nonetheless looking at the access by health pay status we can see that patients with medical card eligibility represented 26.5% of patients accessing the Stop for Good service and 17.4% of patients accessing the ABPM service; both figures are smaller than that which represents the percentage of the population in possession of a valid medical card (34.9% of the Irish population; 1.66m/4.76m) [69]. This is to be expected in the case of ABPM for which a service charge applies but in the case of Stop for Good, where cost is not a barrier to access this points to a potential underutilisation by patients of lower socio-economic class. It is by no means clear however and future studies of this nature should seek to better categorise the patients accessing the service, both in terms of area of habitation and other markers of social class such as educational

attainment in order to better determine whether unequal uptake of services exists amongst different patient populations.

Patient satisfaction with the service can give some insights into the perceived quality which could affect uptake. As a follow-on to the observational study of the ABPM service a sample of patients were followed up to ascertain their satisfaction with the service provided. The results indicated a very high level of patient satisfaction with the service with 95.8% of respondents (91/95) indicating that they were “very satisfied” with the service they received [527]. 95.8% (91/95) stated that the pharmacist explained the results in a way they could understand and 72.6% felt the service represented very good value for money [527].

It is also worth noting that the interventions had the potential to require behaviour change on the part of patients accessing the services. This is particularly true of the Stop for Good programme but equally patients diagnosed with hypertension on foot of ABPM assessment may be encouraged to alter some lifestyle factors (e.g. reduce calorie intake, increase exercise) and/or commence daily medication. Similarly, patients with sub-optimal adherence as detected by the INCA™ device are coached to improve their pattern and technique of medication taking. Behaviour change is difficult [528] and accessing services requiring such change will be limited by the patients’ willingness to engage with the intervention and their readiness to attempt modification of their behaviour [529]. More in-depth analysis of the factors that motivate patients to engage with behavioural support type interventions delivered in the community setting is therefore warranted. As incentives for smoking cessation appear to boost cessation rates while they are in place [530] and because people are more motivated by tangible gains such as a financial benefit, than by long-term intangible gains like a reduction in the chance of negative health outcomes [309], work is now underway on introducing a modification to the Stop for Good programme that will involve an up-front payment and pay back rewards for positive behaviours to ascertain if such an approach will influence both patient uptake of the service and quit rates through the programme.

6.3.3 Inter-professional relationships

The literature review described in chapter two retrieved a number of studies that involved the delivery of an intervention in the pharmacy (*e.g.* screening, medication usage review) followed by onward referral to a GP for further action (*e.g.* diagnosis, therapy adjustment). In the case of referral, post screening information on the number of patients who actually attend their GP

when referred was limited but when reported varying levels of patient attendance at GP post screening were observed ranging from 37% [132] to 64% [103]. As follow up or lack thereof has important consequences for the health of the individual, it is important to understand what motivates patients to act on pharmacist recommendations and attend their GP for follow up.

In the ABPM cohort described in this thesis, patients' willingness to follow up with their GP was high (82.6%) and when a sub sample of patients (n=95) were followed up post ABPM assessment 82/95 (86.3%) indicated that they had discussed the result of their ABPM assessment with their GP. This is likely to be reflective of the high level of GP referral into the service at the outset (86.4%) but it does point to the fact that a team-based approach to care may be more successful in terms of ensuring patient engagement with referral recommendations. To explore this further, a more structured referral pathway could be created around the service where GP referrals are flagged to the pharmacy from the referring surgery and patient referrals back to the GP are facilitated by more active pharmacist involvement in the sharing of the ABPM report with the GP (which is currently the responsibility of the patient). Non-attendance could then be assessed and insights gleaned into patients' likelihood to follow up on referral recommendations. The possibility that health care professional involvement of that nature may reduce patient likelihood to follow referral recommendations as a result of having a less active role in the process cannot be discounted but any analysis would likely provide insights into behaviours either way.

Studies on the identification of drug related problems by pharmacists have shown that pharmacists' recommendations for therapy adjustments are not always fully accepted or implemented [531-534]. Reasons for this are not always clear [534], but it does not necessarily mean that the recommendations or the decisions regarding their implementation were inappropriate, and may be influenced by the working patterns of pharmacists and GPs who are typically remote from each other within the primary care setting. As poorly developed pharmacist GP relationships can impede implementation of new pharmacy services [535] and because there is some evidence of a lack of GP enthusiasm for the expanded role of the community pharmacist [536, 537] taking the time to explore the facilitators of greater inter-professional collaboration in the primary care setting is likely to be beneficial.

6.4 IMPLICATIONS FOR PRACTICE AND FUTURE DIRECTION

All three services described in this thesis were implemented in a chain of community pharmacies in Ireland that support the on-going development and delivery of innovative clinical pharmacy services. The author and another colleague are employed in a national capacity to oversee the design, development, implementation and on-going review of the delivery in practice of these clinical pharmacy services. Internal training programmes, assessment frameworks and authorisation processes as well as standard operating procedures, implementation guidance and operational standard audits are core features of all services in this particular chain. This particular chain setting thus has advantages in terms of resource allocation and standardisation of service delivery across its portfolio of pharmacies. Whilst other chains may be able to replicate such structures, it is considerably more difficult for independent pharmacies to dedicate the time and resources needed for the structured development of evidence based clinical pharmacy services. Thus, if such services are to be implemented across the board national leadership is required.

Full integration of professional pharmacy services into the health system requires that they be funded and reimbursed, either by government or a third party payer such as an insurance company, something that is not yet widespread on a global scale [538]. Levels of reimbursement are increasing in countries such as the United States, Canada and the United Kingdom where the provision of clinical pharmacy services is more established [43]. Such countries have also been active in objectively reviewing the delivery of such services and providing evidence as to their cost effectiveness [59], an essential consideration for payers looking to ensure value for investment [539]. Cost effectiveness analysis of the interventions reported in this thesis was not conducted as part of the current research but recognising the importance of such insight the author is currently supporting another pharmacist in the organisation who is conducting a cost effectiveness analysis of the ABPM service [540]. Future work could seek to review the cost effectiveness of the other interventions described.

Adjusting drug therapy in response to continuous measurement of personal health parameters such a blood pressure is becoming more feasible [541]. Both the ABPM and INCA studies utilised technologies that play in this space and modification of therapy, by the patient alone or in combination with advice from their GP and/or pharmacist, was observed in both cases. Rapid

advances in the information and communication technology space is contributing to the development of a wide range of healthcare devices that are starting to be used in the delivery of healthcare either by patients themselves or in consultation with their healthcare team [542]. As use of these types of devices becomes more prevalent and as Ireland moves towards greater integration of digital technology within the health system under the eHealth Strategy of 2015 [543], pharmacists will need to consider how to integrate such technology into their practice. The impact of the technology on the patient pharmacist interaction, privacy and data governance considerations and use of generated data to support clinical decisions all need consideration and future studies could seek to investigate how best to integrate such tools into day to day practice.

Three discrete services have been described in this thesis each delivered as standalone interventions to interested patients. The interventions were classified as primary, secondary and tertiary disease prevention interventions which presents some limitations if one is to consider how these interventions could work in practice. Whilst a smoking cessation intervention can be targeted at current smokers at future risk of disease, it is equally applicable to patients diagnosed with a condition that would benefit from smoking abstinence. Equally ABPM is well established as a screening tool for the presence of hypertension but its role in the assessment of drug therapy effectiveness is gaining ground [322]. Consideration should be given to how interventions could be packaged together into a pharmacist led disease management programme. Examples of such structured packages are starting to appear such as that report by Wright et al [210] which described the outcomes of a community pharmacy-based COPD support service consisting of structured medication management and smoking cessation support. Whilst this study was somewhat limited by the lack of a control group and high attrition rates, it did demonstrate improved patient outcomes in the form of improved medication taking behaviour and increased uptake of the flu vaccination as well as reducing overall costs of care [210]. This shows the potential of such structured programmes and future research could seek to assess if similar models could be replicated in the Irish setting and also if the model could be applied to other disease states/patients populations.

Much like the interventions described in this thesis, the authors did not report on the views of general practitioners concerning the care programme implemented even though referral to GP when relevant was a core element of the care package. Where “care bundles” (*a small set of*

evidence based interventions for a defined population and care setting) have been introduced in other settings such as the hospital sector teamwork, multidisciplinary co-operation and robust communication have been critical to their success in improving patient outcomes [544]. The situation is likely to be no different in the community setting and future studies should seek to review how a collaborative approach to care in the community might impact on patient outcomes and healthcare costs.

The challenges inherent in such an approach should not be underestimated. Integration of the community pharmacist into healthcare teams still remains a challenge worldwide [2] and the situation in the Irish context is no different. The National Primary Care Strategy considers pharmacists to be part of a primary care network of health care professionals as opposed to active members of the core primary care team (which is said to consist of GPs, nurses/midwives, health care assistants, home helps, physiotherapists, occupational therapists, social workers and administrative personnel) [545]. Given that medicines are the most common intervention in healthcare [546] and considering the growing numbers of people with long term conditions requiring medication the appropriate use of medicines is crucial to primary care. Rational and appropriate use of medicines as facilitated through interventions such as those described in this thesis are likely to be optimised through collaboration and thus this divide between the primary care team and network will need to be addressed if community pharmacy is to play a greater role. There are some suggestions that the role of community pharmacy as more than just a supply route for medication is being acknowledged with the inclusion of community pharmacists in the design and development of the National Clinical Care Programmes (evidence based care pathways for patients with specified conditions/needs) [547, 548] and the current Statement of Strategy from the Department of Health outlining a commitment to “examining the expansion of the role of community pharmacy in managing the health of patients” as a strategic objective within the primary care sector [9]. This is a positive step forward and the onus is on the pharmacy profession to be accountable and prove its worth. It is the hope of the author that this thesis goes some way to supporting that aim.

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Appendices

Appendix 1: Literature review search strategy

1. (community NEAR/4 pharmac*): ab,ti
2. (retail NEAR/4 pharmac*): ab,ti
3. professional NEAR/4 service*
4. pharmacy NEAR/4 service*
5. cognitive NEAR/4 service*
6. clinical NEAR/4 service*
7. pharmaceutical NEAR/4 service*
8. "pharmaceutical care"
9. random\$: ab,ti
10. (controlled NEAR/4 trial): ab,ti
11. (controlled NEAR/4 study): ab,ti
12. (observational NEAR/4 trial): ab,ti
13. (observational NEAR/4 study): ab,ti
14. (cluster NEAR/4 trial): ab,ti
15. (cluster NEAR/4 study): ab,ti
16. "intervention study": ab,ti
17. "time series analysis": ab,ti
18. pre AND test OR pretest OR post AND test OR posttest; ab, ti
19. 1 OR 2
20. 3 OR 4 OR 5 OR 6 OR 7 OR 8
21. 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19
22. 19 AND 20 AND 21
23. Limit 22 to English Language

Appendix 2: Stop for Good consultation record form



Customer Record Form Stop For Good Service

We'll support you every step of the way

Part 1: Customer information

First name Surname
Address
Date of birth Gender: Male Female Phone number
Email address Do you have a medical card? Yes No

Please tick your answers to the following questions:

Are you under 18 years of age? Yes No
Are you pregnant? Yes No
Are you breastfeeding? Yes No
Do you have any medical condition(s)? Yes No If yes, please specify here

Do you take any medicines? Yes No If yes, please list below

Customer declaration

I confirm that the information I have provided is correct to the best of my knowledge. I am aware that the service includes being contacted by a Stop For Good Advisor to support my quit attempt and having my levels of exhaled carbon monoxide measured and recorded. As part of a stop smoking programme, information about Nicotine Replacement Therapy (NRT) may be provided to me but I am aware that to partake in this service I am not obliged to take or purchase NRT. I am aware that Boots will retain this Customer Record Form in a manner consistent with Data Protection requirements for a period of 2 years. I am happy to proceed with the service. Yes No

I give permission for the information gathered during the service to be used to help Boots improve the service. I understand that this means Boots may use and share anonymous information from this service with carefully selected third parties, strictly for medical analysis and research. Yes No

In order to make sure Boots is meeting the needs of customers, Boots may contact some customers for feedback. This may include Boots contacting me by telephone, post or email regarding this service. I am happy to be contacted in this way. Yes No

Customer's signature Date

1st consultation
75-08-212



Part 2: Pharmacy information To be completed by the Stop For Good Advisor

Deciding if you're ready to Stop For Good

Your smoking

Store stamp

How many cigarettes do you usually smoke per day?

10 or less 11-20 21-30 31 or more

Number of years smoking Number of previous quit attempts

Nicotine dependence score (1-10) Level of importance score (1-10) Level of confidence score (1-10)

Customer has started Stop For Good Plan? Yes No If No, please provide reason

Stop For Good Advisor details

Advisor's name Store number





I have recommended that this customer starts the Stop For Good Service. I have provided information about the Service to the customer and I am satisfied that the customer has provided informed consent to enrol on the Service.

Advisor's signature

Part 3: Making a Stop For Good plan

Record of consultations

Quit date

Consultation	Date	Progress update	NRT being used (please detail)	CO reading ppm	SFG Advisor signature
Stop For Good Plan: 1st appointment					
2 week review 75-08-239  <0750 8233>					
4 week review 75-08-247  <0750 8240>					
8 week review 75-08-255  <0750 8257>					
12 week review 75-08-263  <0750 8264>					

Certificate provided to customer on completing the 12 week Stop For Good Programme: Yes No

Appendix 3: ABPM consultation record form

Patient Record Form

To be retained by the store and filed securely



Part 1: Patient information

First name: Surname:

Address:

Email:

Phone no: Date of birth:

Doctor's name:

Contact details:

Male: Female: Are you pregnant? Yes No

Ethnic origin: White Asian (India, Pakistan, Bangladesh or Sri Lanka) Other Asian

Black African Black Caribbean Other Black Mixed

Other (please specify)

I am happy to be contacted by phone: Yes No

I give permission for the results of my blood pressure monitoring and any recommendations to be provided to my Doctor: Yes No

Please answer the following questions

Are you aged 18 years or over? (You must be aged 18 or over to use this service) Yes No

Have you had a 24-hour blood pressure measurement taken before? Yes No

If yes, please detail:

Do you have any of the following? (Please tick one or more as relevant)

Medical Card Doctor Visit Card Health Amendment Card

Long Term Illness book Private Health Insurance

Part 2: Patient information

Do you smoke, or have you ever smoked? Yes No

If yes, how many cigarettes each day?

How long have you been a smoker (no. of years)?

Do you currently smoke? Yes No

How much alcohol on average do you drink per week:

(One standard drink is approximately equal to half a pint of normal beer/lager/cider OR one small glass of wine OR one single measure of spirits)

Number of standard drinks per week Don't drink

Do you take any medication? Yes No If yes please detail:

Do you have diabetes? Yes No

If yes, please select which type: Type 1 or Type 2

Part 2: Patient information continued

Do you have high cholesterol? Yes No Unsure

Have you ever had any of the following: (Please tick one or more as relevant)

Ischaemic Stroke TIA-Trans Ischaemic Attack (mini stroke)

Haemorrhagic Stroke Heart Attack Unsure

Have you ever been diagnosed with any of the following: (Please tick one or more as relevant)

Atrial Fibrillation Heart Failure

Vascular disease (condition that affects your circulatory system) Unsure

Part 3: Patient consent

I confirm that the information I have provided is correct to the best of my knowledge and I understand the information provided to me about the service. I am happy to proceed with having the monitoring device fitted and agree to return the device to the Pharmacy after 24 hours. I understand that my blood pressure results will be provided to me by my Pharmacist when I return to the Pharmacy, and that the Pharmacist may refer me to my Doctor. I am aware that Boots will retain the results from my 24-hour Blood Pressure Monitoring report, along with this Consultation Record Form, in a manner consistent with Data Protection requirements, for a period of 8 years.

Signature: _____

Date: _____

The information gathered during the service may be used to help Boots improve the service. I understand that this means Boots may use and share anonymous information from this service with carefully selected third parties, for medical analysis and research.

If you do not wish for your anonymous information to be shared in this way tick here

In order to assess the benefits of this service, Boots may contact some patients in the future for follow up (e.g. in 6 to 12 months).

I am happy to be contacted for this purpose: Yes No

In order to make sure Boots is meeting the needs of patients, Boots may contact some patients for feedback. I am happy to be

contacted for this purpose: Yes No

For Pharmacy use only

Part 1:

ABPM device connected by: _____

Signature: _____

Patient reference: _____

Battery change complete: Yes No Monitor ID: _____

Night-time hours: _____ pm _____ am Daytime recording interval: _____ mins

Night-time recording interval: _____ mins

Part 2:

Height: _____ m Weight: _____ Kg BMI: _____ Kg/m²

Arm circumference: _____ cm BP reading right arm: _____ mmHg

BP reading left arm: _____ mmHg Date fitted: / /

Right arm: Left arm: Time on: _____

Requested by: _____

Results consultation

Date returned and results consultation: _____

Pharmacist name: _____

Signature: _____

Appendix 4: ABPM follow up survey (telephone)



24 Hour Blood Pressure Monitoring Service Follow up Telephone Interview



Section 1: Interview Details

Interviewer name: _____

Date of interview: _____

Pharmacy: _____

Date of patient's 24-hour blood pressure assessment: _____

Section 2: Request for participation

2.1 Introduction

Interviewer: Hello, may I speak to {*patient name*} please? [If the person you wish to speak to is not there at the time, ask when a good time to phone is].

[When you get the correct person]

Interviewer: My name is {*name*} and I work in Boots {*insert pharmacy name*}. You visited our pharmacy on {*day, date*} when you availed of the Boots 24 Hour Blood Pressure Monitoring Service. At that time, you agreed to allow Boots to contact you for follow up. Is now a good time to talk?

[If yes, proceed to section 2.3]

2.2 Scheduling a more convenient time/survey type

[If no to current time:]

Interviewer: Would I be able to call you at another, more convenient time?

[If yes: ask when a good time to call back is and record time here _____]. **Interviewer:** Thank you for your time I will call back then. [Proceed to end call]

[If no:] **Interviewer:** Would you prefer if I posted you a copy of the survey?

[If yes: verify postal address and proceed to end call]. **Interviewer:** Thank you for your time. I will send the survey to you. [Send survey via post to patient].

[If no:] **Interviewer:** That's no problem. Thank you for your time.

2.3 Overview of survey

Interviewer: The purpose of the survey today is to help us learn a little bit more about your blood pressure management since you availed of the service. It should take less than five minutes to complete. All of your responses will be recorded anonymously (so that you cannot be identified) and they will be used for research purposes, helping us to plan ways to improve the blood pressure monitoring services that we provide. During the survey if there is anything that you do not understand or if anything I am asking is unclear, please stop me. If I ask you a question that you don't want to answer, just let me know and I will move on to the next question. You can ask me to stop at any time.

2.4 Consent to proceed

Are you happy to take part in this survey now?

Record participant consent: Yes No

Section 2: Interview Questions

[Instructions to interviewer: Please ask the question in blue and then tick the appropriate box based on patient response. Note: the options are provided for ease of entering answers - you do not need to read out each option]

1. What was the reason you underwent a 24-hour blood pressure assessment? [Please tick all relevant boxes]

My blood pressure was high when I visited the doctor.....
My blood pressure was high when I visited the pharmacy.....
I was taking medication for high blood pressure.....
I have a 24-hour blood pressure assessment every year.....
Don't know/Can't remember
Other (please detail)

2. Before you availed of the service had you been diagnosed with high blood pressure?

Yes
No
Don't know

[if no/don't know proceed to question 5]

3. If yes, were you already taking medication for your high blood pressure before the 24-hour assessment?

Yes
No
Don't know

4. If yes, were any changes made to your blood pressure medication following the 24-hour blood pressure assessment

Yes, my dose of medication was decreased
Yes, my dose of medication was increased
Yes, I was prescribed a different medication
Yes, I was prescribed an additional medication
Yes, I no longer am prescribed medication for high blood pressure
No
Don't know
Other (please detail)

5. Since your 24-hour blood pressure assessment have you been newly diagnosed with any of the following

Hypertension (high blood pressure)
White-coat hypertension (high blood pressure in clinic, normal at home)
Masked hypertension (normal blood pressure in clinic, high at home)
Atrial fibrillation (rapid and irregular pulse).....
No new diagnosis

6. [Instructions to interviewer: Only ask this question to patients with hypertension/masked hypertension as identified in Q5 above]

6 (a) So you have been newly diagnosed with hypertension (high blood pressure)?

Yes
No
I was not diagnosed with hypertension....
Don't know

[if no/don't know proceed to Q7 (for patients with atrial fibrillation as identified in Q5) or Q9 for all others]

6 (b) Did your doctor prescribe medication for this condition?

- Yes
No
Don't know

[if no/don't know proceed to Q7 (for patients with atrial fibrillation as identified in Q5) or Q8 for all others]

6 (c) If yes, are you still taking medication for your hypertension (high blood pressure)?

- Yes
No
Don't know

7. [Instructions to interviewer: Only ask this question to patients with atrial fibrillation as identified Q5 above]

7 (a) So you have been newly diagnosed with atrial fibrillation (irregular pulse)?

- Yes
No
I was not diagnosed with atrial fibrillation.....
Don't know

[if no/don't know proceed to Q8]

7 (b) Did you have to undergo any further tests before you received your diagnosis?

- Yes
No
I was not diagnosed with atrial fibrillation.....
Don't know

If yes, please detail:

7 (c) Did your doctor prescribe medication for this condition?

- Yes
No
Don't know

[if no/don't know proceed to Q8]

7 (d) If yes, are you still taking medication for your atrial fibrillation (irregular pulse)?

- Yes
No
Don't know

8. Why did you choose to have the 24-hour blood pressure monitoring service in the pharmacy?

[Please tick all relevant boxes]

- My pharmacist recommended the service to me
My doctor referred me to the pharmacy
There was a long waiting list in my doctor's surgery.....
There was a long waiting list in the hospital.....
Convenient opening hours.....
Convenient location.....
Good value for money.....
Can't remember.....
Other (please specify)

9. Were you satisfied with the service you received in the pharmacy?

- Very satisfied
- Fairly satisfied
- Not very satisfied
- Not at all satisfied
- Don't know

10. Did the pharmacist explain the results of 24-hour blood pressure assessment in a way that you could understand?

- Yes
- Yes, to some extent
- No
- Don't know/can't remember

11. In relation to the results as explained by the pharmacist, do you feel they provided the correct level of information?

- I was given some information, but would have liked more
- I was given too much information
- I was given just the right amount of information
- Don't know/can't remember

12. Did you discuss the results of your 24-hour blood pressure assessment with your doctor?

- Yes
- No
- Don't know/can't remember

13. If No, is there a reason why you did not do so?

[Free text; enter answer provided by the patient below]

14. Do you think that the service was good value for money?

[Instructions to interviewer: If patient cannot remember the cost remind them that the service costs €50]

- Very good value
- Fairly good value
- Not very good value
- Not at all good value
- Don't know

Interviewer: Do you wish to make any additional comments or suggestions?

[Enter any comments in the space provided below]

Interviewer: We have come to the end of the survey, thank you very much for taking the time to help us with this research. If you have any questions about your blood pressure or concerns following completion of this interview, please don't hesitate to phone me on *{insert pharmacy phone number}* or come into the pharmacy to speak with us.

Appendix 5: ABPM follow up survey (post)



24 Hour Blood Pressure Monitoring Service



let's feel good
together*

Over the course of the last year, you availed of the Boots 24 Hour Blood Pressure Monitoring Service. We would like to thank you for supporting this service in the pharmacy and invite you to complete a short survey designed to help us learn a little bit more about your blood pressure management since you availed of the service. It should take less than five minutes to complete. All of your responses will be recorded anonymously (so that you cannot be identified) and they will be used for research purposes, helping us to plan ways to improve the blood pressure monitoring services that we provide.

Are you happy to complete the survey? Yes No

Please indicate below the date and location of your 24-hour blood pressure assessment:

Date of assessment: _____

Pharmacy: _____

1. What was the reason you underwent a 24-hour blood pressure assessment? *[Please tick all relevant boxes]*

- My blood pressure was high when I visited the doctor.....
- My blood pressure was high when I visited the pharmacy.....
- I was taking medication for high blood pressure.....
- I have a 24-hour blood pressure assessment every year.....
- Don't know/Can't remember
- Other (please detail)

2. Before you availed of the service had you been diagnosed with high blood pressure?

- Yes
- No
- Don't know

[if no/don't know proceed to question 5]

3. If yes, were you already taking medication for your high blood pressure before the 24-hour assessment?

- Yes
- No
- Don't know

4. If yes, were any changes made to your blood pressure medication following the 24-hour blood pressure assessment

- Yes, my dose of medication was decreased
- Yes, my dose of medication was increased
- Yes, I was prescribed a different medication
- Yes, I was prescribed an additional medication
- Yes, I no longer am prescribed medication for high blood pressure
- No
- Don't know
- Other (please detail)

5. Since your 24-hour blood pressure assessment have you been newly diagnosed with any of the following?
- Hypertension (high blood pressure)
 - White-coat hypertension (high blood pressure in clinic, normal at home)
 - Masked hypertension (normal blood pressure in clinic, high at home)
 - Atrial fibrillation (rapid and irregular pulse)
 - No new diagnosis

6. If you have you been newly diagnosed with hypertension (high blood pressure):

6 (a) Did your doctor prescribe medication for this condition?

- Yes
- No
- Don't know

6 (b) If yes, are you still taking medication for your hypertension (high blood pressure)?

- Yes
- No
- Don't know

7. If you have been newly diagnosed with atrial fibrillation (irregular pulse):

7 (a) Did you have to undergo any further tests before you received your diagnosis?

- Yes
- No
- Don't know

If yes, please detail:

7 (b) Did your doctor prescribe medication for this condition?

- Yes
- No
- Don't know

7 (c) If yes, are you still taking medication for your atrial fibrillation (irregular pulse)?

- Yes
- No
- Don't know

8. Why did you choose to have the 24-hour blood pressure monitoring service in the pharmacy?

[Please tick all relevant boxes]

- My pharmacist recommended the service to me
- My doctor referred me to the pharmacy
- There was a long waiting list in my doctor's surgery.....
- There was a long waiting list in the hospital.....
- Convenient opening hours.....
- Convenient location.....
- Good value for money.....
- Can't remember.....
- Other (please specify)

9. Were you satisfied with the service you received in the pharmacy?

- Very satisfied
- Fairly satisfied
- Not very satisfied
- Not at all satisfied
- Don't know

10. Did the pharmacist explain the results of 24-hour blood pressure assessment in a way that you could understand?

- Yes
- Yes, to some extent
- No
- Don't know/can't remember

11. In relation to the results as explained by the pharmacist, do you feel they provided the correct level of information?

- I was given some information, but would have liked more
- I was given too much information.....
- I was given just the right amount of information
- Don't know/can't remember

12. Did you discuss the results of your 24-hour blood pressure assessment with your doctor?

- Yes
- No
- Don't know/can't remember

13. If No, is there a reason why you did not do so? Please enter details below.

14. At €50, do you think that the service was good value for money?

- Very good value
- Fairly good value
- Not very good value
- Not at all good value
- Don't know

If you wish to make any additional comments or suggestions, please do so in the box below.

**Thank you for taking the time to complete this survey.
Please now return the survey to the pharmacy using the stamped addressed envelope provided.**

Appendix 6: Inhaler Proficiency Schedule

INhaler Compliance Assessment (INCA) – Pharmacy Study

INAHLER PROFICIENCY SCHEDULE (IPS)

Patient ID: _____

Date: ___ / ___ / ___
 dd mm yyyy

Visit No: _____

YES NO

Does the patient hold the outer casing of the inhaler in one hand, whilst pushing the thumb grip away, until a click is heard?		
Does the patient hold the inhaler with mouthpiece towards himself?		
Does the patient slide lever away until it clicks?		
Does the patient hold the inhaler in a horizontal position?		
Does the patient breath out slowly and then put inhaler in front of mouth?		
Does the patient place mouthpiece between lips and breathe in as deeply as possible?		
Does the patient remove inhaler from mouth and hold breath for about 10 seconds?		
After 10 seconds does the patient breathe out slowly?		
Does the patient close the inhaler by sliding thumb grip back towards himself as far as it will go until it clicks?		
Does the patient gargle throat after use?		